

Research paper

Sleep, brain systems, and persistent stress in early adolescents during COVID-19: Insights from the ABCD study

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ABSTRACT

Purpose: The first year of the COVID-19 pandemic constituted a major life stress event for many adolescents, associated with disrupted school, behaviors, social networks, and health concerns. However, pandemic-related stress was not equivalent for everyone and could have been influenced by pre-pandemic factors including brain structure and sleep, which both undergo substantial development during adolescence. Here, we analyzed clusters of perceived stress levels across the pandemic and determined developmentally relevant pre-pandemic risk factors in brain structure and sleep of persistently high stress during the first year of the COVID-19 pandemic. **Methods:** We investigated longitudinal changes in perceived stress at six timepoints across the first year of the pandemic (May 2020–March 2021) in 5559 adolescents (50 % female; age range: 11–14 years) in the United States (U.S.) participating in the Adolescent Brain Cognitive Development (ABCD) study. In 3141 of these adolescents, we fitted machine learning models to identify the most important pre-pandemic predictors from structural MRI brain measures and self-reported sleep data that were associated with persistently high stress across the first year of the pandemic. **Results:** Patterns of perceived stress levels varied across the pandemic, with 5 % reporting persistently high stress. Our classifiers accurately detected persistently high stress (AUC > 0.7). Pre-pandemic brain structure, specifically cortical volume in temporal regions, and cortical thickness in multiple parietal and occipital regions, predicted persistent stress. Pre-pandemic sleep difficulties and short sleep duration were also strong predictors of persistent stress, along with more advanced pubertal stage. **Conclusions:** Adolescents showed variable stress responses during the first year of the COVID-19 pandemic, and some reported persistently high stress across the whole first year. Vulnerability to persistent stress was evident in several brain structural and self-reported sleep measures, collected before the pandemic, suggesting the relevance of other pre-existing individual factors beyond pandemic-related factors, for persistently high stress responses.

1. Introduction

Early adolescence, covering the ages from 10 to 14 years, is a significant transitional period in human development, marking the crucial development of many anatomical and physiological maturation processes, the reorganization of the brain (Giedd et al., 1999), as well as changes in behavior, and social and emotional development (Steinberg, 2005). Situations that are highly unpredictable or uncontrollable, such

as the COVID-19 pandemic, present a challenge to the coping ability of individuals (Russell and Lightman, 2019) and increase stress levels (Ifdil et al., 2021). Evidence suggests that effects of stressors in adolescence may be more enduring and qualitatively different from the impact of similar stress exposure at later periods of life, partially due to the ongoing development of the central nervous system (McCormick et al., 2010; Barker, 2004; Jiao et al., 2020; Kiss et al., 2022). The context of the pandemic required rapid adaptation from adolescents (home school,

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restricted mobility) with limited opportunities for in-person interaction, sport activities, and less access to social support systems (Loades et al., 2020) at a time when they were also exposed to anxiety over personal and parental health threat and economic hardship. All of these factors contributed to a considerable increase in rates of mental health problems among adolescents during the COVID-19 pandemic (Kiss et al., 2022; Zhou et al., 2020; Magson et al., 2021; Alzueta et al., 2021a).

Although much effort has been devoted to studying the effects of the onset of COVID-19 on psychological wellbeing (Kiss et al., 2022; Zhou et al., 2020; Zhao et al., 2022; Wang et al., 2022; Alzueta et al., 2021b), few studies have measured changes in adolescent stress levels over the course of the pandemic, especially as it progressed from 2020 to 2021, or considered pre-pandemic measures as potential risk factors for poor mental health during the pandemic, which requires longitudinal study. The Adolescent Cognitive Brain and Development (ABCD) Study has an advantage of tracking a large, diverse adolescent population distributed across the U.S., starting in 2016 (4 years before the pandemic) and monitoring a wide range of developmental-relevant behaviors each year in addition to brain structure and function with neuroimaging every second year. Our prior work with the ABCD study identified several situational factors during the early months of the pandemic such as low physical activity, poor friend and family relationships, high screen time use, and being separated from friends or family, that were associated with poorer mental health (depression, anxiety, stress) in young adolescents (Kiss et al., 2022). We also found that internalizing disorders and sleep disturbances measured pre-pandemic, as well as female sex, contributed risk for poor mental health in the context of the pandemic.

Here, we extend that work to examine trajectories of perceived stress across the first year of the pandemic in young adolescents participating in the ABCD study. We also examine pre-pandemic risk factors for sustained perceived stress across the pandemic. We focus on pre-pandemic brain structural measures because adolescence is a critical stage for brain development (Giedd et al., 1999; Giedd, 2004; Giedd et al., 2015; Gogtay et al., 2004). Cortical maturation is characterized as increasing in gray matter volume through childhood, peaking around the end of childhood and beginning of adolescence (frontal lobes: 9.5 years in girls and 10.5 years in boys; temporal lobes: 10.0 years in girls and 11.0 years in boys; parietal lobes: 7.5 years in girls and 9 years in boys) (Giedd et al., 2015), followed by a continuous decline thereafter (Gogtay et al., 2004; Ducharme et al., 2016; Gogtay and Thompson, 2010). Cortical thinning, particularly within the frontal cortex, is due in part to synaptic pruning and programmed cell death associated with adolescence (Huttenlocher and Dabholkar, 1997). While many cortical synapses are eliminated (Gogtay et al., 2004; Huttenlocher and Dabholkar, 1997; Pfefferbaum et al., 1994; Sowell et al., 2001), there is an increase in white matter volume enhancing both the quantity and quality of connections among disparate brain components throughout adolescence (Giedd et al., 2015), accompanied by changes in the neurotransmitter systems as well (Murrin et al., 2007). Synaptic pruning and myelination enhance the precision of information processing, and contribute to greater capacity for complex problem-solving (Luna et al., 2004). During the occurrence of these remarkable changes, the adolescent brain is particularly sensitive to environmental and psychosocial insult; yet, relatively little is known about the neuroanatomical components that underlie vulnerability of adolescents to prolonged stress, such as occurred during the pandemic. Recent studies conducted in adults have demonstrated that neural markers are important indicators of individuals' responses to the challenges presented by the COVID-19 pandemic (Liu et al., 2023; Wang et al., 2023; Lai et al., 2023; Zhang et al., 2023). To our knowledge, studies about neural markers and sleep in relation to COVID stress responses have not been done in adolescents.

We focus on pre-pandemic measures of sleep, given the profound changes in sleep behavior across adolescence (Colrain and Baker, 2011; Baker et al., 2016; Gradsar et al., 2011; Feinberg and Campbell, 2010; Feinberg and Campbell, 2013; Carskadon, 2011) with later bedtime, and shorter sleep duration during weekdays (Ohayon et al., 2004),

concomitant with brain changes (Dahl and Lewin, 2002) and our prior findings of the importance of sleep behavior as an early marker of vulnerability to poor mental health, including perceived stress, in the early stages of the pandemic in young (Kiss et al., 2022) and older (Alzueta et al., 2021b) adolescent samples.

This study had two main aims: first, to explore different trajectories of perceived stress over the first year of the pandemic; and second, to identify the brain structural and sleep behavioral predictors of elevated and persistent (across all six assessments) stress during early adolescence.

2. Methods

2.1. Participants

Data were obtained from the US-based, multi-site ABCD Study®, (21 research sites from 17 states - <https://abcdstudy.org/study-sites/>) that is tracking >11,000 children, aged 9–10 years at baseline (Garavan et al., 2018). Starting in May 2020, participants in the ongoing ABCD Study® were invited to complete online surveys, which were distributed electronically at six time points from 2020 to 2021, to assess the effect of the pandemic on youth and families (ABCD COVID-19 Rapid Response Research (RRR) Surveys First and Second Data Release - DOI: 10.1515/4/1520584, 10.1515/4/1522601). DOIs can be found at <https://nda.nih.gov/study.html?id=901> and <https://nda.nih.gov/study.html?id=1041>.

Starting dates for distribution of the COVID surveys were May 16, 2020 (Survey 1), June 24, 2020 (Survey 2), August 4, 2020 (Survey 3), October 8, 2020 (Survey 4), December 13, 2020 (Survey 5), and March 12, 2021 (Survey 6). 2003 participants did not participate in any of these surveys and 4240 participants only completed one or two surveys and were excluded from analysis. In the trajectory analysis we included data from the remaining 5559 adolescents who completed at least three of online COVID-19 surveys. For the prediction model, we used data from a subset of 3141 participants who had also completed the ABCD protocol (ABCD 3.0 data release) at the Year 2 visit before the start of the pandemic. The 3.0 data release included data from participants who had completed the Year 2 assessments by February 2020 (approximately half the sample).

Written informed consent and assent were obtained from a parent/guardian and the adolescent, respectively. Procedures were approved by a centralized institutional review board (University of California, San Diego, protocol number: #160091AW). Sample demographics are described in Table 1. Compared to the full ABCD Study® sample at study entry, youth completing surveys during the pandemic were less likely to be Hispanic/Latino (16 % vs. 20 %), less likely to be Black (7 % vs. 15 %), more likely to be Asian (5 % vs. 4 %), and their parents were more likely to have higher education (e.g., having Post Graduate Degree 42 % vs. 34 %).

2.2. Clusters of perceived stress trajectories across the pandemic

The 4-item perceived stress scale (PSS) (Cohen et al., 1983) was used to measure stress levels of ABCD study participants at six timepoints during the pandemic. The PSS provides a brief measure of stress perception during the last month (Cohen et al., 1983). Scores range from 0 to 16, with higher scores reflecting greater perceived stress.

We identified subgroups of individuals following a similar pattern of change in their perceived level of stress over time, by efficiently clustering their perceived stress trajectories. To do so, we concatenated the 4 items of the PSS of the 6 surveys to obtain various stress patterns (feature vectors of size 24). Then, we clustered the feature vectors by solving the *k*-medoids problem. This process was done efficiently using techniques from submodular optimization (Wolsey, 1982). Compared to *k*-means clustering, *k*-medoids clustering can be solved efficiently, scales to larger datasets, is deterministic, does not depend on initialization, and is much

Table 1
Demographics of ABCD Study® participants and the subset included in the current analysis.

Variable	Release 3.0 baseline data N = 11, 878	Survey 1 N = 5559
Age (years) Mean (range)	9.91 (9–11)	12.48 (11.83–13.17)
Sex		
Female	5682 (47.8 %)	2802 (50.4 %)
Male	6196 (52.1 %)	2757 (49.6 %)
Race		
White	8244 (69.4 %)	4295 (77.3 %)
Black	1895 (15.9 %)	524 (9.4 %)
Asian	498 (4.1 %)	329 (5.9 %)
Multi-racial/multi-ethnic	184 (1.5 %)	58 (1.0 %)
Other	852 (7.1 %)	293 (5.3 %)
Unknown/not reported	143 (1.2 %)	60 (1.1 %)
Ethnicity		
Hispanic/Latino	2411 (20.3 %)	918 (16.5 %)
Not Hispanic	9314 (78.4 %)	4579 (82.4 %)
Unknown/not reported	143 (1.2 %)	62 (1.1 %)
Parental education		
≤High school diploma	1395 (11.7 %)	357 (6.4 %)
GED	330 (2.7 %)	85 (1.5 %)
Some college	3080 (25.9 %)	1145 (20.6 %)
Bachelor's degree	3015 (25.3 %)	1609 (28.9 %)
Post graduate degree	4044 (34 %)	2358 (42.4 %)
Unknown/not reported	14 (0.1 %)	5 (0.1 %)

^aCategories for race for the ABCD cohort were defined as in Goldstone et al., 2020.

less sensitive to noise and outliers. Besides, using the submodular formulation allows varying the number of clusters efficiently, without having to solve the clustering problem with a different number of clusters from scratch. More details can be found in the supplementary material (see Supplement section 1). The above formulation allows finding non-linear trends within a large number of trajectories, and enables easy interpretation of the identified stress patterns.

2.3. Modeling pre-pandemic predictors of the persistent high perceived stress trajectory

2.3.1. Data preprocessing

We tested for multicollinearity in the predictors. In cases where the pairwise correlation was higher than $r = 0.7$, we included only one of the two measures in the model.

For missing questionnaire responses, we imputed the values by multiple imputation (Royston, 2004) with the scikit-learn Python package (Pedregosa et al., 2011).

2.3.2. Predictor variables - measures included in the models

2.3.2.1. Demographics and developmental factors. Biological sex at birth, race and ethnicity of the child, family annual income, site of the data collection, the highest education status of the parents/caregivers, reported at the baseline year, were included in the model. From Year 2, we used parent reports of pubertal development status measured with the Pubertal Developmental Scale (PDS) (Petersen et al., 1988), which combines ratings of body hair development, growth spurt, skin changes, breast development, and menarche status for girls, and deepening of voice, growth spurt, growth of facial hair scored for boys. Scores ranged from 1 (no) to 4 (development seems complete). As part of the demographic factors, we also considered the body mass index (BMI, weight/height²) computed from Year 2 measures of Height (Carpenter's

square, steel tape measure) and Weight (Health-o-meter 844KL High-Capacity Digital Bathroom Scale; Jarden Corporation; Rye, NY). Age in months, assessed during the first COVID survey (May 2020), was also included.

2.3.3. Brain structural MRI measures

We used sMRI morphometric measures recorded as part of the regular annual assessments from the second-year visit (Year 2). Youth underwent an approximately 2 h long T1- and T2-weighted MRI, diffusion tensor imaging, resting state MRI, and three functional MRI scans (recorded by Siemens, GE, and Philips scanners using either 32 channel head or 64 channel head/neck coils) (Hagler Jr et al., 2019). The current analysis focuses on the T1-weighted structural MRI data. For more details about the ABCD Study MRI data acquisition and image processing see (Hagler Jr et al., 2019). Summary metrics of cortical surface area, cortical surface thickness, cortical surface sulcal depth, cortical and subcortical regional volumes were included in the analysis.

2.3.4. Sleep measures

We used multiple sleep measures collected from the Year 2 visit. The Sleep Disturbance Scale for Children (Bruni et al., 1996) was administered to the caregivers of adolescents to assess whether adolescents had any sleep disorders, as well as measure their overall sleep disturbance. Caregivers responded to questions using a 5-point Likert scale ranging from 1 (never) to 5 (daily) on the adolescent's various sleep behaviors. As part of the KSADS-5 (Townsend et al., 2020), adolescents were asked if they had problems falling or staying asleep in the past two weeks. We also included youth reported measures of sleep behavior from the Munich Chronotype questionnaire (Roenneberg et al., 2003) (Year 2). Variables included sleep timing, duration, sleep onset latency, sleep inertia (time taken to get out bed) on school and free days, social jetlag and chronotype-proxy.

2.4. Definition of the outcome – persistent high perceived stress levels

Given the uncertainty and unprecedented nature of the early stages of the Covid-19 pandemic, it was expected that the population would experience elevated stress levels. Therefore, we did not limit our analysis to only those adolescents who had high stress levels at the beginning of the pandemic. Instead, our target population consisted of the adolescents who experienced persistent stress throughout the pandemic. Using trajectory analysis, we identified a cluster of 284 participants (5.1 %) who reported consistently high stress levels across all six timepoints and trained machine learning models to discriminate them from the rest of the adolescent population. These adolescents are particularly vulnerable to the negative mental health impacts of the pandemic and identifying them could facilitate targeted interventions and support to mitigate these impacts.

2.5. Prediction model

We developed classification models to differentiate the adolescents reporting persistent stress from the rest of the sample. Classification models such as Bagging Classifier (Breiman, 1996), SGD Classifier (Zadrozny and Elkan, 2002), XGBoost (Chen and Guestrin, 2016), and Multilayer perceptron (Minsky and Papert, 1969) (3-layer) were used to investigate the relationship between selected predictors and persistent pandemic stress. Grid search and 5-fold cross validation were implemented to tune hyperparameters in the models discussed above. For performance evaluation we used the Area Under the Receiver Operating Characteristic Curve (AUC), that is considered a robust and the most reliable metric for unbalanced datasets in binary classification tasks (Ling et al., 2003; He and Ma, 2013).

Based on the performance metrics listed in Table 2, XGBOOST outperformed the other models. As this model showed the highest predictive power, we decided to further investigate the importance of the

Table 2
Predictive performance – test set performance of classification models.

	Bagging classifier	SGD classifier	XGBoost	Neural networks
Highest AUC	0.504	0.65	0.77*	0.75
Average AUC (5-fold)	0.502	0.60	0.74*	0.56
Accuracy	0.934	0.89	0.941*	0.94

Note: * represents the highest performance.

predictors using the best performing XGBOOST model.

For model interpretation we calculated the SHapley Additive ex-Planations (SHAP) values (ϕ) (Lundberg et al., 2020). For XGBoost models, the SHAP algorithm computes the contribution of the individual variables in log odds values, providing an overall ranking of features according to their importance (mean absolute SHAP value). For the sake of interpretability, we categorized the top features into six color-coded domains based on the collected measures: demographics (e.g., age, sex); pubertal development; parent reported sleep problems, youth reported sleep timing; sMRI measures, and sMRI Destrieux parcellations.

3. Results

3.1. Clusters of stress trajectories across the pandemic

Our algorithm identified 15 perceived stress trajectories (Fig. 1), with each trajectory representing a cluster of similar stress patterns. The red curve in Fig. 1 represents a cluster of participants who had elevated stress levels across all pandemic timepoints, consisting of 284 participants (5.1 %). In our sample 5.73 % ($N = 319$) of participants reported a

medium stress at the early stages of the pandemic (May 2020), but their perceived stress decreased as the pandemic progressed. 11.4 % of the sample ($N = 631$) reported consistently low stress across the pandemic. The rest of the sample fluctuated in their stress levels without a particular pattern (77.77 %) (Fig. 1). The weighted average based on the size of this group is shown in blue). Given that some level of stress is expected during Covid due to the unprecedented circumstances, such as health concerns, social isolation, disruptions to daily routines, and uncertainty about the future, we decided to focus our downstream analysis on the group of adolescents who had persistently high stress levels at all assessments. Our objective was to investigate the predictors that differentiate this group from the rest of the sample.

3.2. Feature importance in classification models

The final XGBOOST model included 435 features. Fig. 2 shows the top 15 features by mean absolute SHAP value for predicting stress during the pandemic. Specifically, the most important predictor was the measure of youth reported sleep problems ($\phi = 0.05$) at Year 2, meaning that the more difficulties falling asleep and maintaining sleep was associated with persistently high stress. Additionally, sleep-related behaviors (shorter sleep duration ($\phi = 0.03$) and longer sleep latency ($\phi = 0.03$), i. e., the time it takes to fall asleep) predicted persistent high stress. Another top-ranked variable was the Pubertal Development Scale Score ($\phi = 0.05$), which reflected that participants with higher pubertal maturation are more likely to experience high stress levels in the pandemic. Out of the 202 sMRI volume measures, the model identified 3 cortical volumes in temporal regions. As shown, the middle temporal cortical volume ($\phi = 0.05$) was a strong indicator of adolescents' stress behaviors, meaning that higher cortical volume of the left middle temporal cortex corresponds to a lower stress level. Out of the 141 sMRI

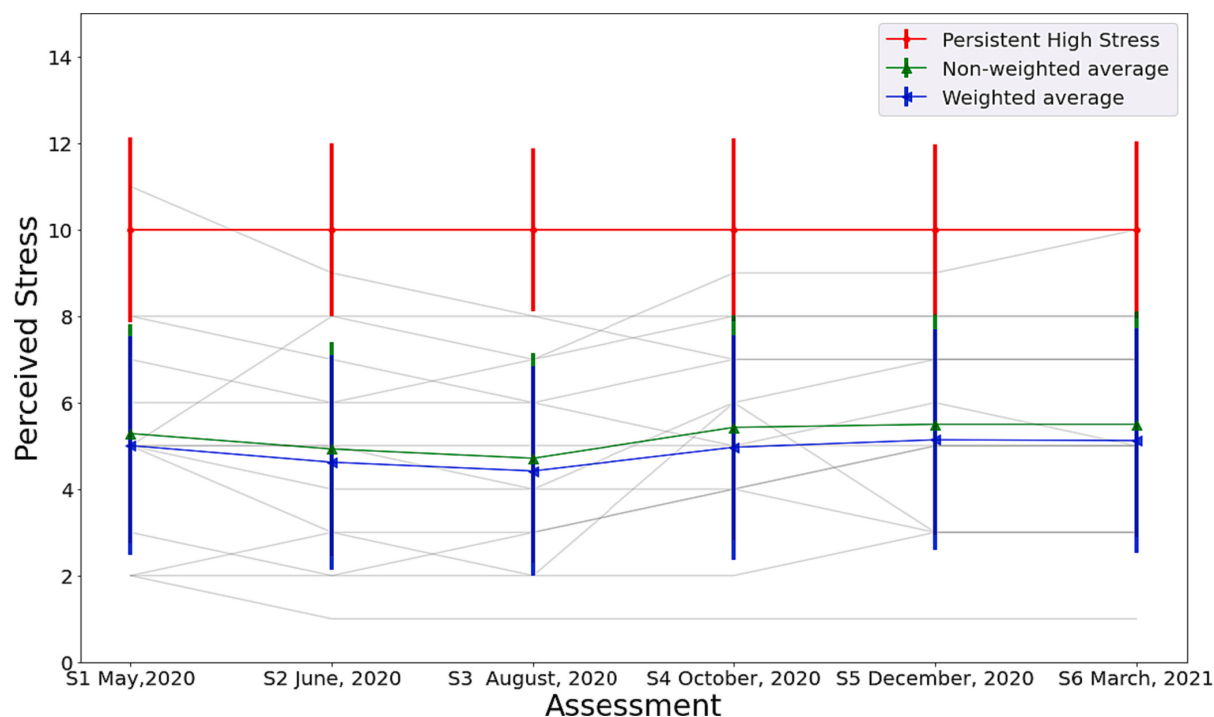


Fig. 1. Identified stress level trajectories during the COVID-19 pandemic. We identified 15 different trajectories showing fluctuations in the stress levels of the adolescents across the first year of the pandemic. The red line represents the stress scores of groups that showed high levels of stress across all 6 timepoint. Other identified categories are shown in gray. The blue line represents the mean of the stress scores in the 14 different clusters weighted by the size of the groups at each timepoint (green: shows the non-weighted average). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

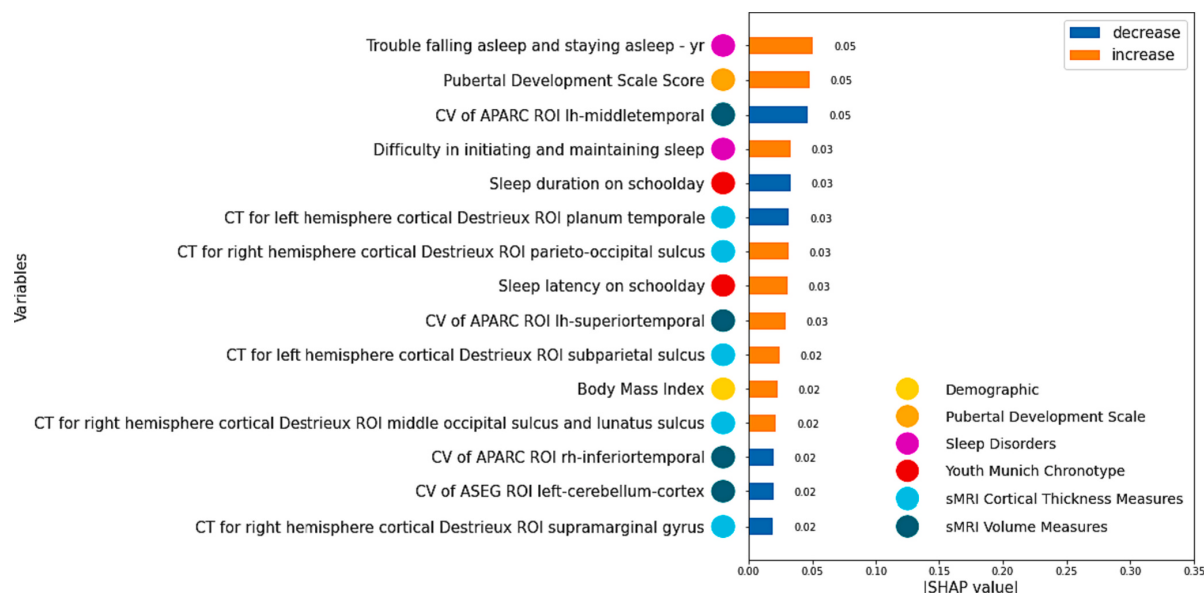


Fig. 2. Feature importance of the GBT model trained to predict adolescents during the pandemic. Top 15 features are sorted by mean absolute SHAP (Shapley Additive Explanation) value. The color of the bars represents the direction of the effect (orange: variable value is positively correlated with stress; blue: variable value is negatively correlated with stress). In variable names, “CV” cortical volume (mm³); “CT” cortical thickness (mm). “yr”- youth reported measure, “lh”-left hemisphere, “rh” – right hemisphere, “MRI” - Magnetic Resonance Imaging, sMRI: structural MRI, ROI: region of interest, ASEG: Automated Segmentation, APARC: Automated Parcellation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cortical thickness measures (Destrieux Parcellation), the model identified 5 in various regions of the brain. Here, the most significant factor, cortical thickness for left hemisphere cortical planum temporale ($\phi = 0.05$), demonstrated a negative correlation with stress level during the pandemic. Within the 15 top features predicting stress, eight were entailing posterior cortical (volume, thickness) features.

4. Discussion

Using a large and racially diverse group of 11-to-14-year-old adolescents, enrolled in the ongoing ABCD Study®, the present study investigated stress level trajectories of early adolescents across the first year of the COVID-19 pandemic in the U.S. and identified pre-pandemic risk factors primarily from brain structure and sleep measures associated with a pattern of persistently high stress.

These longitudinal data show divergent trajectories in stress across the first year of the pandemic, with 5.1 % of adolescents having high stress levels across all six assessments from May 2020 to March 2021. The relatively high prevalence of persistent stress in our sample is particularly alarming given that the duration of stress is critical for later psychological and brain functioning of adolescents and young adults (Pechtel and Pizzagalli, 2011). While moderate levels of stress can be adaptive (Finsterwald and Alberini, 2014), chronic stress exposure has been associated with poor physical health (Rosenberg et al., 2014; Landeo-Gutierrez and Celedón, 2020; Kudielka and Wüst, 2010) and various psychiatric illnesses, including substance use disorder (Brady and Sinha, 2005), bipolar disorder (Kim et al., 2007) and anxiety (Landeo-Gutierrez and Celedón, 2020). Persistent stress may directly affect the cognitive system and induce alterations in gray and white matter of the brain (Lupien et al., 2009), impacting the overall neural development (Sheth et al., 2017), resulting in lower academic achievements (Schraml, 2013), and poorer emotion regulation (Barch et al., 2016). Persistent levels of perceived stress may also reflect poor mental health overall, since prior literature showed strong correlation between levels of perceived stress, depressed mood, and anxiety (McLaughlin and

Hatzenbuehler, 2009).

We identified the associations of pre-pandemic sleep and structural MRI measures with persistently high levels of stress considering relevant demographic and developmental factors with the XGBOOST model, which exhibited better performance compared with other machine learning models. Results demonstrated that self-reported pre-pandemic difficulties falling asleep or maintaining sleep, short sleep duration, and longer sleep latency are associated with persistently elevated levels of stress during the pandemic. These results are in line with prior studies reporting that poor sleep and short sleep duration before the pandemic was associated with high perceived stress during the COVID-19 pandemic (Gruber et al., 2021), and with our own prior work in the ABCD Study that showed that poor sleep pre-pandemic was associated with high perceived stress in the early stages of the pandemic (Kiss et al., 2022). The current results extend these findings and indicate that several facets of sleep behavior during late childhood/early adolescence in the pre-pandemic period places adolescents at risk for elevated stress. There may be multiple pathways through which poor or insufficient sleep could predispose adolescents to higher perceived stress levels in the context of a stressor like the pandemic, including affecting coping abilities in times of crisis (Owens and Group ASW, 2014), altered affect regulation via effects on neural networks and affective/cognitive control systems (Stenson et al., 2021), or via direct sleep-stress system links (Meerlo et al., 2008). Maintaining a healthy sleep routine, including obtaining sufficient undisturbed sleep at appropriate times (Paruthi et al., 2016), can serve as a stress buffer, particularly prior to significant life-stress events. Healthy sleep plays a critical role in emotion and behavioral regulation and optimal mood (Gregory and Sadeh, 2012), while sleep problems predict poor mental health in adolescents (Johnson et al., 2006; Roberts and Duong, 2014; Gregory et al., 2009; Orchard et al., 2020; Willis and Gregory, 2015; Mrug et al., 2016).

Furthermore, in our model, persistent stress during the pandemic was predicted by pre-pandemic brain structural measures. The predictive model including structural brain measures along with sleep and demographic factors was robust, and performed as well as a model used

in prior work that relied solely on self-reported data that were mostly collected during the pandemic (Kiss et al., 2022). Brain measures are objective measures, and these results highlights the potential utility of pre-existing brain measures as early indicators for chronic stress during challenging periods such as the pandemic. It emphasizes that the brain's structural characteristics, which may be influenced by genetic, developmental, and environmental factors, can play a role in shaping an individual's stress response and susceptibility. Our data also show the importance of such pre-existing (pre-pandemic) measures beyond situational/environmental conditions during the pandemic as predictors of perceived stress.

We found that specifically smaller pre-pandemic volumes in posterior occipito-temporo-parietal cortical regions predicted continuous high levels of pandemic-related stress in the following year. The individual response to stressors is heterogeneous and depends on multiple factors, among which are maturation processes of specific brain regions during early adolescence that could contribute to enhanced susceptibility to experiencing sustained effects to stress events. Keeping with a posterior-to-anterior gradient of maturation (Mills et al., 2016; Ziegler et al., 2017), prominent age-related gray matter volume reductions occur at younger ages in occipital and parietal cortices and later during adolescence in frontal areas (Group BDC, 2012). Possibly, our results that smaller volumes in posterior regions are associated with higher stress, could reflect developmentally related differences: more developmentally-advanced adolescents who already show maturation of occipital, parietal, and temporal brain regions, systems underlying attentional, perceptual, and socioemotional skills (Tooley et al., 2022), than less developed adolescents, may be at greater risk for sustained high stress during the pandemic. In support of this possibility, we also found that a higher pubertal developmental score before the pandemic predicted experiencing persistent stress across the first year of the pandemic. Alternatively, smaller posterior cortical regions could reflect a pre-existing condition unrelated to development, such as exposure to childhood adversity. Numerous studies have demonstrated that early life trauma can lead to widespread changes in brain structure, including reductions in cortical thickness (Lim et al., 2014; De Bellis and Kuchibhatla, 2006; De Bellis et al., 2002). For example early life adversities have been associated with the thinning in the posterior cingulate cortex (Heim et al., 2013), reduced cerebellum volume (De Bellis and Kuchibhatla, 2006), and increased volumes in the superior temporal gyrus in maltreated children and adolescents (De Bellis et al., 2002). Moreover, reduced gray matter volume of the middle temporal gyrus, a region implicated in various key processes, including theory of mind (Van Veluw and Chance, 2014) and autobiographical memory retrieval (Holland et al., 2011) has been reported in children with early life adversities (De Brito et al., 2013). The involvement of these regions in stress might be related to their role in the default mode network, which is active when the mind is at rest and is thought to be involved in self-referential thinking. Chronic stress might disrupt this network, leading to changes in these regions, that could potentially contribute to increased vulnerability to stress and other mental health conditions later in life. Although our models did not account for chronically stressed individuals prior to the pandemic, other studies have shown that pre-existing mental health problems increased vulnerability during the pandemic (Singh et al., 2020). It's important to note that while these associations have been found, the relationship between brain structure and mental health is complex and bidirectional, with changes in brain structure potentially both a cause and a consequence of mental health conditions.

In addition, our results on the role of BMI for persistent stress experiences support emerging studies, including in adolescents (Pervanidou and Chrousos, 2012; Pervanidou and Chrousos, 2011), showing greater vulnerability for stress in individuals with higher body mass index (BMI). The relationship between elevated stress and higher BMI is likely bidirectional (Pervanidou and Chrousos, 2016), involving both behavioral and biological pathways. While a higher BMI may primarily

reflect normal bodily changes during puberty, it is noteworthy that children with a higher BMI prior to the pandemic were more prone to experiencing weight gain during this period (Vogel et al., 2022). Adolescents experiencing chronic stress are characterized by low adherence to a healthy lifestyle and by disturbed eating behaviors. Additionally, alterations in stress hormone secretion may contribute to elevated BMI, obesity, and associated complications (Pervanidou and Chrousos, 2012). The ABCD Study, being an ongoing longitudinal study, holds the potential to shed light on some of these questions through its follow-up years and provide valuable insights into the relationship between body mass index (BMI), stress, and associated factors, enhancing our understanding in this area.

Prior studies documented the elevated stress levels in adolescents at the early stages of the pandemic (Kiss et al., 2022; Gruber et al., 2021; Mohler-Kuo et al., 2021), however to our knowledge this is the first study that reported data about stress trajectories over multiple time points during the first year of the pandemic, and that is especially considering sleep and neuroimaging predictors in a large sample of adolescents. Nonetheless, the following study limitations should also be considered: Our study cannot delineate causal relationships between the predictors and the stress. Further, low variable importance for the factors that are not listed in our top list does not necessarily imply that they are weakly related to the outcome, just that they do not contribute to outcome prediction given all the other variables in the simultaneous model. For example, age and sex are included as inputs in the model but are not in the top 20 significant predictors. Rather, pubertal development was an important predictor and could encompass variability from sex (with females typically maturing earlier than males) and age (older age is associated with more advanced pubertal development). This suggests that the effects of sex may be absorbed or mediated by differences in pubertal development. While we identified brain structural measures that predicted persistent stress during the pandemic, the current analysis cannot determine pathways of how or why these factors are linked or determine whether rate of developmental change in brain structure is critical for susceptibility to stress over and above structural measures at a single pre-pandemic timepoint. Despite using a demographically diverse cohort, the generalizability of the results is limited by the fact that the sample is not necessarily representative of the US population, and we only included a subsample here who had sufficient data from the pre-pandemic ABCD assessments and COVID-19 surveys. The COVID-19 pandemic may have impacted participants differently, and the heterogeneity in the experience or severity of this impact was not specifically examined or included in the models within the scope of this study. In addition, the self-reported, and parent reported (pubertal development) questionnaires could have introduced bias from social desirability and recall period (Althubaiti, 2016) and did not assess the presence of chronic stress. We used the 4-item PSS, which is the shortened version of the PSS-10 and was designed for quick assessment (Cohen et al., 1983), as part of the COVID Rapid Response Survey. While it captures a general sense of perceived stress, it may have limitations and lack the depth and nuance provided by the longer versions. Future research is required to consider the relative importance for pandemic-related stress and mental health problems of rate of change in functional and structural brain measures and behaviors like sleep across development, as well as the importance of pre-existing childhood exposure to trauma or other chronic stressors.

5. Conclusions

The results highlight the role of sleep and brain structure in early adolescence for building resilience (vs. vulnerability) towards chronic stressors. Adding sleep assessment into the clinical routine and asking adolescents about sleep could be critical for early intervention.

CRediT authorship contribution statement

OK: Conceptualization, Methodology, Formal analysis, Visualization, Writing - original draft, Writing - review & editing; ZQ: Methodology, Formal analysis, Visualization, Writing - original draft; FCB, EMM: Investigation, Writing - review & editing; BM: Conceptualization, Formal analysis, Funding acquisition, Writing - review & editing; All authors contributed data, critically reviewed the manuscript, and approved the final manuscript for submission.

Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2023.10.158>.

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