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Effects of the COVID-19 Pandemic on Mental Health and Brain Maturation in Adolescents: Implications for Analyzing Longitudinal Data

Ian H. Gotlib, Jonas G. Miller, Lauren R. Borchers, Sache M. Coury, Lauren A. Costello, Jordan M. Garcia, Tiffany C. Ho

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Authors: Ian H. Gotlib[1], Jonas G. Miller[1], Lauren R. Borchers[1], Sache M. Coury[1], Lauren A. Costello[1], Jordan M. Garcia[1], Tiffany C. Ho[2]

Affiliations: [1]Department of Psychology, Stanford University; [2]Department of Psychiatry and Weill Institute for Neurosciences, University of California, San Francisco

Corresponding author: Ian H. Gotlib

Email: ian.gotlib@stanford.edu

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Abstract

Background: The COVID-19 pandemic has caused significant stress and disruption for young people, likely leading to alterations in their mental health and neurodevelopment. In this context, it is not clear whether youth who lived through the pandemic and its shutdowns are comparable psychobiologically to their age- and sex-matched peers assessed before the pandemic. This question is particularly important for researchers who are analyzing longitudinal data that span the pandemic.

Methods: In this study we compared carefully matched youth assessed before the pandemic (*n*=81) and after the pandemic-related shutdowns ended (*n*=82).

Results: We found that youth assessed after the pandemic shutdowns had more severe internalizing mental health problems, reduced cortical thickness, larger hippocampal and amygdala volume, and more advanced brain age.

Conclusions: Thus, not only does the COVID-19 pandemic appear to have led to poorer mental health and accelerated brain aging in adolescents, but it also poses significant challenges to researchers analyzing data from longitudinal studies of normative development that were interrupted by the pandemic.

Effects of the COVID-19 Pandemic on Mental Health and Brain Maturation in Adolescents: Implications for Analyzing Data from Longitudinal Studies

The COVID-19 pandemic has been a generation-defining event and a major source of adversity. Given the shelter-in-place orders in the Spring of 2020 that led to school closures, academic disruptions, social restrictions, and reduced access to school-based mental health services (1), the pandemic appears to have been particularly difficult for children and adolescents (2–4). In fact, a recent meta-analysis found that the prevalence of internalizing symptoms in youth has doubled since the onset of the COVID-19 pandemic (5). Despite this alarming statistic, however, the potential implications of the pandemic for children's neurodevelopment have not been delineated.

Research conducted prior to the pandemic has found that exposure to early life adversity, including violence, neglect, and family dysfunction, is associated not only with poorer mental health, but also with maladaptive neurodevelopmental outcomes that indicate accelerated brain maturation or aging (6). For example, cortical thickness, which decreases with age (7), is further reduced in youth with a history of early adversity (6). Recently, researchers have used machine learning algorithms to predict individuals' ages from their neuroanatomical features (8). In adolescents, exposure to adversity has been associated with a brain age gap estimate (BrainAGE) suggestive of accelerated aging (i.e., having a predicted brain age older than one's chronological age) (9). As a result of social isolation and distancing during the shut-down, virtually all youth experienced adversity in the form of significant departures from their normal routines. In addition, financial strain, threats to physical health, and exposure to increased familial violence were alarmingly common during the pandemic (10, 11). If the pandemic has adversely affected adolescents' mental health and neurodevelopment, such that adolescents who are assessed now differ in significant respects from their age-and sex-matched peers who were assessed prior to the pandemic, researchers must give serious

consideration to how they accurately analyze and interpret longitudinal developmental data that span years on both sides of this extraordinary event.

In this study we matched a group of adolescents who experienced the pandemic shut-down (the “peri-COVID” group) with a group of adolescents, matched on age, sex, puberty, exposure to early life stress, and socioeconomic status, who underwent the same assessment before the pandemic (the “pre-COVID” group). We expected that compared with the pre-COVID group, the peri-COVID group would report more severe mental health problems and have older, or more mature, brains.

Methods

Participants

Participants in this study were 163 adolescents (103 females) living in the San Francisco Bay Area who were participating in a larger longitudinal study assessing the effects of early life stress on psychobiology across puberty (*N*=214) (12–14). Exclusion criteria were post-pubertal status, non-fluency in English, inability to undergo magnetic resonance imaging, and history of neurological disorder or major medical illness. Participants were invited to return for follow-up assessments approximately every two years; however, the approximately one-year-long COVID-19 pandemic shut-down beginning in March 2020 interrupted participants’ in-person assessments (see 15 for more details). All participants and their legal guardians gave informed assent and consent, respectively, and were compensated for their time. All study procedures were approved by the Stanford University Institutional Review Board.

From this larger cohort, we constructed two matched subsamples using data collected either before the pandemic (from November 2016 to November 2019; “pre-COVID group,” *n*=81) or during the pandemic but following the end of the Bay Area shutdown (from October 2020 to March 2022; “peri-COVID group,” *n*=82). We constructed these subsamples to maximize group sizes and to match the two groups on sex, age, pubertal status, race/ethnicity, parental education, annual household income, and severity of early life stress based on panel

ratings of participants' responses to interview (12, 13). Specifically, we attempted to match the peri-COVID participants with pre-COVID participants with respect to age and sex as closely as possible at the group level. Not all peri-COVID participants could be matched to pre-COVID participants given their older age, and not all pre-COVID participants were needed to be matched to the smaller peri-COVID group (and the youngest pre-COVID participants were too young to be matched to the peri-COVID participants). For the "mental health symptoms" sample of 81 pre-COVID and 82 peri-COVID participants (see below), we excluded from analyses 50 pre-COVID and 12 peri-COVID participants who could not be appropriately matched. For the "neuroimaging" sample, we were able to age- and sex-match 64 of the 104 participants who were scanned peri-COVID with 64 pre-COVID participants.

Mental Health Symptoms

Participants self-reported their depressive symptoms using the 10-item version of the Children's Depression Inventory (16). This widely used reliable measure (17) has been shown to have convergent validity with clinician ratings of depression symptoms and diagnosis (18). We assessed anxiety symptoms using total score of the Social Anxiety and Physical Symptom subscales of the Multidimensional Anxiety Scale for Children (MASC; 19). The full MASC assesses a wide range of anxiety symptoms, including those that are not as relevant for the age range of our participants (e.g., Separation Anxiety). For this reason and to reduce participant burden, we administered only the Social Anxiety and Physical Symptoms subscales of the MASC for this study; therefore, the MASC total score in this study reflects the sum of these two subscales. Finally, we assessed internalizing and externalizing symptoms using the validated subscales of the Youth Self Report version of the Child Behavior Checklist (20).

Neuroimaging

A subset of these participants (matched *n*=64 per group) completed a T1-weighted magnetic resonance imaging (MRI) scan at the Center for Cognitive and Neurobiological Imaging at Stanford University. All participants in the pre-COVID group completed their scans

using a 3T Discovery MR750 (GE Medical Systems, Milwaukee, WI, USA). As of 03/16/2020, the Discovery MR750 was upgraded to an Ultra High Performance (UHP) system. Thus, all peri-COVID participants were scanned on the upgraded scanner. Participants in both groups were scanned using a 32-channel head coil (Nova Medical, Wilmington, MA, USA). Prior work suggests that FreeSurfer-based cortical thickness and subcortical measures are highly reliable across scanner upgrades (21–23). For example, Han et al. (22) did not find evidence that scanner upgrades introduce bias for cortical thickness measures, and Brown et al. (23) found that hippocampal measures are reliable across scanners. In addition, we conducted analyses with our own data to assess potential differences in T1-weighted image quality related to scanner upgrade. Specifically, in a subset of 31 participants with imaging data before and after the scanner upgrade, we tested within-participant changes in gray-white matter contrast-to-noise ratio (CNR) using FreeSurfer's *mri_cnr* quality metric command. We did not find significant differences in CNR from pre- to post-upgrade in either the left ($t(30)=0.81$, $p=.425$) or the right hemisphere ($t(30)=0.66$, $p=.513$). Thus, the scanner upgrade does not appear to have introduced a systematic bias in image quality. Whole-brain T1-weighted images were collected for all participants using the following spoiled gradient echo (SPGR) pulse sequence: 186 sagittal slices; TR (repetition time)/TE (echo time)/TI (inversion time)=6.24/2.34/450ms; flip angle=12°; voxel size = 0.9 mm×0.9 mm×0.9 mm; scan duration=315s. The SPGR sequence was repeated up to two additional times if the first acquisition did not yield clear images. For each participant with multiple acquisitions, the single SPGR image with the clearest structural boundaries (i.e., that was free from motion or other artifacts) was used for further analysis.

Segmentation of Cortical and Subcortical Regions

We used FreeSurfer v. 6.0 (http://surfer.nmr.mgh.harvard.edu/) *recon-all* function to automatically skull strip and segment cortical and subcortical volumes from the T1-weighted structural images (24), which has been shown to have acceptable scan-rescan reliability (21) and comparable accuracy to manual labeling techniques (24–26). We implemented structural

image processing protocols established by ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) (http://enigma.ini.usc.edu/protocols/imaging-protocols) to extract and perform quality assurance checks on the cortical thickness and subcortical volume estimates from the FreeSurfer outputs. Using FreeView image viewer, all cortical and subcortical outputs were visually inspected to quality check for processing and segmentation errors. As previously described (27, 28), we converted gray matter volumes from each hemisphere into z-scores; volumes with z-scores greater than 2.5 or less than -2.5 were visually examined again for accuracy and any segmentations that failed any of these steps were removed from final analyses. We focused on mean cortical thickness (average of cortical thickness values across individual regions as defined by the Desikan-Killany atlas) (29) and unstandardized residuals of subcortical volumes regressed on total intracranial volume.

Brain Age Gap Estimates

Based on cortical and subcortical features, we computed BrainAGE (brain age gap estimate) values for male and female participants using sex-specific machine learning-based models developed by the ENIGMA-Brain Age working group (30). These models use data from 14 subcortical gray matter volumes, 2 lateral ventricles, 68 cortical thickness measures, 68 surface area measures, and total intracranial volume to predict chronological age (i.e., predicted brain age). We computed brain age gap estimates by subtracting chronological age from predicted brain age. Given that BrainAGE values are often overestimated in younger individuals and underestimated in older individuals, Le et al. (31) proposed adjusting for chronological age in analyses of BrainAGE. Therefore, we regressed gap estimates onto chronological age and used the unstandardized residuals as the BrainAGE outcome variable in our statistical analyses.

Statistical Approach

All statistical analyses were conducted using *R* v. 4.0.2. To examine whether adolescents who experienced the pandemic differed from their pre-pandemic peers, we conducted between-group tests on measures of internalizing and externalizing symptoms,

cortical thickness, subcortical volume (regions of interest: the bilateral amygdala, hippocampus, and nucleus accumbens). For analyses of mental health problems, we first conducted a one-way multiple analysis of variance (MANOVA) test to examine whether there were group differences in overall mental health scores across measures. We conducted follow-up independent sample t-tests to examine whether the pre-COVID and peri-COVID groups differed in specific aspects of mental health as assessed by different measures. We repeated these steps for analyses of brain metrics. Given our expectations based on recent work suggesting that mental health problems have increased during the pandemic (5), we used one-tailed hypothesis tests for follow-up analyses of mental health outcomes. We used two-tailed hypothesis tests for follow-up analyses of brain outcomes.

All participants and their parent(s)/legal guardian(s) signed assent and consent forms, respectively, and were compensated for their participation in the study. This study was approved by the Stanford University Institutional Review Board.

Results

Participant Characteristics

The demographic and clinical characteristics of the pre- and peri-COVID subgroups of participants are presented in Table 1. Participants' parents reported on their annual household income, from which we computed an income-to-needs ratio by dividing the midpoint of their reported income bin by the low-income value for Santa Clara County. Importantly, this calculation considers the number of people in the home and the time period in which the study occurred (https://www.huduser.gov/portal/datasets/il/il2017/2017summary.odn; (32). Attesting to the success of our careful matching procedure, there were no significant group differences in participant characteristics between the pre-COVID and peri-COVID subgroups for either the "mental health" or the "brain" samples (all individual *p*s>.06).

Mental Health

Group differences on the mental health measures are presented in Fig. 1. A one-way multivariate analysis of variance (MANOVA) indicated that the pre- (*n*=81) and peri-COVID (*n*=82) groups differed significantly in their self-reported mental health difficulties ($F(4,158)=2.67$, $p=.034$). Follow-up t-tests showed that the peri-COVID group reported more severe symptoms of anxiety ($t(161)=3.15$, $p<.001$; Cohen's $d=0.49$), depression ($t(161)=1.92$, $p=.029$; $d=0.30$), and internalizing problems ($t(161)=1.77$, $p=.039$; $d=0.28$); the two groups did not differ in externalizing problems ($t(161)=1.25$, $p=.108$).

Brain Metrics

Group differences in cortical thickness, subcortical volumes, and BrainAGE are shown in Fig. 2. A MANOVA conducted on all of the brain metrics yielded a significant difference between the pre-COVID (*n*=61-64) and peri-COVID (*n*=63-64) groups ($F(5,116)=7.13$, $p<.001$). Follow-up tests indicated that the peri-COVID group had reduced bilateral cortical thickness ($t(122)=3.67$, $p<.001$; $d=0.66$) and, controlling for intracranial volume, larger bilateral hippocampal volume ($t(125)=3.56$, $p<.001$; $d=0.63$) and bilateral amygdala volume ($t(125)=2.01$, $p=.047$; $d=0.36$); the two groups did not differ in bilateral nucleus accumbens volume ($t(125)=0.68$, $p=.248$; $d=0.12$). Finally, despite the fact that the two groups were matched on age and other relevant demographic characteristics, adolescents in the peri-COVID group had an older BrainAGE than did their peers who were assessed before the pandemic ($t(125)=2.31$, $p=.022$; $d=0.41$).

Interval Between the COVID-19 Shutdown and the peri-COVID Assessments

Finally, given the possibility that participants' mental health difficulties and their brain metrics increased with the duration of the pandemic, we examined our clinical functioning and brain metrics as a function of time since the Bay Area shelter-in-place orders were initiated (March 17, 2020). The peri-COVID participants completed measures of clinical functioning between 01/10/21 and 09/30/2021 and MRI scans between 10/13/2020 and 03/22/2022. Within the peri-COVID group, we examined associations between the number of days from the start of shelter-in-place orders to the dates that participants completed measures of psychopathology

(*M*=346.49 days, *SD*=131.70 days, range=133-720 days). There were no significant associations between this interval and participants' scores on the measures of depression (r(80)=0.01, *p*=.901), anxiety (*r*(80)=-0.06, *p*=.544), internalizing symptoms (*r*(80)=0.07, *p*=.506), or externalizing symptoms (*r*(80)=0.00, *p*=.980). We repeated these analyses for the brain metrics (mean interval = 379.00 days, *SD*=119.24 days, range=210-735 days). Again, there were no significant associations between the interval and residuals of amygdala volume (*r*(62)=0.01, *p*=.935), hippocampal volume (*r*(62)=0.15, *p*=.245), NAcc volume (*r*(62)=0.05, *p*=.681), mean cortical thickness (*r*(61)=0.04, *p*=.303), or residuals of brainAGE (*r*(62)=-0.09, *p*=.459).

Discussion

In addition to replicating prior findings that the pandemic has adversely affected the mental health of young people (5), we found that adolescents assessed during the pandemic have neuroanatomical features that are more typical of individuals who are older or who experienced significant adversity in childhood. Compared to carefully matched peers assessed before the pandemic, adolescents assessed during the pandemic showed signs of advanced cortical thinning and had larger bilateral hippocampal and amygdala volumes. Given that volume in these structures typically increases over adolescence (33), these neural alterations may reflect accelerated brain maturation in the context of the pandemic. Indeed, adolescents assessed during the pandemic also had larger positive brain age gap estimates, indicative of older-appearing brains.

It appears, therefore, that the pandemic not only has adversely affected adolescents' mental health, but also has accelerated their brain maturation. These findings have critical implications for researchers who are conducting longitudinal studies that were interrupted due to pandemic-related shutdowns. In our own longitudinal study, we had been assessing a sample of approximately 200 adolescents at each of four timepoints, at two-year intervals, to examine the effects of early adversity on trajectories of neurodevelopment and clinical symptoms. At the time

of the shutdown, we were two-thirds of the way through the third assessment, when our participants were 13-17 years of age. We had originally planned to simply use participants' age in analyzing trajectories from our four timepoints of data. Although some participants would have had a longer interval than others between assessments that bracketed the shut-down, we would control statistically for those differences. It is important to recognize that this analytic approach assumes that, for example, 16-year-olds who were assessed after the shutdown ended are equivalent in their clinical functioning and neurodevelopment to 16-year-olds who were assessed before the pandemic, and would simply be grouped together. Our results suggest that this assumption is not correct. Rather, the pandemic appears to have altered adolescent mental health and neurodevelopment, at least in the short term, which will present a challenge for researchers in analyzing longitudinal data from studies of normative development that were interrupted by the pandemic.

In order to not confound age-related changes in brain maturation with experiences and consequences of the COVID-19 pandemic, some researchers, including our group, have used a dummy-coded variable to control statistically for whether participants were assessed pre- or during the pandemic (e.g., 34). Nevertheless, restrictions around COVID-19 are constantly changing; therefore, additional measures may need to be used as covariates, including the interval between shelter-in-place orders and time of assessment, as well as the nature and severity of the individual's stress and experience during the pandemic (e.g., COVID-19 infection, upheaval in living situation, financial strain, etc.).

We should note that our sample is of relatively high socioeconomic status and represents the racial/ethnic composition of the San Francisco Bay Area. Researchers have reported that sample composition influences age-related effects on brain structure (35) and, more specifically, that the psychosocial and health consequences of the pandemic have been more severe among individuals from socially marginalized groups (e.g., lower socioeconomic status; 36–38). Therefore, it is important that investigators examine the effects of the COVID-19

pandemic on psychopathology and brain metrics in more diverse samples of adolescents that are representative of the broader population.

Another critical task for future research is to determine whether these alterations are temporary effects of the pandemic or stable changes that will characterize the current generation of youth. If these changes are found to be enduring, accounting for and interpreting data acquired during this period will require additional attention and consideration. For example, as more researchers publish data concerning normative developmental trajectories of MRI-derived anatomical features (e.g., 39), it will be possible to compare COVID-impacted neurodevelopmental trajectories with normative trajectories and, indeed, to compute COVID-adjusted metrics of brain maturation. Regardless, however, we emphasize that it is important that we continue to follow and assess individuals who were recruited and assessed prior to the pandemic; this type of research offers the strongest possibility for us to examine the effects of a major stressor experienced on a global scale.

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Figure Captions

Figure 1. Group differences on the Children's Depression Inventory (CDI), Multidimensional Anxiety Scale for Children (MASC; sum of the Social Anxiety and Physical Symptom subscales), and Youth Self-Report (YSR) internalizing and externalizing. **p*<.05, ***p*<.01, ****p*<.001.

Figure 2. Raw data are plotted for visualization. Significance levels are based on group differences on subcortical volumes (in mm) adjusted for intracranial volume, cortical thickness, and on BrainAGE adjusted for chronological age. **p*<.05, ***p*<.01., ****p*<.001.

Table 1. *Participant characteristics.*

Variable	Pre-COVID "Mental Health" (*n*=81) *M* (*SD*) or *n*	Peri-COVID "Mental Health" (*n*=82) *M* (*SD*) or *n*	Pre-COVID "Brain" (*n*=64) *M* (*SD*) or *n*	Peri-COVID "Brain" (*n*=64) *M* (*SD*) or *n*
Sex (female)	51 (63%)	52 (63%)	34 (53%)	34 (53%)
Age	15.87 (1.14)	16.17 (0.93)	16.08 (0.90)	16.43 (1.19)
Race				
White	43 (53%)	33 (40%)	35 (55%)	26 (41%)
Asian / Asian American	13 (16%)	11 (13%)	7 (11%)	9 (14%)
Hispanic / Latin-X	5 (6%)	7 (9%)	4 (6%)	6 (9%)
Black / African American	6 (7%)	7 (9%)	3 (5%)	7 (11%)
Biracial	9 (11%)	21 (26%)	11 (17%)	12 (19%)
Other race	5 (6%)	3 (4%)	4 (6%)	4 (6%)
Income-to-needs ratio	1.37 (0.53)	1.27 (0.54)	1.30 (0.59)	1.31 (0.53)
Early Life Stress	6.60 (4.89)	6.31 (4.97)	7.30 (5.88)	5.84 (4.68)
Parental Education				
No GED/No High School Diploma	0 (0%)	1 (1%)	0 (0%)	1 (%)
GED/High School Diploma	0 (0%)	4 (5%)	0 (0%)	0 (0%)
Some College	10 (12%)	15 (18%)	4 (6%)	10 (%)
2-year College Degree	5 (6%)	7 (9%)	5 (8%)	5 (%)
4-year College Degree	29 (36%)	25 (30%)	24 (38%)	27 (%)
Master's Degree	30 (37%)	20 (24%)	20 (31%)	17 (%)
Professional Degree	1 (1%)	5 (6%)	3 (5%)	3 (%)
Doctorate	4 (5%)	2 (2%)	2 (3%)	0 (0%)
Not reported	2 (2%)	3 (4%)	6 (9%)	1 (%)
COVID-19 Impact				
Individual Diagnosis	n/a	1 (1%)	n/a	1 (1%)
Household Diagnosis	n/a	3 (4%)	n/a	2 (3%)
Financial Strain	n/a	13 (16%)	n/a	11 (17%)
Job Loss	n/a	7 (9%)	n/a	8 (13%)

Note. "Mental Health" refers to the subsample of participants who completed the measures of mental health; "Brain" refers to the subsample of these participants who also successfully completed the neuroimaging protocol.

KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Antibody				
Bacterial or Viral Strain				
Biological Sample				
Cell Line				
Chemical Compound or Drug				
Commercial Assay Or Kit				
Deposited Data; Public Database				
Genetic Reagent				
Organism/Strain				
Peptide, Recombinant Protein				
Recombinant DNA				
Sequence-Based Reagent				
Software; Algorithm	3T Discovery MR750. AND FreeSurfer v. 6.0			
Transfected Construct				
Other				

Key Resource Table