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COVID-19 lockdown effects on adolescent brain structure suggest accelerated maturation that is more pronounced in females than in males

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Adolescence is a period of substantial social–emotional development, accompanied by dramatic changes to brain structure and function. Social isolation due to lockdowns that were imposed because of the COVID-19 pandemic had a detrimental impact on adolescent mental health, with the mental health of females more affected than males. We assessed the impact of the COVID-19 pandemic lockdowns on adolescent brain structure with a focus on sex differences. We collected MRI structural data longitudinally from adolescents prior to and after the pandemic lockdowns. The pre-COVID data were used to create a normative model of cortical thickness change with age during typical adolescent development. Cortical thickness values in the post-COVID data were compared to this normative model. The analysis revealed accelerated cortical thinning in the post-COVID brain, which was more widespread throughout the brain and greater in magnitude in females than in males. When measured in terms of equivalent years of development, the mean acceleration was found to be 4.2 y in females and 1.4 y in males. Accelerated brain maturation as a result of chronic stress or adversity during development has been well documented. These findings suggest that the lifestyle disruptions associated with the COVID-19 pandemic lockdowns caused changes in brain biology and had a more severe impact on the female than the male brain.

adolescent cortical thinning | accelerated brain maturation | normative modeling

Significance

We report that the lockdown measures enacted during the COVID-19 pandemic resulted in unusually accelerated brain maturation in adolescents and that this accelerated maturation was much more pronounced in females than in males. These findings indicate greater vulnerability of the female brain, as compared to the male brain, to the lifestyle changes resulting from the pandemic lockdowns. They additionally provide a potential neurophysiological mechanism for alterations in adolescent mental health and other behaviors associated with the lockdowns. Since accelerated brain maturation has been associated with increased risk for the development of neuropsychiatric and behavioral disorders, these findings highlight the importance of providing ongoing monitoring and support to individuals who were adolescents during the COVID-19 pandemic.

The COVID-19 pandemic resulted in illness and mortality across the world, but its effects on societies were much broader than that of the respiratory illness alone. Due to the high transmissibility of the illness, governments across the world enacted restrictive measures, including stay-at-home orders, social distancing requirements, and school shutdowns. The result was a massive disruption to daily routines, including the inability to work and go to school, and severe restrictions in social activities for billions of people around the world. These restrictive measures had a substantial negative impact on the mental health of adolescents, with females more adversely affected than males (1).

Adolescence is a period of dramatic change in emotional, behavioral, and social development. During this period, individuals become more independent of their parents and spend more time with peers. These peer interactions provide necessary opportunities for learning how to navigate social relationships. This time period is also one in which a sense of self-identity, self-confidence, and self-control are developed (2), but it is also a period of emergence of many neuropsychiatric disorders, including anxiety, depression, and behavioral disorders (3). Females are at a higher risk for developing anxiety and mood disorders than males during typical adolescent development (4). For both sexes, exposure to stress over long durations of time can often be a trigger for the onset of neuropsychiatric disorders.

The pandemic lockdowns reduced the ability of teens to interact with their peers and dramatically increased isolation in general. This reduction in social interactions had a detrimental impact on adolescent mental health. There are many reports of increases in anxiety, depression, and feelings of stress in both females and males after the pandemic lockdowns as compared to levels before the pandemic, and many studies suggest that the mental health impacts in females were much larger than in males (e.g., refs. 1, 5, and 6). A review of longitudinal studies of the effect of the COVID-19 lockdowns on children and adolescents reported that females were at a higher risk than males of experiencing internalizing symptoms, anxiety and depression, feelings of stress, and feelings of poor well-being as compared to prepandemic levels (7). Males were more at risk than females for attention problems, addictive gameplay, and decreases in feeling of life satisfaction (7).

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Adolescence is also a period of significant structural remodeling of the brain (2). During childhood and adolescence, the brain is neurally plastic and undergoes many structural changes, which are highly dependent on environmental factors. Cortical gray matter volume and cortical thickness peak during childhood, steadily decrease throughout adolescence (8), and continue to decrease across the rest of the lifespan (9). Myelination and synaptic pruning are active processes in many regions of the brain during adolescent development. The decreases in cortical thickness observed during adolescence are likely primarily caused by synaptic pruning, but myelination of axons within the cortical layer may also play a role (10–12).

To date, there have been few studies of the effect of the COVID-19 pandemic lockdowns on brain structural development in adolescence. Two recent studies have investigated how the pandemic affected cortical thickness and regional cortical volumes, but neither examined sex as a potential factor. One study of 9- to 13-y-old subjects reported accelerated maturation of the medial prefrontal cortex, as reflected by a reduction in cortical thickness over what would be expected from normal aging, and accelerated development of the hippocampus, as reflected in an increase in hippocampal volume (13). A study of 16-y-old adolescents reported reduced average brain cortical thickness and larger bilateral hippocampal and amygdala volumes in a group that experienced pandemic lockdowns as compared to a pre-COVID-19 group (14). The findings from both of these studies suggest that COVID-19 pandemic-associated lifestyle changes resulted in accelerated brain aging. Numerous previous studies of adversity in children and adolescents have found that adversity leads to similar premature maturation of the brain (for a review, see ref. 15).

The aforementioned literature on the effects of COVID-19 pandemic-associated lifestyle changes on the mental health of adolescents documents significantly larger impacts on females than on males. Previous studies of the effects of the COVID-19 pandemic lockdowns on brain structure have not investigated sex differences. Therefore, the goal of the current study is to test the hypothesis that sex is a significant factor in the effects of the COVID-19 pandemic lockdowns on brain structural development during adolescence. The current study reports findings from data collected as part of a longitudinal investigation of adolescent brain development. MRI data were collected for adolescents at 9, 11, 13, 15, and 17 y of age in 2018, prior to the pandemic. The original objective for data collection was to evaluate longitudinal changes in brain structure during typical adolescence, and the plan was for adolescent participants to return in 2 y at a second time point. However, the COVID-19 pandemic lockdowns that occurred in 2020 prevented subjects from returning for data collection at the appointed time. As a result, the second time point data were collected from all study subjects in 2021, 3 y after the first time point, with 81% of the original cohort returning for the second time point data collection visit.

The pandemic provided a unique opportunity for evaluation of the effects of the pandemic lockdowns on brain structural development and, in particular, allowed us to test the hypothesis that females were more adversely affected than males. Evaluation of this hypothesis using traditional statistical analysis techniques that would quantify the difference by comparing adolescents affected versus those unaffected by the pandemic was not possible because the pandemic was a global experience that affected virtually all individuals. Instead, to test our hypotheses, we turned to a statistical technique termed *normative modeling,* which has been only recently adapted for neuroimaging applications. Normative modeling quantifies deviations of measurements from individual subjects from an expected trajectory due to typical aging and development. This technique allows for the differentiation between the effects of typical aging on the brain and effects that are the result of a developmental disorder or an environmental event (16, 17).

Normative Modeling. Normative models are a class of statistical techniques that characterize changes that occur during typical development. By comparing new data to these models, deviations from typical development can be revealed (16, 17). This approach has recently been adopted by a number of investigators to differentiate between the effects of typical development or aging on brain structural changes from the effects of a neuropsychiatric disorder or an external event without using traditional group comparison statistics, which obscure heterogeneity of brain alterations between individuals in a diagnostic group. These normative models are analogous to the normative growth charts used in pediatric offices worldwide to track weight and height in young children. In neuroscientific studies of development or aging, a normative model of change in a specific brain anatomical feature as a function of age and sex is constructed for a group of subjects not affected by the disorder or environmental influence of interest (termed a "reference group"). The model provides normative trajectories of change for individual brain regions (18). Measurements from individuals in a "target group," typically a diagnostic group of interest, are then compared to this model. Each subject in the target group is assigned a centile score that describes the deviation of the subject's development from the expected, or normative, trajectory (19). This centile score represents how much that individual's brain measures deviate from the expected patterns associated with typical development or aging. One of the benefits of this approach is that, since a centile score is calculated for each individual in the target group, the heterogeneous impacts of events, disorders, or disease on individual subjects are captured. This technique also affords improved sensitivity in detecting group differences (20, 21).

Normative modeling has been used to quantify deviations from typical brain structural change with age by a number of investigators. For example, normative modeling has been used to examine the effects of socioeconomic disadvantage (22) and traumatic stress (23) on the developing brain. It has also been extensively used to evaluate brain structural alterations in samples containing broad ranges of ages in autism spectrum disorder (ASD) (24–27), to identify subtypes of individuals with ASD (24, 25), to study heterogeneity in structural brain features within ASD (24–27), and to identify functional brain connectivity networks that are clinically relevant to ASD (28). Normative modeling has additionally been used to investigate interindividual heterogeneity in brain structural alterations in individuals with attention deficit hyperactivity disorder (29), to evaluate the extent and heterogeneity of brain structural (30, 31) and functional (32) alterations in major depressive disorder, and to identify regions of and evaluate heterogeneity in structural alterations in individuals with schizophrenia (21, 33) and bipolar disorder (33). Brain structure and function change across the lifespan, and all of the aforementioned studies used normative modeling to differentiate between changes associated with typical growth or aging and those associated with the disorder or an environmental factor of interest.

The Current Study. For the current study, we constructed normative models for all regions of the cerebral cortex in a subset of adolescent subjects based on our measurements of cortical thickness collected prior to the COVID-19 pandemic lockdowns. We then used these normative models to assess whether cortical thickness at the post-COVID-19 lockdown time point in a different subset of subjects from the same sample of adolescent subjects deviated from what would be expected at that age. This

statistical technique allowed us to make a comparison between developmental trajectories in independent samples before and after the COVID-19 pandemic lockdowns to test the hypothesis that the lifestyle changes associated with the COVID-19 pandemic had an impact on adolescent brain development and that these effects were greater in females than in males.

As is typical in normative modeling studies, our design followed three steps: 1) developmental changes in cortical thickness were modeled first exclusively in a pre-COVID-19 sample (the "train" sample) from our cohort of adolescent participants; 2) this normative model was then validated in another independent pre-COVID-19 sample from our cohort of adolescent participants (the "validation" sample), and finally, 3) the normative model was tested on a second independent sample of post-COVID-19 pandemic lockdown adolescent participants from our cohort (the "test" sample). This normative modeling procedure allowed us to characterize the trajectory of change in brain structure as a function of age in typical development in the absence of the effects of the COVID-19 pandemic lockdowns, and then to identify effects that deviated from what is expected during typical development in the post-COVID-19 lockdown data.

There are multiple strengths of the design of the current study. All study participants were selected from adolescents living in the same community, using identical exclusion criteria; all study participants experienced similar pandemic lockdown timelines; and all brain data were acquired on the same MRI instrument. This design strategy mitigated concerns that arise when normative models are developed on populations with different demographic characteristics and using different imaging systems (34, 35).

In summary, the hypotheses for the current study are 1) the COVID-19 pandemic lockdowns altered the normal pattern of adolescent brain development, creating accelerated cortical thinning, and 2) the accelerated cortical thinning was more pronounced in females than in males.

Results

Cortical Thickness Findings by Sex. A subset of subjects in the pre-COVID-19 lockdown sample (the train sample) was used as a normative reference cohort to create a model of cortical thickness change across adolescence for each of 68 brain regions. The validity of this model for modeling pre-COVID-19 adolescent cortical thickness change with age was evaluated on a separate independent sample of pre-COVID-19 subjects (the validation sample). The normative model was then used to evaluate regional cortical thickness values collected post-COVID-19 lockdowns in a separate subset of subjects (the test sample). This allowed for deviations of the post-COVID-19 lockdown cortical thickness values from what would be expected during typical adolescent development to be evaluated. As an example, the normative model for the right hemisphere fusiform gyrus, superimposed on the pre-COVID-19 data train sample, on the validation sample, and on the post-COVID-19 lockdown test sample, is shown in Fig. 1.

For the post-COVID-19 lockdown data, Z-scores provided a measure of the magnitude of deviation for each subject from the normative model. *P* values for mean post-COVID-19 lockdown Z-scores were found to be significantly different than zero in 30 regions of the female brain and in 2 regions of the male brain. Z-score distributions for regions of the brain showing the most significant deviations from the normative reference pre-COVID-19 values are shown in Fig. 2. Z-score distributions for all 68 regions studied are shown in *SI Appendix*, Figs. S1–S3. The anatomical locations of the regions showing significant deviations from the normative values for the male and female brain are shown in Fig. 3. In the female sample, the regions with significant cortical thinning were located in all lobes of the brain, and in both hemispheres. In the male sample, the regions with significant cortical thinning were located only in the occipital lobe. A list of all regions showing significant cortical thinning by lobe and sex is shown in *SI Appendix*, Table S1. The effect size for each brain region is shown in Fig. 4, and the 95% CI for the effect sizes are shown in *SI Appendix*, Fig. S4. The magnitude of the effect size for post-COVID-19 lockdown cortical thinning was greater than 0.5 for 29 regions (43% of all cortical regions investigated) in the female brain and four regions (6% of all regions) in the male brain. An alternative model fit separately for males and for females shows nearly identical results (*SI Appendix*, Fig. S5).

Age Acceleration. An additional normative model was created to evaluate average cortical thickness change with age across the entire brain in the pre-COVID-19 lockdown normative reference cohort. When the model was created after averaging across all 68 brain regions, we found post-COVID-19 lockdown Z-scores to be significantly different from zero for females (P = 0.00021), but not significantly different for males (P = 0.16). The actual age for subjects in the post-COVID-19 lockdown sample subset was subtracted from the predicted age to calculate average age acceleration. This analysis revealed that for males, the mean average age difference between the age predicted by the model and actual age in the post-COVID-19 lockdown test sample was 1.4 y, with a 95% CI of –0.39 to 3.35 y. For females, the mean average age

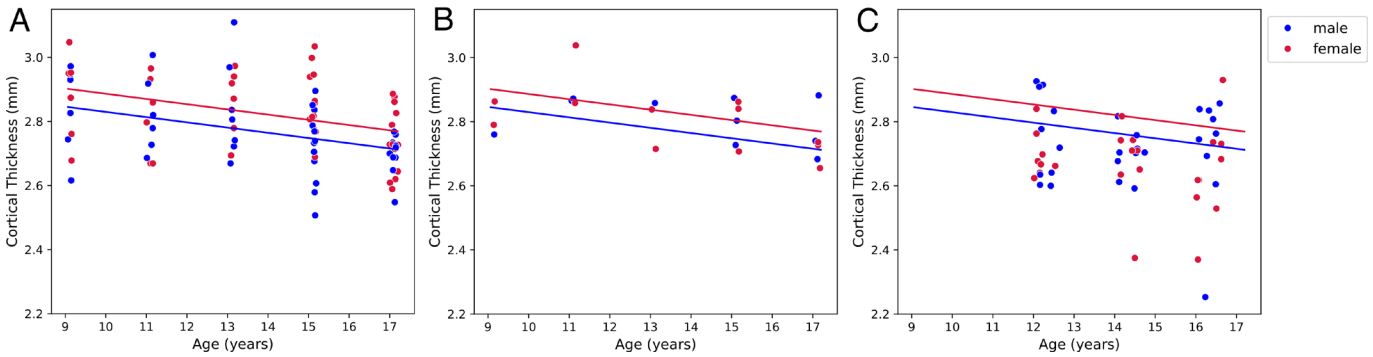

Fig. 1. A comparison of the pre- and post-COVID-19 pandemic lockdown data for the right hemisphere fusiform gyrus region. (*A*) Bayesian linear regression was used to fit a normative model (blue and red lines) to cortical thickness data in the pre-COVID-19 train sample (each data point represents a subject) for both males (blue) and females (red). The model characterizes changes in cortical thickness as a function of age and sex during typical adolescent development. (*B*) The same normative model (blue and red lines from Panel *A*) is shown superimposed on cortical thickness data for a separate sample of pre-COVID-19 data (validation sample). (*C*) The normative model (blue and red lines from Panel *A*) is shown superimposed on cortical thickness data for the post-COVID-19 lockdown (test) sample.

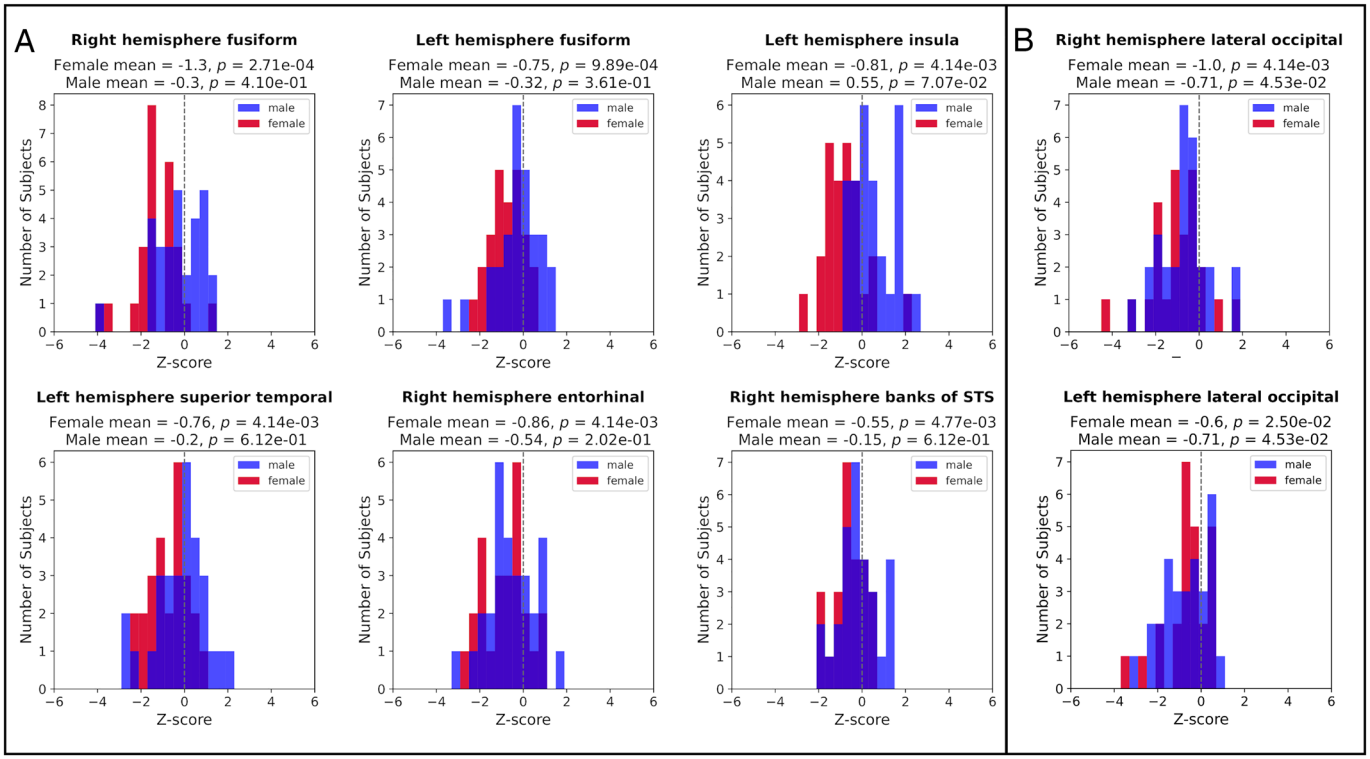

Fig. 2. Z-score distributions for example brain regions in which statistically significant deviations from the normative mean in the post-COVID-19 lockdown data were observed. Normative mean cortical thickness is indicated by a vertical dashed line. (*A*) Histograms for six regions where females but not males showed significant deviation. (*B*) Histograms for the two regions where both females and males showed significant deviation.

difference between the age predicted by the model and actual age in the post-COVID-19 lockdown test sample was 4.2 y, with a 95% CI of 2.36 to 6.05 y (Fig. 5). The difference in the mean acceleration between females and males was 2.8 y. An alternative model fit separately for males and females showed very similar results (*SI Appendix*, Fig. S6).

Discussion

In this investigation comparing adolescent brain structure before and after the COVID-19 pandemic lockdowns, we found accelerated cortical thinning in both the male and female brain. Whereas this thinning was found to be widespread throughout the female brain, occurring in 30 brain regions across both hemispheres and all lobes of the brain, we found it to be limited to only two regions in the male brain, both located in the occipital lobe. In our calculation of average age acceleration based on the whole brain, we found the magnitude of the age acceleration to be more than twice as large in females (4.2 y) as in males (1.4 y). The effect size for the cortical thinning was greater than 0.5 for 43% of the regions investigated in the female brain and only 6% of the regions investigated in the male brain.

The regions with the greatest acceleration in cortical thinning in females were the bilateral fusiform, the left insula, and the

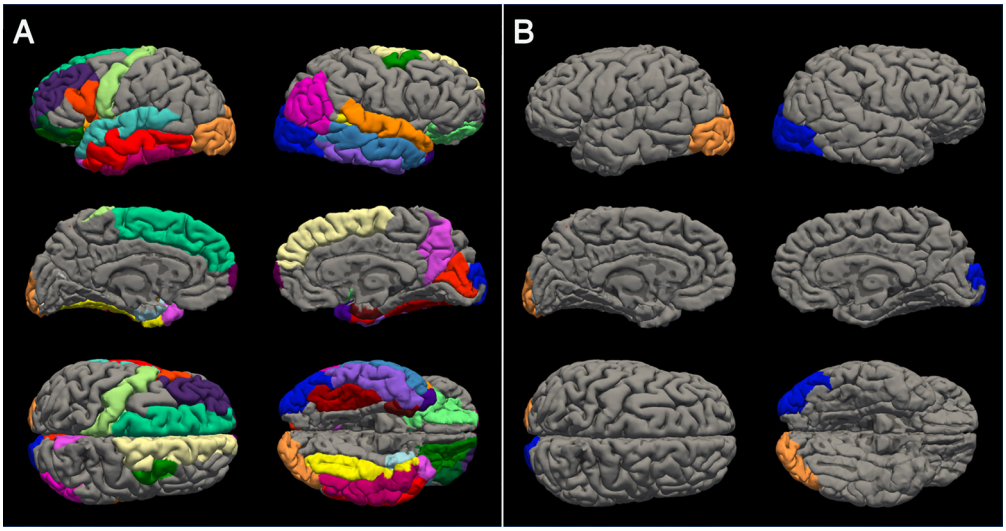

Fig. 3. Regions with significantly accelerated cortical thinning in the post-COVID-19 lockdown adolescent brain. Regions with accelerated thinning in the female brain (*A*) and male brain (*B*) are shown in color. These data are superimposed on the FreeSurfer adult sample brain (gray). Regional boundaries are from the Desikan–Killiany parcellation scheme.

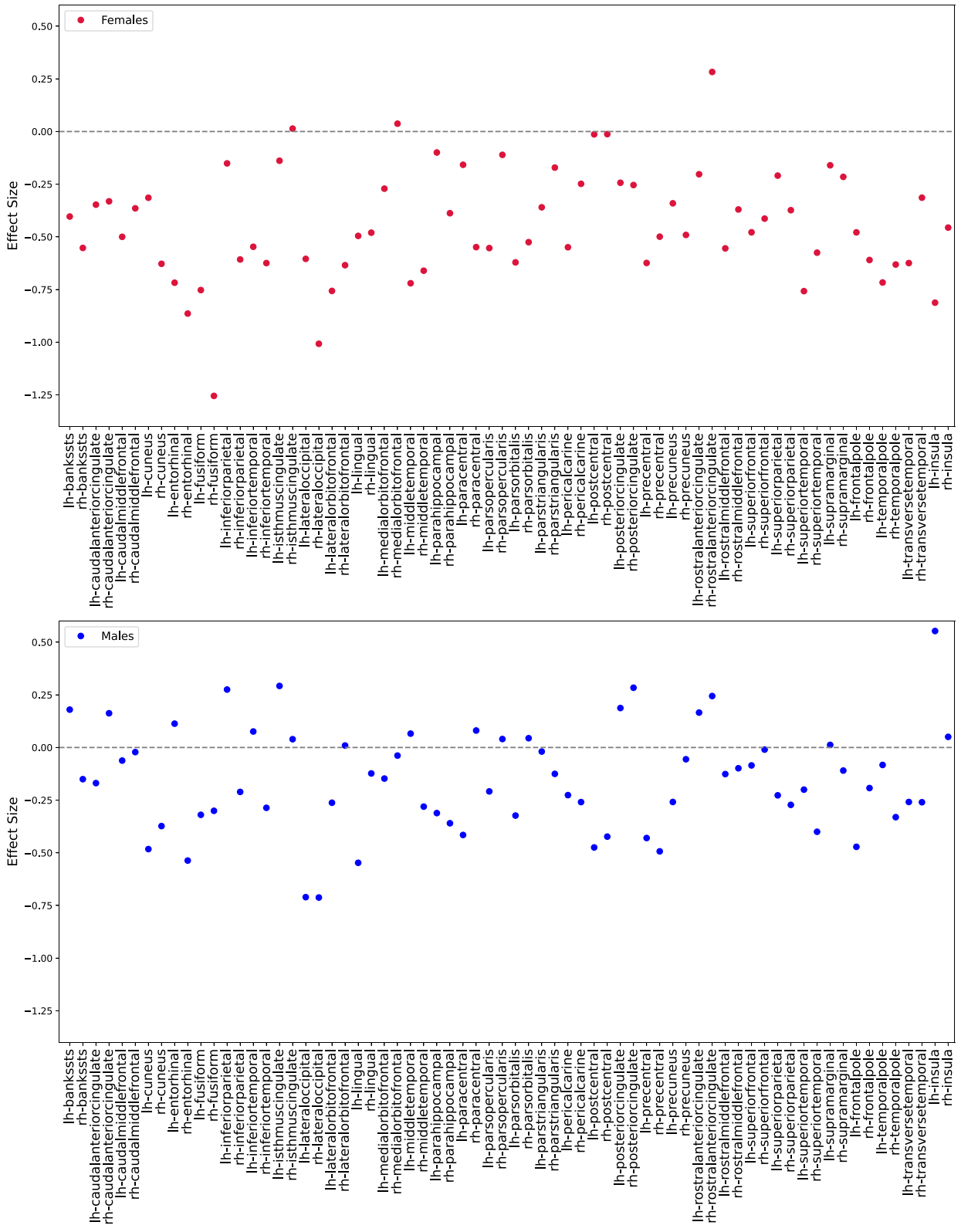

Fig. 4. Effect size by brain region for males and females.

left superior temporal cortex. While all of these regions are involved in many cognitive functions, one commonality is that they have all been linked to social cognition. The fusiform gyrus is key in recognizing and processing faces and facial expressions (36), allowing for appropriate interactions in a social environment. The insula plays an essential role in the processing of social and emotional experiences, as well as in empathy and compassion (37). The superior temporal gyrus plays a key role in language comprehension (38), which is critical for communication in all settings, including social interactions. The regions with accelerated cortical thinning in males were the left and right hemisphere lateral occipital cortex. The lateral occipital cortices, which are adjacent to the fusiform gyri, are well documented to be involved in processing objects in the visual field

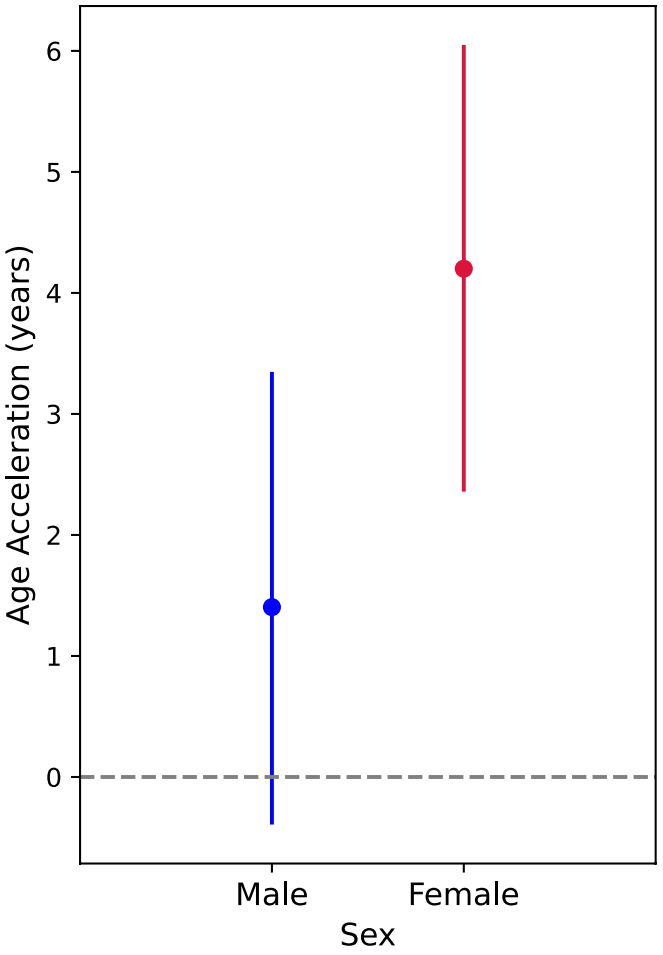

Fig. 5. Mean age acceleration by sex with 95% CI.

but also have been reported to play a significant role in the processing of faces (39).

Accelerated brain development has long been reported to be associated with trauma, abuse, deprivation, and neglect in childhood (15). The link between the two has not been fully elucidated, but previous research provides some clues. One prominent theory as to why the brain ages faster in an environment with adverse stimuli is the "stress acceleration hypothesis" (40). This hypothesis posits that a protracted period of dependence on caregivers and environmental influences in a low-stress environment is beneficial for long-term well-being and survival. However, in a high-stress environment, development may shift toward earlier maturation in order to protect emotional circuits in the brain, as well as regions involved in learning and memory. This early maturation would reduce the detrimental effects of an adverse environment on brain structural development. Other research linking acceleration in cortical thinning and heightened stress in animal models provides a more mechanistic hypothesis. Cortical thinning has been found to be related to the activity of the hypothalamic–pituitary–adrenal (HPA) axis (22), which regulates the response to stress. Activation of the HPA axis results in the release of cortisol by the adrenal cortex. This, in turn, activates glucocorticoid receptors throughout the brain. Higher levels of glucocorticoid receptors have been associated with decreased cortical thickness (41). These findings in animals are consistent with a report of a negative correlation between cortisol levels in the saliva and cortical thickness in many regions of the frontal lobe in human adults (42). Since glucocorticoid receptors are present in most brain regions (43), it is possible that the presence of this hormone for a long duration of time throughout the brain may result in widespread reduced cortical thickness (44).

The sex differences in the patterns of cortical thinning observed in this study are notable. They closely mirror the well-established sex differences in the prevalence of neuropsychiatric disorders between males and females, both in adolescence and adulthood, with females being markedly more affected. The reasons for this marked sex difference in psychology and neurophysiology are unclear. A recent study of the effects of life stressors on cortical thickness in a sample of adolescents and young adults reported greater stress to be associated with thinner mean cortical thickness across the brain in females but not in males (44). The authors note that previous work has shown differing effects of glucocorticoids on the male and female brain (45), as well as interactions between sex hormones and stress hormones on gray matter alterations in adult rodents (46), and suggest these as possible explanations for the sex differences in their findings. In a study of the effects of chronic stress in a rodent model, significant sex differences were found in brain structural characteristics at the cellular level, where chronic stress can cause growth or atrophy of dendrites in specific regions, depending on the sex of the rodent (45). To date, the effects of chronic stress on the human brain have not been studied at a microscopic level, but it is possible that these types of differences may underlie acceleration in brain aging and may lead to downstream sex effects in neuropsychiatric stress-related disorders (45).

Another possible source of the sex difference reported in this study is research that indicates that reactivity to stressors for males and females differs greatly depending on the type of stressor. For females, peer relationships are of vital importance for the development of self-identity, and females rely on these relationships for emotional support more than males. For males, peer relationships are more characterized by companionship and shared activities than on emotional support (47). One very prominent lifestyle change associated with the COVID-19 pandemic was the dramatic decrease in interpersonal and peer-to-peer interactions. The effect of the resulting isolation on the needs of male and female adolescents may have been very different, with females perhaps experiencing more stress than males associated with this prolonged isolation, resulting in a larger cascade of physiological effects. Our finding that regions associated with social cognition were the most affected in females are consistent with this hypothesis.

The findings of the current study are important for understanding the effects of low-level chronic stress on the brain. Previous research has demonstrated an increase in the risk of onset of psychopathology in individuals who have experienced early life adverse events, including mood, anxiety, and behavioral disorders. However, most of these studies were of children who experienced extreme trauma, such as abuse or severe neglect. The COVID-19 pandemic restrictions provided a natural experiment which allows for the study of the effects of lower levels of chronic stress on a population of hundreds of millions of people. Early findings suggest that the effects of this lower-level chronic stress have been detrimental to the health of children, adolescents, and adults. A recent study of individuals who were college freshmen at the onset of the pandemic has reported a substantial increase in depression over pre-COVID-19 levels, especially in females (6). This study reports that the effects have extended well beyond the lockdown period and it is not yet clear how long these individuals might continue to experience such effects. The present study, along with two previous studies (13, 14), demonstrate an effect of lockdown-related chronic stress directly on brain structure in adolescents. Accelerated cortical maturation might make individuals who were adolescents during the pandemic lockdowns more susceptible to

developing neuropsychiatric disorders and possibly even neurodegenerative disorders as they age, as has been well documented for individuals who have experienced other types of early life adversities (48–51).

The findings of this study are also valuable for understanding the full impact of COVID-19 policy-mandated restrictions on adolescents. Even prior to the pandemic, mental health was an unappreciated public health issue (52, 53), and these findings add evidence for the necessity of new public health campaigns to provide support for adolescents and young adults struggling with mental health challenges, as the pandemic lockdowns dramatically increased the incidence of these types of disorders.

The present study replicates the findings of two previous studies reporting accelerated cortical thinning in adolescents in association with the COVID-19 pandemic lockdowns (13, 14) and extends these previous findings by demonstrating a significant effect of sex in which females show more dramatic accelerated cortical thinning when compared to males. Nevertheless, there are limitations to the current study. First, the size of the sample measured here is small relative to several ongoing large-scale multisite studies of adolescent brain development, some of which collected data both before and after the pandemic (e.g., (54–56)). Future work should focus on replicating the effects of sex reported here on these larger cohorts using data collected before and after the pandemic. Second, it would be beneficial to have behavioral data that would allow characterization of specific lockdown-related stressors that might be correlated with brain structural findings. The current study did not collect such behavioral measures, nor did we collect data on families' job security, financial insecurity, and/or food insecurity, which might also be associated with structural brain changes. Data on exercise, sleep, or diet, which have been reported to have been greatly affected by the pandemic lockdowns, would also be valuable (57–59). Third, it is not clear whether the effects observed in this study are specific to the age range of our sample. Our post-COVID-19 lockdown test sample consisted of children ranging from 12 to 16 y of age. It is unclear whether our findings extend to younger children or to young adults. And finally, we do not know whether contraction of the COVID-19 virus itself may have contributed to these findings, though in the community from which our study sample was derived, COVID-19 prevalence was widespread, and we have found no reports of a sex disparity in contraction of the virus.

In summary, the findings of the present study suggest that the lifestyle changes associated with the COVID-19 pandemic lockdowns resulted in a deviation from the normal pattern of cortical thinning during adolescent development and that the effects were more dramatic in females than in males. As accelerated cortical thinning during brain development is associated with increased risk in the development of neuropsychiatric and behavioral disorders, the findings from this study highlight the importance of providing ongoing monitoring and support to adolescents who experienced the pandemic lockdowns.

Methods

Experimental Design. The objectives of this study were to determine whether the COVID-19 lockdowns altered the normal pattern of cortical thinning across adolescent development and to determine whether the effects were more pronounced in females than in males. As described below in detail, a subset of the pre-COVID-19 lockdown sample was used as a normative reference cohort to create a model of cortical thickness change across typical adolescent development. This model was validated on a separate subset of the pre-COVID-19 lockdown sample. Finally, the model was used to evaluate cortical thickness values in a subset of the post-COVID-19 lockdown sample.

Sample. MRI data were acquired from adolescents longitudinally at two time points: in 2018, prior to the pandemic lockdowns, and then 3 y later, starting in August of 2021 and continuing into early 2022 (see *SI Appendix*, Table S2 for how these dates compared to the COVID-19 pandemic restrictive measure dates in Washington State). All study subjects were recruited from the local community. The ages of the participants at the prepandemic time point were 9, 11, 13, 15, and 17 y. The ages of participants at the postpandemic time point were 12, 14, 16, 18, and 20 y. Participants were excluded from the study if they were left-hand dominant (as determined by the Edinburgh Handedness Inventory); if English was not the primary language spoken in the home; if they had any history of speech, language, or hearing difficulties; if they had an uncorrected vision problem; if they had ever been diagnosed with a developmental or psychiatric disorder; if they had any surgical implants or dental work that could interfere with the MRI; if they identified as a different gender than that assigned at birth; or if they were taking psychotropic medications. At the first time point, MRI data were collected from a total of 160 subjects (30 nine-year-olds, 33 eleven-year-olds, 34 thirteen-year-olds, 31 fifteen-year-olds, and 32 seventeen-year-olds). Data from 1 seventeen-year-old were excluded due to an incidental finding. At the second time point, MRI data were collected from a total of 130 subjects (26 twelve-year-olds, 25 fourteen-year-olds, 31 sixteen-year-olds, 23 eighteen-year-olds, and 25 twenty-year-olds). All study procedures were approved by the UW Human Subjects Board, and informed consent was obtained from each participant and a parent.

MRI Data Acquisition. MR data were acquired on a 3.0 T Philips Ingenia MRI system using a 32-channel head coil. A Pearltec Crania (Pearltec AG, Schlieren/Zurich Switzerland) head fixation system was used to minimize head motion. High-resolution T1-weighted images of the head were acquired using a multiecho MPRAGE sequence with FOV=240 x 240 x 200, acquisition voxel size 1.0 × 1.0 × 1.0 mm^3, reconstructed voxel size 0.5 × 0.5 × 0.5 mm^3, TR/TI/TE1/TE2 = 13.6/1,100/3.7/9.8 ms, shot interval 2,200 ms, and flip angle = 12°.

MRI Data Analysis.

Cortical parcellation. Cortical reconstruction, volumetric segmentation, and cortical parcellation were performed with the FreeSurfer image analysis suite (version 7, http://surfer.nmr.mgh.harvard.edu) using the recon-all processing stream. The Desikan–Killiany atlas was used as the parcellation scheme.

Quality control. The Euler number from the FreeSurfer output was utilized as a proxy measure of cortical reconstruction quality. For each subject, the square root of the Euler number was calculated. A threshold of 10 for this value was utilized to identify poor-quality reconstructions (19). Data from all subjects in this study were found to have a value below this threshold, and thus, no subjects were excluded for poor reconstruction quality.

Normative modeling. A normative modeling approach (19) was used to compare cortical thickness in the data collected at time point 1 (prior to the COVID-19 lockdowns) to the data collected at time point 2 (after the COVID-19 lockdowns). Data from a subset of subjects in the pre-COVID-19 lockdown sample were used as a normative reference cohort to create a model of cortical thickness change between 9 and 17 y of age. Data from a separate subset of subjects in the pre-COVID-19 lockdown sample were used to validate the model. The normative model was then used to evaluate the cortical thickness values at time point 2 on a separate subset of subjects, at 12, 14, and 16 y of age.

Creation of subject groups. Most of the subjects in this study had data collected at both the pre- and post-COVID-19 lockdown time points. To avoid within-subject correlations associated with repeated measures, data from only one time point for each subject were included in the analysis. The subjects were divided into three groups: the train sample used to fit the model, the validation sample used to validate the model, and the test sample used to evaluate the post-COVID lockdown data.

To create these samples, a determination was first made as to which subjects were to be used for the pre-COVID-19 and post-COVID-19 lockdown analysis. Subjects to be included in the pre-COVID-19 lockdown analysis were selected as follows: Subjects at 15 and 17 y of age with data at time point 1 were automatically included. Subjects at 9, 11, and 13 y of age with data at time point 1 only were also included. For subjects at ages 9, 11, and 13 that had data collected at both time points, subjects were selected at random so that, for each sex and age, the total number of subjects selected would be the same as the number of

subjects with data at both time points that were not selected. The subjects that were not selected were reserved for evaluation of the post-COVID-19 lockdown data collected at time point 2.

The pre-COVID-19 lockdown sample was then further split into train (80%) and validation (20%) samples, stratified by age and sex, using the "train_test_split" function of the scikit-learn Python library (60). This resulted in a total sample size of 87 subjects for the pre-COVID-19 lockdown train sample and 22 subjects in the validation sample. Age and sex information for the pre-COVID-19 lockdown train and validation samples are shown in Tables 1 and 2, respectively. The post-COVID-19 lockdown test sample was composed of subjects at 12, 14, and 16 y of age at time point 2 who had data collected at both time points but were not included in the pre-COVID-19 train or validation samples, as well as four additional subjects that only had MRI data collected at time point 2. This resulted in a total sample size of 54 subjects. Age and sex information for this sample is shown in Table 3.

Creating the normative model. Bayesian linear regression (BLR) models based on the pre-COVID-19 lockdown cohort were fit for each of the 68 regions of the brain defined by the Desikan–Killiany atlas. BLR was chosen for its relative simplicity and scalability (61). The normative models utilized age (specified in days) and sex as covariates, and cortical thickness as the target variable. Models were fit using custom Python (v. 3.8) scripts that utilized functions available in the Predictive Clinical Neuroscience (PCN) Toolkit [v. 0.27, (19)]. The PCN toolkit BLR implementation uses a spline basis, and a spline order of 1 with 2 kn (i.e., linear model) was determined to best fit the data, based on the results of a separate fivefold cross-validation procedure conducted only within the train sample. The "estimate" module of the PCN toolkit, with BLR specified as the algorithm, and "powell" specified as the optimization method, was used to calculate the estimated cortical thickness for each region, as well as individual Z-scores for every subject in the sample. The model was trained on the train sample and then evaluated on the validation sample. For the validation sample, the coefficient of determination, which quantifies how well the model fits the data, was positive for 61 out of 68 regions, with positive values ranging from 0.013 for the left hemisphere entorhinal cortex to 0.78 for the left hemisphere inferior parietal cortex. The "predict" function of the PCN toolkit was used to calculate Z-scores for the validation set, using the model built with the train set, and the mean Z-scores for all brain regions were found to not be significantly different from the zero.

Table 1. Subject information by age group for the pre-COVID-19 lockdown normative modeling train sample

	Sample Size		Mean Age ± SD	
Age Group (years)	Male	Female	Male	Female
9	6	6	9.1 ± 0.03	9.1 ± 0.03
11	6	6	11.1 ± 0.07	11.1 ± 0.06
13	7	6	13.1 ± 0.05	13.1 ± 0.04
15	12	13	15.1 ± 0.03	15.1 ± 0.05
17	12	13	17.1 ± 0.04	17.1 ± 0.06
Total	43	44		

Table 2. Subject information by age group for the pre-COVID-19 lockdown normative modeling validation sample

	Sample Size		Mean Age ± SD	
Age Group (years)	Male	Female	Male	Female
9	1	2	9.2	9.1 ± 0.02
11	2	2	11.1 ± 0.03	11.2 ± 0.01
13	1	2	13.1	13.1 ± 0.07
15	3	3	15.1 ± 0.03	15.2 ± 0.01
17	3	3	17.1 ± 0.04	17.1 ± 0.03
Total	10	12		

Table 3. Subject information by age group for the post-COVID-19 lockdown test sample

	Sample Size		Mean Age ± SD	
Age Group (years)	Male	Female	Male	Female
12	10	8	12.3 ± 0.19	12.2 ± 0.16
14	9	8	14.4 ± 0.26	14.4 ± 0.19
16	10	9	16.4 ± 0.18	16.3 ± 0.28
Total	29	25		

The model was saved to file and used in the evaluation of the post-COVID-19 lockdown test sample.

Evaluation of the post-COVID-19 lockdown data. Design matrices were calculated for the post-COVID-19 lockdown test sample in the same manner as for the pre-COVID-19 lockdown normative reference train sample based on age and sex covariates and using order 1 splines with 2 kn. The models fit on the normative reference cohort were used to predict the cortical thickness, using the "predict" function of the PCN toolkit. This function calculated the Z-score for each subject in the post-COVID-19 lockdown sample. After all Z-scores were calculated, a single-sample *t* test was performed for each brain region and sex using the "stats" function of the SciPy Python library [v. 1.10.1, (62)]. A two-tailed significance threshold of 0.05 was used to test the null hypothesis that the mean value of the Z distribution was equal to zero. *P* values were corrected using false discovery rate correction with the "stats.multitest.multipletests" function of the Statsmodels Python library [v. 0.13.5, (63)].

Calculation of effect size. The effect size for each brain region was estimated as the mean of the Z-scores of the post-COVID-19 lockdown test sample for that region.

Estimation of brain age acceleration. To quantify the amount of acceleration in cortical thinning for the male and female samples, an additional normative model was created for average cortical thickness change with age in the pre-COVID-19 lockdown normative reference train sample. Average cortical thickness was calculated as the average cortical thickness over all 68 brain regions in the Desikan–Killiany atlas. The design matrix included age and sex as covariates and a spline with order 1 and 2 kn. For each subject in the post-COVID-19 lockdown test sample, the equation for the normative model derived from the normative reference cohort was used to calculate the age of each subject predicted by the model, given the subject's average cortical thickness. The actual ages were then subtracted from the predicted ages. These brain age difference values were then averaged separately for the males and females in the sample to compute an estimated average brain age acceleration in years for each sex. Ninety-five percent CI for brain age acceleration for each sex were calculated by performing bootstrapping with resampling of the post-COVID-19 lockdown data using 1,000 bootstrap samples.

Alternative Analysis. Our normative model included sex as a covariate, which did not allow it to model the effects of possible interactions between the two sexes. An additional analysis was performed to allow for interactions between genders. In this alternative analysis, the normative modeling was performed as described above, except separate models were created for males and females. Instead of age and sex, only age was included as a covariate in these models. Evaluation of the post-COVID-19 lockdown data and estimation of brain age acceleration were performed as described above, but using the separate models for males and females.

Data, Materials, and Software Availability. The demographic and cortical thickness data reported in this paper, and code to reproduce the analysis, have been deposited in the Zenodo repository (https://doi.org/10.5281/zenodo.13227189) (64). The code to reproduce the analysis is also available on GitHub at (65).

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