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Archival Report

Biological Psychiatry: GOS

Hippocampal-Prefrontal Connectivity Prior to the COVID-19 Pandemic Predicts Stress Reactivity

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ABSTRACT

BACKGROUND: By adolescence, foundational cognitive and affective neurobehavioral processes specialize based on environmental demands, such as stress, to determine the basis of adult trajectories. The ongoing COVID-19 pandemic has increased stress for everyone, particularly adolescents who face unique stressors such as restrictions in socialization and education. However, variability in brain processes supporting stress reactivity is not well understood. Here, we leverage pre-pandemic brain development studies to identify how maturity of prefrontal connectivity with the amygdala and hippocampus (HPC) is associated with response to COVID-19. We hypothesized that age-related changes in connectivity of affective and cognitive brain systems may underlie the emotional response of adolescents during the pandemic.

METHODS: In this study, 10- to 31-year-old participants (n = 111) completed resting-state functional magnetic resonance imaging scans prior to the pandemic and then completed a questionnaire 9 months into the pandemic measuring worry, COVID-related stress, sadness, perceived stress, and positive affect. Associations between pairwise functional connectivity of HPC/amygdala subregions with prefrontal cortex subdivisions and affective reactivity during the pandemic were examined.

RESULTS: Regression analyses indicated that both worry and COVID-19–related stress increased with age (false discovery rate–corrected $p < .05$). Furthermore, greater connectivity between the anterior ventromedial prefrontal cortex and posterior HPC was associated with greater worry and COVID-19–related stress ($p < .05$ corrected), which was primarily driven by individuals younger than 18 years.

CONCLUSIONS: Taken together, our results indicate that increases in stress reactivity to the COVID-19 pandemic across the transition to adulthood are driven by maturation of posterior HPC–ventromedial prefrontal cortex coupling, which integrates stress response and emotional memory processing.

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Adolescence is a developmental period defined by the onset of puberty and characterized by maturation of cognitive and affective systems (1,2). During adolescence, relationships take on a central role as the social brain continues to develop (3,4). In fact, having social experiences during adolescence seems to be critical for both normative social (5) and cognitive (6) development. Furthermore, adolescent social experiences may play a role in the onset of critical period plasticity, driving maturation of association cortex (7). Thus, a disruption to an adolescent's ability to engage with their environment during this time may have a heightened impact on their developmental trajectory.

Unfortunately, the COVID-19 pandemic has presented a challenging backdrop for adolescent development, increasing stress related to health, employment, and caretaking demands. As of this writing, COVID-19 prevention measures, including lockdowns and mask mandates, have been in place for more than 1 year, with more than 203 million cases and 4.3 million deaths reported worldwide (8). Social distancing measures and remote learning have severely limited adolescents' opportunities to socialize with peers at a time when these experiences are essential for healthy brain development. Indeed, recent studies have shown that depressive symptoms have increased among adolescents since the pandemic's onset (9) and that internalizing symptom severity scaled with the level of pandemic-related stress (10). Although this pandemic is a historically unique event, similar stressful events of a comparable nature, such as natural disasters, have been shown to lead to lasting brain changes. For example, a study of children in the Adolescent Brain Cognitive Development (ABCD) initiative who experienced Hurricane Irma in Florida found decreased neurogenesis and altered memory function in the hippocampus (HPC) compared with nonexposed children (11).

A growing literature indicates that stress affects systems that are undergoing significant maturation across adolescence, such as the HPC, amygdala, and their connectivity to prefrontal cortex (PFC) regions. The HPC, which is primarily implicated in cognitive functions such as memory, has been found to be affected by chronic stress leading to alterations in volume (12), microstructure (11), function (11,13), and connectivity with other regions, particularly the PFC (12,13). Similarly,

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the amygdala, which is involved in emotion processing, shows substantial change following exposure to chronic stress at the neuronal level (14) as well as in its connectivity with the PFC (15–17). Notably, resting-state functional connectivity of both the amygdala and HPC with the PFC shows protracted development during adolescence. Developmental reductions in amygdala-PFC connectivity throughout adolescence have been associated with anxiety and depression (18), while developmental HPC–ventromedial PFC (vmPFC) increases have been associated with cognitive processes such as planning (19). In addition, the uncinate fasciculus and the cingulum, primary white matter tracts that integrate these systems, continue to strengthen into young adulthood (20,21).

While there is evidence that stress may affect connectivity, little is known regarding how variability in connectivity prior to stress may influence stress response. Initial studies have found some connectivity-based indices of stress predisposition. For example, connectivity between bilateral HPC in 20 male adults was found to be predictive of cortisol release following a stress test (22). Furthermore, connectivity between the anterior cingulate cortex (ACC) and the salience network in 49 adolescents was associated with an individual's cortisol reactivity in response to a stressful task (23). These results suggest that predisposition to stress reactivity may be reflected at the level of connectivity. However, it is unclear how connectivity of stress-responsive regions is predictive of real-life stressful experiences, and how this may differ between the developmentally dynamic stage of adolescence and stable adulthood. Here, we leveraged resting-state functional brain data in 10- to 31-year-old participants (n = 111) obtained before the pandemic to identify neurobiological markers of variability in stress response.

METHODS AND MATERIALS

Participants

Neuroimaging data were collected from 286 participants (age, 10–31 years; 152 female) across two multimodal accelerated longitudinal studies. Participants were recruited from the community and were excluded if they reported that they or a first-degree relative had received a diagnosis of a psychiatric or neurological disorder, or if they reported magnetic resonance imaging (MRI) contraindications such as metal in the body. COVID-19 questionnaires were sent 9 months into the pandemic to all eligible participants (N = 286) in both studies and completed by a subgroup of 111 (60 females) participants (see demographics in Figure S1). There were no significant differences in the age ($\beta = -0.0034$, $p = .91$), sex ($F_{1,278} = 0.14$, $p = .71$), or race ($F_{4,269} = 0.59$, $p = .67$) of responders compared with nonresponders.

COVID-19 Questionnaire

Participants completed a COVID-19 questionnaire that was developed by the ABCD Study, a longitudinal study examining brain development in 11,878 children across the United States (24). The questionnaire includes 109 questions for adults and 91 questions for children, which ask about the direct impacts of the pandemic, such as job loss, and about effects on mood, anxiety, stress, and sleep. For participants younger than 18 years, a questionnaire was also sent to parents of the participants to ask about topics such as financial hardship and severity of COVID-19 illness in the participants' families.

Five measures were used from the ABCD COVID-19 assessment, including Worry and Sadness measures from the National Institutes of Health (NIH) Toolbox Child forms (25), the 4-item Perceived Stress Scale (26), a COVID Stress score, and a Positive Affect score (for specific items included, see Figure S2).

- Worry Score: ratings from 8 questions (taken from the NIH Toolbox Fear measure) on a 5-point Likert scale were summed, and the equivalent t-score was used from the unstandardized t-score table for Fear in the NIH Toolbox Scoring Manual.
- Sadness Score: ratings from 9 questions (taken from the NIH Toolbox Sadness measure) on a 5-point Likert scale were summed, and the equivalent t-score was used from the unstandardized t-score table for Sadness in the NIH Toolbox Scoring Manual.
- COVID Stress Score: ratings from 5 questions on a 5-point Likert scale were z-scored and summed.
- Perceived Stress Score: ratings from 4 questions (taken from the Perceived Stress Scale – 4 Item) on a 0–4 point scale were summed.
- Positive Affect Score: ratings from 9 questions (taken from the NIH Toolbox Positive Affect measure) on a 4-point Likert scale were z-scored and summed. The unstandardized t-scores for the NIH Toolbox measure could not be used due to differences in the rating scales.

MR Data Acquisition

Imaging data were acquired from two ongoing neuroimaging studies. In the first study (n = 150 participants; n = 33 with COVID-19 questionnaire data), MRI data were acquired on a 3T Siemens Biograph molecular MR positron emission tomography/MRI scanner with a 12-channel head coil. Structural images were acquired using a T1-weighted magnetization prepared rapid acquisition gradient-echo sequence (repetition time [TR] = 2300 ms; echo time [TE] = 2.98 ms; flip angle = 9°; inversion time = 900 ms, voxel size = 1.0 × 1.0 × 1.0 mm). Functional images were acquired using a blood oxygen level–dependent signal from an echo-planar sequence (TR = 1500 ms; TE = 30 ms; flip angle 50°; voxel size, 2.3 × 2.3-mm in-plane resolution; 3× multiband acceleration) with contiguous 2.3-mm-thick slices aligned to maximally cover the whole brain. The resting-state acquisition included 320 volumes for a total duration of 8 minutes (eyes open; blank screen).

In the second study (n = 136 participants; n = 74 with COVID-19 questionnaire data), data were acquired on a 7T Siemens Magnetom scanner. Structural images were acquired using an MP2RAGE T1-weighted acquisition (1.0-mm isotropic resolution, TR = 6000 ms; TE = 2.87 ms; flip angle 1 = 4°, flip angle 2 = 5°). Functional images were acquired using a three-dimensional blood oxygen level–dependent echo-planar imaging sequence (TR = 2180 ms; TE = 23 ms; flip angle = 7°; voxel size = 2.0 × 2.0 × 2.0 mm). The resting-state acquisition included 220 volumes for a total duration of 8 minutes (eyes open; blank screen).

Functional MRI Preprocessing

Structural MRI data preprocessing included skull stripping and warping to the Montreal Neurological Institute standard brain using both linear (FLIRT) and nonlinear (FNIRT) transformations (27). Functional images were processed using a pipeline previously developed by our group to reduce the effects of head motion (28), including four-dimensional slice-timing and head motion correction (29), wavelet despiking (30), coregistration to the structural image and nonlinear warping to Montreal Neurological Institute space (27,31), local spatial smoothing with a 4-mm Gaussian kernel, intensity normalization, nuisance regression based on head motion (based on 6 degree-of-freedom motion estimates and their derivatives) and nongray matter signal (white matter, cerebrospinal fluid, and their derivatives), and bandpass filtering between 0.009 and 0.08 Hz (32). Framewise motion estimates were computed, and volumes containing framewise displacement (FD) $>$ 0.3 mm were censored from connectivity computations. To ensure that any residual motion effects were not driving age-related findings, all analyses included mean FD as a covariate (see Figure S3 for distribution of mean FD across age).

Regions of Interest

Hippocampal regions were defined as in Calabro *et al.* (19) (Figure 1). Briefly, following Murty *et al.* (33) and Staresina *et al.* (34), the Harvard-Oxford Atlas HPC region was divided into thirds, with the anterior and posterior thirds defined as the anterior HPC and posterior HPC (pHPC), respectively. The middle subdivision was excluded to minimize possible signal overlap between these regions. Given the distinct functions of basolateral (BL) and centromedial amygdala, we identified each using stereotaxic probabilistic maps based on cytoarchitectonic boundaries (35) as in Jalbrzikowski *et al.* (18) (Figure 1). PFC regions of interest (ROIs) included anatomically defined subdivisions of the vmPFC (36), as well as vlPFC (Brodmann area [BA] 44, BA 45, and BA 47) and dlPFC (the middle frontal gyrus bordered by the superior frontal and precentral sulci including BA 9 and BA 46) as defined in Calabro *et al.* (19) (Figure 1). We additionally included regions of the ACC based on anatomical definitions specified in the Brainnetome Atlas (37) (Figure 1).

Statistical Analysis

For each ROI, time courses were extracted from each subject's data by taking the first principal component across all voxels within the ROI from the preprocessed and head motion–censored time courses. Pearson correlation coefficients were computed between the eight HPC (left and right hemispheres, anterior and posterior) and amygdala (left and right BL and centromedial) seeds and each of the PFC ROIs.

Effects of age on affective scores and pairwise connectivity values, as well as interaction effects of age and connectivity on affective scores, were evaluated using linear regression in R (38). Linear regression models included age, connectivity, or the interaction of age and connectivity as independent variables, and connectivity or affective scores as the dependent variable. Connectivity values were averaged across hemispheres before including in all regression models. In addition, all models included sex, mean FD, and study as covariates. In the significant interaction model, a Johnson-Neyman plot was generated using the R package 'interactions' to determine the age range in which the association between connectivity and affective score was significant (39). Statistical correction for multiple comparisons was done using false discovery rate (FDR) correction with the Benjamini-Hochberg procedure through the 'stats' R package (38).

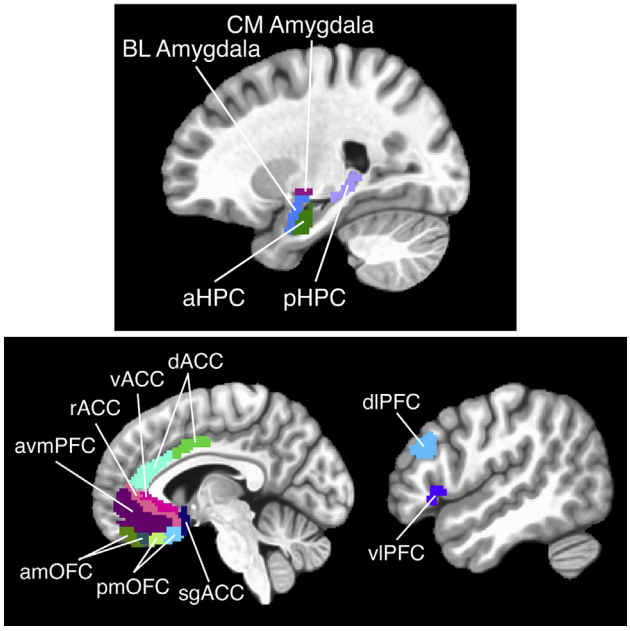

Figure 1. Regions of interest selected for computing pairwise connectivity values between (top) amygdala and hippocampus (HPC) subdivisions and (bottom) prefrontal cortex (PFC) and anterior cingulate cortex (ACC) subdivisions. aHPC, anterior HPC; amOFC, anterior medial orbitofrontal cortex; avmPFC, anterior ventromedial PFC; BL, basolateral; CM, centromedial; dACC, dorsal ACC; dlPFC, dorsolateral PFC; pHPC, posterior HPC; pmOFC, posterior medial OFC; rACC, rostral ACC; sgACC, subgenual ACC; vACC, ventral ACC; vlPFC, ventrolateral PFC.

RESULTS

Effects of Age on Affective Scores

Linear regression was used to examine the association of age with COVID-19 questionnaire measures, controlling for the effect of sex and study (Figure 2 and Figure S4). We found a significant main effect of age on COVID Stress score (β = 0.34, $p_{uncorrected}$ = .00037, p_{FDR} = .0019), such that greater COVID-related stress was associated with increasing age. We also found a significant main effect of sex, with females reporting more stress than males (β = −0.54, $p_{uncorrected}$ = .0023, p_{FDR} = .012). Similarly, worry increased with age (β = 0.25, $p_{uncorrected}$ = .014, p_{FDR} = .036). For the Perceived Stress Scale score, there was no age effect (β = 0.080, p = .43), but females reported somewhat higher levels than males (β = −0.39, $p_{uncorrected}$ = .040, p_{FDR} = .066). For the Sadness score, there was no age effect (β = 0.16, p = .11), but females reported greater levels of sadness (β = −0.45, $p_{uncorrected}$ = .017, p_{FDR} = .042). There was no age effect of positive score (β = −0.12, p = .24) and no associations with any covariates.

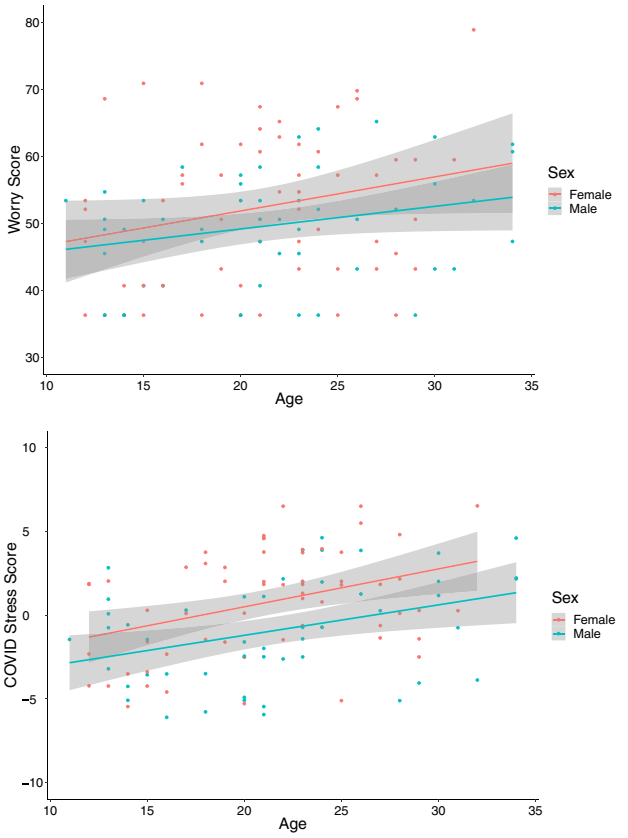

Figure 2. Significant age-associated changes in Worry score and COVID-19 Stress score. Color of lines corresponds to the sex of participant. Age corresponds to age at the time of questionnaire.

For all models, there was no effect of study and no interactions between age and other covariates.

Given the similarity between the Worry and COVID Stress scores, both of which were significantly associated with age, we examined the correlatedness of these two scores. The Worry and COVID Stress scores were significantly correlated (r = 0.58, $p = 1.98 \times 10^{-11}$), even with age regressed out (r = 0.55, $p = 3.31 \times 10^{-10}$). Thus, a composite anxiety score was created by z-scoring the Worry and COVID Stress scores and calculating the per-subject mean. This anxiety composite also showed significant increases with age (Figure 3) (β = 0.30, p = .00070), in addition to a main effect of sex ($\beta = -0.42$, p = .0089), with females reporting higher anxiety composite scores than males. There was no effect of study and no interaction between age and other covariates.

Effects of Age on Pairwise Connectivity Between Amygdala, HPC, and PFC Subregions

To identify developmentally sensitive connectivity pairs that may underlie age-related changes in anxiety, pairwise connectivity values were computed for subregions of the amygdala and HPC with subdivisions of the PFC (see Table S1 for age effects with all ROI pairs). Connectivity between two ROI pairs, anterior ventromedial PFC (avmPFC) and pHPC, as well as rostral ACC (rACC) and BL amygdala, was significantly associated with age (Figure 4) ($p < .05$). avmPFC-pHPC connectivity increased with age (β = 0.16, $p_{uncorrected}$ = .012), while connectivity between the rACC and BL amygdala decreased with age ($\beta = -0.15$, $p_{uncorrected}$ = .023). While these findings did not survive multiple comparisons correction, they were consistent with our previous work from Calabro *et al.* (19) and Jalbrzikowski *et al.* (18), respectively. We observed no effect of sex, motion, or study in this effect.

Associations Between Age, Anxiety Composite Score, and Connectivity

For connectivity pairs where an age effect was identified (avmPFC-pHPC and rACC-BL amygdala), we investigated associations between connectivity and anxiety composite score (see Tables S2 and S3 for results from exploratory analyses of associations between other connectivity pairs and anxiety composite score, as well as the interaction with age). Linear regression models were used to examine the association between connectivity prior to the pandemic and composite anxiety score during the pandemic, controlling for age at scan and sex. To control for the effects of study and head motion on connectivity, a linear regression model with study and head motion as independent variables and connectivity as the dependent variable was used to generate residual connectivity values, which were used in all subsequent analyses.

Connectivity between the avmPFC and pHPC was significantly associated with composite anxiety score (β = 0.22, $p_{uncorrected}$ = .0057, p_{FDR} = .012), such that higher connectivity was associated with higher composite anxiety scores. This model also showed main effects of age (β = 0.26, $p_{uncorrected}$ = .0013, p_{FDR} = .0026) and sex ($\beta = -0.41$, $p_{uncorrected}$ = .011, p_{FDR} = .022) and no effect of motion or study. There was no significant association between rACC-BL amygdala connectivity and the anxiety composite score ($\beta = -0.70$, p = .10). Post hoc analyses revealed a significant age-by-connectivity interaction in the avmPFC and pHPC (Figure 5) ($\beta = -0.16$, p = .027), such that in younger participants only, greater connectivity was associated with a higher composite score.

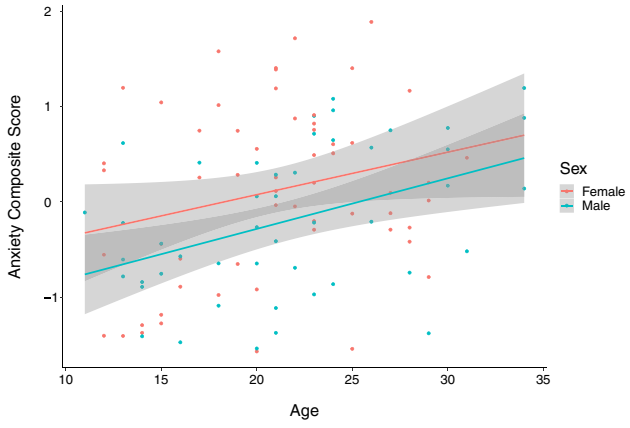

Figure 3. Significant age-associated change with the anxiety composite score. Color of lines corresponds to the sex of participant.

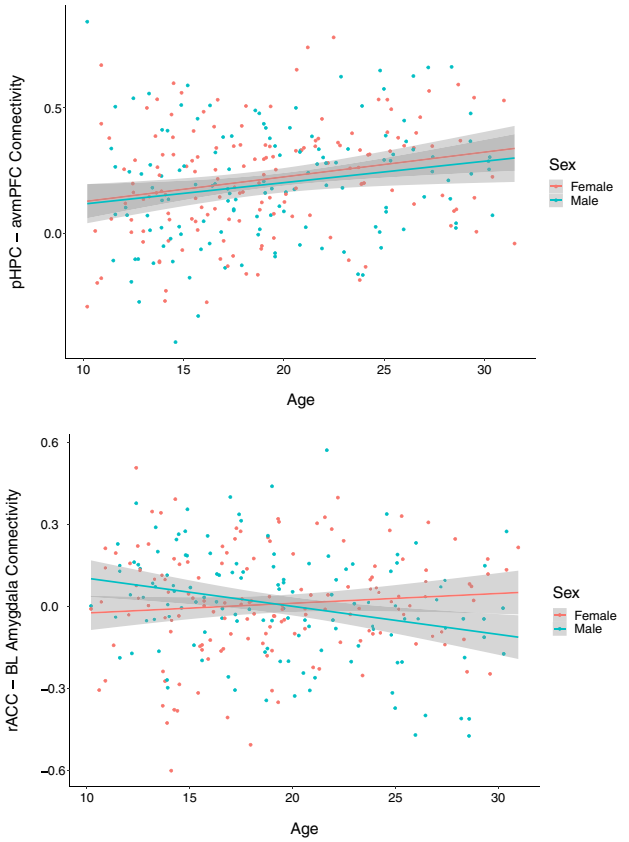

Figure 4. Significant age-associated change with connectivity between (top) anterior ventromedial prefrontal cortex (avmPFC) regions-posterior hippocampus (pHPC) and (bottom) rostral anterior cingulate cortex (rACC)-basolateral (BL) amygdala. Color of lines corresponds to the sex of participant.

This interaction model included sex as a covariate and used connectivity residuals, which controlled for the effects of study and head motion. A Johnson-Neyman analysis revealed that this association between avmPFC-pHPC connectivity and anxiety composite score was significant only between the ages of 10 and 18.59 (Figure 6). Notably, a pre-pandemic measure of anxiety from the Youth Self-Report (YSR) and Adult Self-Report (ASR) was also significantly associated with avmPFC-pHPC connectivity (p = .026). Interestingly, the YSR/ASR score was not associated with age, nor was there an age interaction between this measure and connectivity (see Supplemental Methods and Supplemental Results). Importantly, this difference suggests that the impacts of the pandemic extended beyond individuals who were predisposed to anxiety. Thus, avmPFC-pHPC connectivity may underlie a broad range of affective reactivity to stress, including predisposition for anxiety as well as reactive anxiety.

DISCUSSION

In this study, we examined associations between the functional connectivity of HPC and amygdala subregions with PFC pre-pandemic and emotional responses during the COVID-19 pandemic in a cohort of adolescents and young adults. We found that older participants reported greater levels of COVID-specific stress, worry, and anxiety during the pandemic. In addition, females reported greater levels of anxiety and sadness during the pandemic than males, independent of age. Resting-state functional connectivity analyses revealed that the presence of more adult-like connectivity between pHPC and avmPFC prior to pandemic onset was associated with greater levels of self-reported anxiety during the pandemic.

Stress hormone receptors are concentrated in the HPC (40), and its prolonged neurogenesis is interrupted by glucocorticoids released during stress (41,42). In addition, one study examined hippocampal BDNF (brain-derived neurotrophic factor) expression, which promotes neurogenesis, during stress in rodents (43). Results indicated that reduced BDNF in the rodent analog of the pHPC was associated with prolonged corticosterone elevation in young, but not adult, rats. Our results showed that the relationship with self-reported anxiety during the pandemic was specific to PFC functional connectivity with the pHPC, which primarily supports storing of memories, in contrast to the anterior HPC, which supports flexible representations of previous experiences (44,45). Activity in the pHPC has been associated with trait anxiety levels in humans, such that greater threat-related activation in the pHPC is associated with greater trait anxiety (43). Studies show that HPC-vmPFC connectivity plays a critical role in stress response, such as that following stress exposure in adults with posttraumatic stress disorder (12,44), childhood trauma (45), and childhood institutionalization (46). Given this literature and the association we see between HPC-vmPFC connectivity and the ASR/YSR data gathered in our sample prior to the pandemic, this connection's influence on stress may generalize beyond once-in-a-lifetime pandemics.

The results seen here were also specific to the vmPFC and its connectivity with the pHPC. The vmPFC has been implicated in many higher-order functions including decision making and value judgment, but most relevant here is its role in emotional, specifically fear, processing (46–49). Furthermore, connectivity between the pHPC and vmPFC has been associated with the construction of episodic memories and the

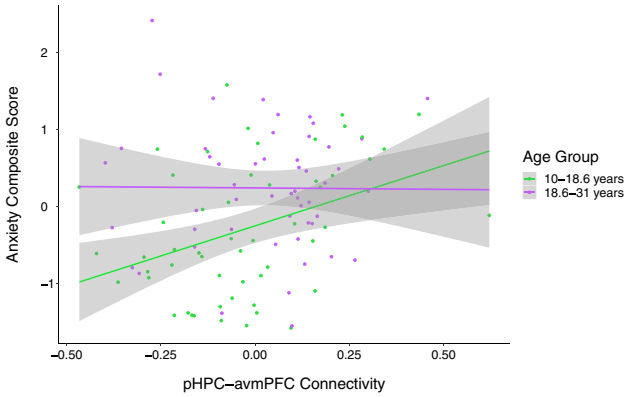

Figure 5. Significant age-by-connectivity interaction on the Anxiety score. Sample divided into two age groups based on a Johnson-Neyman analysis. avmPFC, anterior ventromedial prefrontal cortex; pHPC, posterior hippocampus.

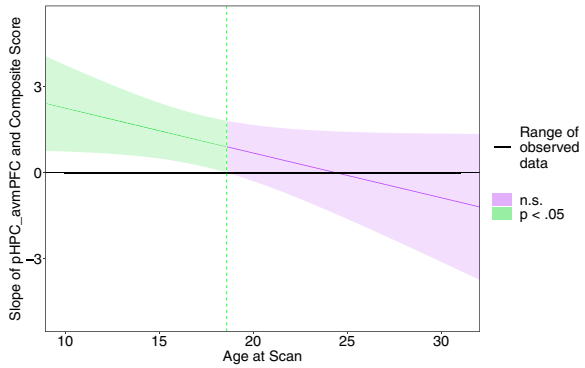

Figure 6. A Johnson-Neyman plot showing that age significantly moderates the relationship between connectivity and composite score only at younger ages (below 18.59 years of age). avmPFC, anterior ventromedial prefrontal cortex; n.s., not significant; pHPC, posterior hippocampus.

elaboration of emotional memories (50,51). Previous research suggests that an individual's episodic memory and episodic future thinking may relate to anxiety symptoms (52–54). Our previous findings indicate that age-related increases in pHPC-vmPFC connectivity through adolescence support future planning (19), suggesting that as cognitive processes mature, there may be greater ability to think in a future-oriented manner, thereby increasing potential for stress-related worry. Taken together with our current results, this suggests that adolescents with more mature pHPC-vmPFC connectivity may have a greater ability to process stressful events in an adult-like way, resulting in greater self-reported anxiety.

It is notable that age-related changes were not observed in the connectivity of other pairs of regions besides the pHPC-vmPFC and rACC-BL amygdala. This is in contrast to previous studies, including ours, that have additionally found age-related decreases between the centromedial amygdala and the rACC, anterior vmPFC, and subgenual cingulate (18) as well as age-related increases between the anterior HPC and vmPFC (19). There are several possibilities as to why these changes were not observed in these data. First, this study used only cross-sectional data while these previous studies incorporated longitudinal data. Because our goal was prospective prediction, we chose to limit analyses to include a single scan per subject to provide an individual pre-COVID baseline. However, this limits our statistical power to detect developmental change compared with these previous studies. Second, while one of our included studies started at age 10, the other began at age 12, and both had sparser sampling at younger ages. Thus, compared with other studies that had samples slightly younger than ours (18), our data may be less powered to detect age-related change occurring in these early developmental periods.

Many studies have examined the impact of stress during development on the adolescent brain (55). Studies looking specifically at the impact of stress on the maturation of adolescent brain connectivity have shown that stress is associated with accelerated development of fronto-amygdala connectivity, which may be adaptive at the time but may later confer risk for psychopathology such as anxiety (56,57). However, in this prospective study, accelerated development of connectivity preceded the stress response, with more adult-like connectivity between the pHPC and avmPFC during adolescence associated with worse anxiety during the pandemic.

While it cannot be ruled out that pre-pandemic stress may have already accelerated brain development in certain individuals, it may also be the case that having more adult-like connectivity could predispose individuals to engage in anxiogenic thought processes and behaviors. Some developmental cognitive models of worry propose that a more adult-like ability to imagine future outcomes may be a mechanism underlying increased capacity for worry at younger ages (58,59). Thus, having a more adult-like understanding of the pandemic and ability to imagine future or large-scale outcomes may lead to more adult-like emotional responses in younger participants, i.e., greater anxiety and worry. Prospective studies that include anxiety and brain connectivity measurements prior to stressful events could better elucidate if the maturation of HPC-PFC connectivity is predictive of stress reactivity.

In addition, consistent sex differences were observed across multiple affective measures, indicating that the COVID-19 pandemic is causing greater stress and sadness in females than males, regardless of age. It should be noted that this study did not collect these measures prior to pandemic onset, so it is unclear whether these sex differences are directly related to the pandemic. However, this result is consistent with existing research showing worse mental health outcomes for females worldwide during the pandemic (60–66). Greater distress in females could be related to a number of factors, such as increased child care burden, as well as the significantly higher number of women in health care and other fields heavily affected by the pandemic, such as the service industry (66,67). Females are also known to experience higher rates of internalizing symptoms and may react differently to stressful events (68–71). One possible explanation for these sex differences that has been suggested is that earlier onset of puberty, as seen in females, may confer risk for psychological distress because of many social and biological factors (72–74). The idea that earlier maturation may increase risk for greater distress also supports the idea that more adult-like brain connectivity may result in greater anxiety, as suggested above.

Certain limitations of this study should be noted. First, COVID-19 affective measures were not collected prior to pandemic onset, so we cannot confirm whether these differences were preexisting. By incorporating the ASR/YSR measure, we were able to look broadly at anxiety levels in this sample prior to the pandemic, but this measure is more sensitive to clinically significant levels of anxiety, and thus may not pick up on less significant variability. Similarly, we did not obtain stress reactivity to other life events, limiting our ability to discern if reactivity to the pandemic generalizes to other situations. In addition, this study is cross-sectional, which limits our ability to look at age-related change. Furthermore, we were not able to obtain responses on the COVID-19 questionnaire from every participant we collected MRI data from, thus decreasing our sample size.

Conclusions

Our results indicate that during the transition to adulthood, increasing age is associated with greater levels of stress and

worry during the COVID-19 pandemic. This may relate to the maturation of HPC-vmPFC connectivity, which may facilitate future planning and episodic future thinking. While this study investigated a normative sample with no clinical diagnoses of mood disorders, it identifies HPC-vmPFC as an important circuit underlying stress reactivity that could inform risk for the development of anxiety or depression relating to chronically stressful events. Given that adolescence is a period of not only heightened brain plasticity but also heightened vulnerability for the emergence of psychopathology, adolescence is a window of opportunity for affecting mental health outcomes. Thus, understanding the neural basis of variability in stress reactivity may provide insight into who may be at greater risk, allowing for earlier, more effective intervention.

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ARTICLE INFORMATION

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