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Review

Pre-pandemic brain structure and function and adolescent psychopathology during the COVID-19 pandemic

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Abstract

The COVID-19 pandemic has presented unprecedented challenges for youths and families, dramatically increasing exposure to stressors and stress-related psychopathology. Increasing work has leveraged pre-pandemic neuroimaging data to predict adolescent psychopathology and stress responses during the pandemic, with a particular focus on internalizing symptoms. We review this recent literature on pre-pandemic brain structure and function and adolescent internalizing psychopathology during the pandemic. At present, existing studies have not consistently identified specific alterations in brain structure and function that predict anxiety or depressive symptoms during the pandemic. In contrast, exposure to stress and adversity before and during the pandemic as well as access to peer and family support have emerged as consistent and reliable predictors of youth mental health during the pandemic.

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Keywords

COVID-19 pandemic, Adolescence, Psychopathology, Brain, Neuroimaging.

Introduction

The COVID-19 pandemic led to unprecedented and dramatic changes in youth's daily lives. Symptoms of depression and anxiety among children and adolescents increased sharply during the pandemic worldwide [1]. A growing body of research has examined predictors of risk and resilience to stress-related psychopathology in youth during the pandemic. Neuroimaging studies conducted prior to the pandemic have been increasingly leveraged to examine whether pre-pandemic brain structure and function predict increases in internalizing symptoms or stress-related psychopathology during the pandemic. We review existing studies that have used structural or functional neuroimaging to predict psychopathology symptoms in children and adolescents during the COVID-19 pandemic (Table 1). These studies may be used to identify predictors of psychopathology in youth during large-scale stressors, such as the COVID-19 pandemic.

Stress-related psychopathology during the COVID-19 pandemic

The stressors associated with the COVID-19 pandemic have been well characterized. Due to social distancing measures and stay-at-home orders, substantial reductions in social interactions were common and led to increased social isolation [2]. Families experienced substantial changes in daily routines and novel stressors, including potential loss of loved ones, parental job loss and changes, school and daycare closures, and increased food insecurity, among many others [3–6]. These changes dramatically increased exposure to stressors for children and families throughout the pandemic. These increases in stress exposure disproportionately affected those with low socioeconomic status, including families whose economic situations worsened during the pandemic [7,8], contributing to widening socioeconomic disparities in stress-related psychopathology in youth.

The prevalence of mental health problems among children and adolescents increased during the pandemic, including in large, longitudinal samples collected within and outside of the United States [9–12]. In a recent meta-analysis of 29 studies, prevalence of depression and anxiety symptoms in youth during the first year of the pandemic doubled compared to pre-pandemic estimates [1]. Depression and anxiety symptoms were higher in samples collected later in pandemic relative to earlier. This rise in psychopathology occurring alongside meaningful increases in exposure to stressors is consistent with substantial prior work documenting that exposure to stressful life events increases vulnerability to youth internalizing symptoms [6]. Indeed, exposure to pandemic-related stressors has been associated with

Table 1

Summary of papers linking pre-pandemic brain structure or function and youth psychopathology during the pandemic.

Paper	N	Type[a]	Brain measure	Psychopathology outcome	Association
Gotlib et al., 2022	163	S	Grey matter volume and cortical thickness, brain age	N/A	Youth had larger amygdala and hippocampal volume and more advanced cortical thinning during the pandemic compared to a pre-pandemic matched sample.
Chahal et al., 2022	214	S	Cingulum morphometry	Depressive symptoms	Low cingulum fiber density and cross-section was associated with increased depressive symptoms in female adolescents.
Jamieson et al., 2021	30	S	White matter integrity	Anxiety symptoms	Youth with greater structural integrity of the posterior limb of the internal capsule and anterior corona radiata had more COVID-related worry.
Weissman et al., 2021	145	F, S	Grey matter volume and fMRI passive face-viewing task	Internalizing symptoms	Amygdala activation to neutral faces compared to fearful faces was associated with higher internalizing symptoms.
Carosella et al., 2023	64	F, S FC	Amygdala volume, fMRI passive face-viewing, resting-state functional connectivity	Non-suicidal self-injury	Greater amygdala activation to emotional faces compared to neutral faces predicted continued engagement in non-suicidal self-injury.
Hardi et al., 2022	174	F	fMRI passive face-viewing	Anxiety symptoms	One subgroup of youth with more connections in the amygdala, subgenual anterior cingulate cortex and striatum had greater anxiety.
Haller et al., 2022	47	F	fMRI Dot Probe task	Anxiety symptoms	Greater activation to neutral faces compared to angry faces in the anterior cingulate, middle frontal gyrus, and bilateral putamen was associated with higher anxiety.
Sequeira et al., 2021	93	F	fMRI social evaluation task	Depressive symptoms	Reduced activation to positive peer feedback compared to neutral feedback in the caudate, putamen, and insula was associated with greater depressive symptoms.
Hutchinson et al., 2021	93	F	fMRI social evaluation task	Suicidal ideation	Greater caudate and insula activation to anticipated positive peer feedback compared to neutral feedback was associated with reduced suicidal ideation.
Kitt et al., 2023	28	F	fMRI passive face-viewing with presence or absence of parent	Anxiety symptoms	Higher amygdala reactivity to fearful faces compared to neutral faces when in the presence of a parent (relative to alone) was associated with stronger link between stress and COVID-related fears.
Chahal et al., 2021	85	FC	Resting-state network coherence	Internalizing symptoms	Higher executive control network coherence buffered the association between advanced pubertal timing and internalizing symptoms.
Miller et al., 2021	214	FC	Resting-state functional connectivity	Depressive symptoms	Greater amygdala-subgenual anterior cingulate cortex connectivity was associated with heightened depressive symptoms.
Perica et al., 2021	111	FC	Resting-state functional connectivity	Anxiety symptoms	Resting posterior hippocampus connectivity with ventromedial prefrontal cortex was associated with higher anxiety and COVID-related stress.

[a] S = Brain structure data, F = fMRI data, FC = Resting-state functional connectivity

increases in youth psychopathology in numerous studies during the COVID-19 pandemic [10,13–16].

Identifying factors that enhance risk or resilience to stress-related psychopathology during the COVID-19 pandemic may help to generate targets for intervention during periods of heightened stress for youth. For example, social support from peers and parents has been well-documented as a protective factor that buffers against stress-related psychopathology during the pandemic. For youth, maintaining in-person and digital social experiences with peers and a sense of social connection reduced vulnerability to psychopathology when exposed to pandemic-related stressors [2]. Parental support and emotion coaching of negative youth emotions also buffered the associations between pandemic stressors and youth psychopathology [16,17]. Conversely, parent suppression of their own emotions exacerbated the association between pandemic stressors and psychopathology [18]. Finally, pre-pandemic early pubertal maturation may have exacerbated internalizing psychopathology during the pandemic [19].

Thus, some evidence suggests that neurobiological factors may play a role in risk or resilience to stress-related psychopathology during the COVID-19 pandemic. An increasing number of studies have utilized structural and functional neuroimaging data acquired prior to the pandemic to predict increases in mental health problems during the pandemic [20]. Here, we characterize studies that have used brain structure or function to predict stress-related psychopathology in youth during the pandemic.

Neural predictors of stress vulnerability

We first review studies that examined associations of brain structure and function with vulnerability to stress-related psychopathology during the pandemic. Overall, findings indicate alterations in amygdala structure and amygdala reactivity to emotional stimuli associated with pandemic stressors. First, one study has compared changes in brain structure before and after the COVID-19 pandemic in youth. Adolescents in the United States had larger amygdala and hippocampal volume and more advanced cortical thinning during the pandemic compared to a pre-pandemic matched sample [21], suggesting that the pandemic is associated with structural changes that have often been observed in youths who have experienced early-life adversity [22,23]. One study examined neural activation when viewing emotional faces to create subgroups of participants and identified one subgroup—characterized by greater network density and more connections involving the amygdala, subgenual anterior cingulate cortex (ACC), and striatum—that had more anxiety during the pandemic [24]. Within this subgroup, pandemic-related economic stressors were also associated with greater anxiety, thus identifying a specific pattern of pre-pandemic brain function that predicted susceptibility to future stressors.

In general, the presence of a parent is typically associated with reduced amygdala reactivity to threat-related stimuli in youth [25]. In youth with anxiety disorders, amygdala reactivity to fearful faces—relative to neutral ones—in the presence versus absence of a parent (i.e., parental buffering) prior to the pandemic moderated the association between pandemic stress and COVID-19-related fear, such that greater parental buffering was associated with a weaker association of stress with fear [26]. This study suggests that developmentally appropriate parental buffering of amygdala reactivity may mitigate the impact of pandemic-related stressors on youth with anxiety disorders. Finally, greater amygdala activation to neutral faces—compared to fearful ones—prior to the pandemic was associated not only with greater internalizing symptoms during the pandemic but also a stronger association between pandemic-related stressors and internalizing problems [13]. These studies on youth in the United States suggest that individual differences in pre-pandemic amygdala reactivity to emotional faces may alter associations between pandemic stressors and internalizing psychopathology in youth, although findings have been mixed across studies.

Neural predictors of internalizing symptoms

Existing studies have leveraged structural and functional neuroimaging data collected prior to the pandemic to predict increases in adolescent internalizing psychopathology during the pandemic. There has been little consistency in the findings across these studies. One study of 214 youth 9–13 years old utilizing brain structure found that lower fiber density and cross-section of the cingulum bundle predicted increases in depression symptoms in female adolescents during the pandemic [27]. A second study utilizing brain structure reported no associations between volume of the amygdala and hippocampus prior to the pandemic with increases in adolescent internalizing symptoms during the pandemic [13]. Finally, one study found that youth with greater structural integrity of the posterior limb of the internal capsule (PLIC) and anterior corona radiata had more COVID-related worry and rumination [28].

Little consistency in findings has been observed in studies using resting-state functional connectivity data prior to the pandemic as a predictor of pandemic-related increases in internalizing symptoms. Greater coherence in the executive control network—including the dorsolateral prefrontal and superior parietal cortex—buffered against risk of increases in internalizing symptoms during the pandemic associated with early pubertal maturation, although no direct association of network coherence with later internalizing symptoms was observed [19]. In

another study, greater connectivity between the hippocampus and ventromedial prefrontal cortex (vmPFC) was associated with higher anxiety and COVID-related stress during the pandemic in adolescents [29]. Hippocampus and vmPFC connectivity increased across age [30], suggesting that adolescents with more mature functional connectivity reported more anxiety during the pandemic. A final study using resting-state functional connectivity reported that stronger pre-pandemic amygdala-subgenual ACC connectivity was associated with greater depressive symptoms during the pandemic [31]. This study also evaluated if parenting mediated the association between amygdala-subgenual ACC connectivity and depressive symptoms and found no indirect effect.

Studies utilizing task-based fMRI acquired prior to the pandemic have similarly revealed few consistent patterns associated with risk for pandemic-related increases in internalizing problems. However, two studies revealed that greater neural response to ambiguous social cues may confer higher risk for internalizing problems during the pandemic. In the first, greater activation in the anterior cingulate, middle frontal gyrus, and bilateral putamen to neutral faces—as compared to angry ones—during a threat attention task was associated with greater anxiety during the pandemic in a sample of youth diagnosed before the pandemic with a range of transdiagnostic mental health problems [32]. Greater amygdala activation to neutral faces—relative to fearful faces—predicted later increases in internalizing symptoms during the pandemic in a separate study [13]. A final study observed that females with a shy or fearful temperament and blunted activation to social reward in the dorsal striatum and insula experienced greater depressive symptoms during the pandemic [33].

Two studies examined risk of suicidal ideation (SI) and non-suicidal self-injury (NSSI) in youth during the pandemic using pre-pandemic neuroimaging measures. Among adolescents with NSSI prior to pandemic, greater amygdala activation to fearful and angry faces relative to shapes before the pandemic was associated with continued engagement in NSSI during the pandemic [34]. In a different study, greater caudate and anterior insula activation in response to positive peer feedback was associated with reduced risk of SI during the pandemic controlling for depressive symptoms [35].

Summary of existing findings

Three overlapping findings emerged across existing work examining whether differences in brain structure and function as predictors of internalizing problems during the COVID-19 pandemic. First, multiple studies in the United States found that pre-pandemic differences in amygdala reactivity to emotional faces [13,24,26] or amygdala connectivity with the subgenual ACC [24,30] predicted internalizing symptoms during the pandemic. Exposure to trauma prior to the pandemic has been consistently associated with increases in amygdala activation to emotional stimuli [36–38]. Some prior research on early adversity has also found differences in amygdala-ACC connectivity, which has been associated with internalizing symptoms [39,40]. However, the directions of associations of neural activation with psychopathology during the pandemic has varied across studies.

Second, two studies using the same sample of girls in the United States found that changes in neural activation to social reward in the dorsal striatum, including the caudate and putamen, were associated with greater risk of depression and SI during the pandemic [33,35]. These studies are aligned with work showing that social connection is an important protective factor for adolescents during the COVID-19 pandemic and that stress associated with social isolation is associated with increased internalizing symptoms for youth [2,41,42]. This initial work suggests that blunted neural activation to social reward prior to the pandemic may serve as one risk factor related to social changes and associated mental health symptoms across the pandemic.

Finally, two studies in the United States found changes in the structure and function of regions associated with executive control are associated with internalizing symptoms during the pandemic [19,27], although the specific measures varied. These studies highlight that difficulties with executive functioning in the context of large-scale stressors such as the COVID-19 pandemic may be a relevant risk factor for stress-related psychopathology. Because executive functioning was not measured directly in these studies, this possibility remains to be examined empirically in future studies.

Limitations of current approaches

Recent work has focused on the reproducibility of brain-wide association studies and has emphasized that large samples sizes ($n > 1000$) are needed to reliably examine associations with psychopathology given that effect sizes tend to be quite small [43,44]. The work characterized in the present review all includes substantially smaller sample sizes than recommended to be replicable. While the above studies can identify initial avenues for future research, researchers interested in examining brain-wide associations may also benefit from using large-scale open-source datasets to examine constructs of interest such as the Human Connectome Project [45], the Adolescent Brain Cognitive Development (ABCD) study [46], and others [47].

Additionally, it is important to connect associations with brain development and psychopathology with specific changes in youth's daily lives attributable to the COVID-19 pandemic. For example, some of the current

research has connected associations between pre-pandemic neuroimaging and psychopathology with peer connectedness, pandemic-related economic stressors, and parenting behavior to describe what components of the drastic changes that teens experienced during the pandemic is associated with increased psychopathology [24,31,35]. Through this work, pre-pandemic brain structure and function could be used to identify avenues to mitigate increases in psychopathology in adolescence associated with the pandemic, such as leveraging emotion regulation skills, or social connectedness to ameliorate risk for psychopathology.

Importantly, adolescent psychopathology during the pandemic is reliably predicted using methods that are simpler and less expensive than neuroimaging. Exposure to pandemic-related stressors is a reliable and replicable predictor of increases in psychopathology during the pandemic [6], in addition to other risk and protective factors like prior exposure to adversity, social experiences, parent mental health, social media use, and family relationships. Although neuroimaging measures have great utility for understanding brain development, existing approaches have yet to produce replicable associations with psychopathology during the pandemic.

Conclusions and future directions

This review summarizes initial work linking pre-pandemic brain structure and function with adolescent psychopathology across the COVID-19 pandemic when risk for internalizing symptoms increased over time. As new studies emerge, harnessing large and more representative samples is vital to better characterize changes in brain structure and function that are associated with adolescent psychopathology during the pandemic. Findings related to adolescent psychopathology during the COVID-19 pandemic will also continue to change as acute stressors (e.g., stay-at-home orders) have shifted to long-term adaptations that youth and their families have made in response to the pandemic. To date, findings have yet to produce replicable associations of pre-pandemic brain structure and function with youth psychopathology during the pandemic. However, other measures of pandemic-related stressors, such as social isolation, peer support, and parenting behavior have produced links between pandemic stressors and the emergence of psychopathology in adolescents during the COVID-19 pandemic [2,16,48]. Ultimately, this work should be used to identify supports and strategies that likely to be beneficial to adolescents experiencing significant depression and anxiety symptoms following large-scale stressors such as the COVID-19 pandemic.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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* of special interest
** of outstanding interest

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In a large meta-analysis of 29 studies including over 80,000 youth worldwide, anxiety and depression symptoms were found to have doubled during the COVID-19 pandemic compared to pre-pandemic estimates. Additionally, prevalence rates were higher in adolescents than younger youth and in data collected later in the pandemic. This study suggests that the COVID-19 pandemic has taken a substantial toll on adolescent mental health and has continued to impact youth as the pandemic progresses.

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In response to the COVID-19 pandemic, this review highlights relevant conceptual models for how environmental stressors, such as those that occurred during the COVID-19 pandemic, may increase risk for psychopathology. The review differentiates between environmental stress models, which identify who is most at-risk for psychopathology as a function of stressful experiences, as compared to stress pathway models, which suggest targets for intervention to reduce stress-related psychopathology. The paper also highlights that brief digital interventions that target mechanisms known to link stress and psychopathology may be one strategy to reduce stress-related psychopathology during the COVID-19 pandemic.

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In a longitudinal community sample of 145 adolescents 10–15 years old, structural and functional MRI data was collected prior to the pandemic and then adolescents were followed across early stay-at-home orders and six months later. The study found that high exposure to pandemic-related stress was associated with the emergence of internalizing symptoms during the pandemic. Amygdala activation to neutral faces compared to fearful faces during a passive face-viewing fMRI task pre-pandemic was associated with higher internalizing symptoms during the pandemic. Greater use of maladaptive emotion regulation strategies was also associated with greater internalizing symptoms early during the pandemic.

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In a community sample of 214 youth, the authors examined whether cingulum morphometry predicted changes in depressive symptoms across four timepoints in adolescence, including during the COVID-19 pandemic. The study found that female adolescents had lower fiber density and cross-section (FDC) of the cingulum compared to male adolescents and that cingulum morphometry predicted changes in depressive symptoms in female adolescents. Specifically, low cingulum FDC was associated with increased depressive symptoms across adolescence into the COVID-19 pandemic.

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In a longitudinal sample of adolescents 9–19 years old across the study duration, the authors examined associations between adolescent-reported positive parenting, resting-state functional connectivity between the amygdala and ACC, and depressive symptoms during the COVID-19 pandemic. Results showed that amygdala-

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A sample of 93 adolescent girls 12–17 years old (oversampled for a shy or fearful temperament) completed an fMRI task pre-pandemic that compared neural activation when youth believed they were being observed by a peer providing positive, negative, or neutral feedback. Girls with a shy or fearful temperament who showed reduced neural activation to positive peer feedback compared to neutral feedback in the caudate, putamen, and insula experienced higher levels of depressive symptoms during the COVID-19 pandemic. This study highlights that social motivation may be critical for adolescents to prevent mental health symptoms or improve internalizing symptoms during the COVID-19 pandemic.

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In a sample of 93 adolescent girls 12–17 years old, authors examined rates of suicidal ideation during initial stay-at-home orders during the COVID-19 pandemic. Youth also completed an fMRI paradigm pre-pandemic that compared when youth believed they were being observed by a peer comparing positive and neutral peer feedback. Greater caudate and insula activation to anticipated positive peer feedback compared to neutral feedback was associated with reduced odds of reporting suicidal ideation during initial stay-at-home orders controlling for depressive symptoms.

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