Title

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Journal

Journal of Behavioral Addictions, 12(1)

ISSN

2062-5871

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Publication Date

2023-03-30

DOI

10.1556/2006.2023.00006

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Journal of Behavioral Addictions

12 (2023) 1, 80–93

DOI:
10.1556/2006.2023.00006

FULL-LENGTH REPORT

Brain structural co-development is associated with internalizing symptoms two years later in the ABCD cohort

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Received: November 2, 2022 • Revised manuscript received: January 23, 2023 • Accepted: February 13, 2023
Published online: March 20, 2023

ABSTRACT

Background and aims: About 1/3 of youth spend more than four hours/day engaged in screen media activity (SMA). This investigation utilized longitudinal brain imaging and mediation analyses to examine relationships among SMA, brain patterns, and internalizing problems. *Methods:* Data from Adolescent Brain Cognitive Development (ABCD) participants with baseline and two-year follow-up structural imaging data that passed quality control (N = 5,166; 2,385 girls) were analyzed. Joint and Individual Variation Explained (JIVE) identified a brain co-development pattern among 221 brain features (i.e., differences in surface area, thickness, or cortical and subcortical gray-matter volume between baseline and two-year-follow-up data). Generalized linear mixed-effect models investigated associations between baseline SMA, structural co-development and internalizing and externalizing psychopathology at two-year follow-up. *Results:* SMA at baseline was related to internalizing psychopathology at year 2 ($\beta = 0.020, SE = 0.008, P = 0.014$) and a structural co-development pattern ($\beta = 0.015, SE = 0.007, P = 0.029$), where the co-development pattern suggested that rates of change in gray-matter volumes of the brainstem, gray-matter volumes and/or cortical thickness measures of bilateral superior frontal, rostral middle frontal, inferior parietal, and inferior temporal regions were more similar than those in other regions. This component partially mediated the relationship between baseline SMA and future internalizing problems (indirect effect = 0.020, P-value = 0.043, proportion mediated: 2.24%). *Discussion and conclusions:* Greater youth engagement in SMA at ages 9–10 years statistically predicted higher levels of internalizing two years later. This association was mediated by cortical-brainstem circuitry, albeit with relatively small effect sizes. The findings may help delineate processes contributing to internalizing behaviors and assist in identifying individuals at greater risk for such problems.

KEYWORDS

screen media activity, addictive behaviors, brain co-development pattern, internalizing behavior, substance use problems, addiction circuit

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INTRODUCTION

Screen media activity (SMA) is among the most common recreational behaviors of youth, and its relationships to health and disease have been debated. Both better (Chaarani et al.,

2022; Sauce et al., 2022) and worse (Fors & Barch, 2019; Sanders, Parent, Forehand, Sullivan, & Jones, 2016; Twenge & Campbell, 2018; Zhao et al., 2022) health measures have been associated with SMA. Although the impact of SMA on mental health may be modest, the processes that contribute to these associations remain poorly understood. Findings relating the extent of SMA to psychopathology across different developmental stages have been mixed (Eirich et al., 2022; Neville, McArthur, Eirich, Lakes, & Madigan, 2021). More recently, several studies (Kanai et al., 2012; Paulus et al., 2019; Su, Han, Yu, Wu, & Potenza, 2020; Von Der Heide, Vyas, & Olson, 2014; Zhao et al., 2022) support the hypothesis that SMA may alter brain structure and function. This view is in line with the general observation (Alexander-Bloch, Giedd, & Bullmore, 2013) that human brains have evolved to dynamically and adaptively reorganize network structures along common developmental paths in responses to environmental characteristics. There is also some evidence that youth who engage in high-frequency SMA may do so to the exclusion of other activities or schoolwork (Adelantado-Renau et al., 2019), altering their developmental trajectories and leading to depression, anxiety and other concerns. Alternatively, individuals with mental health concerns may seek escape through SMA (Eden, Johnson, Reinecke, & Grady, 2020; Nabi, Perez Torres, & Prestin, 2017; Wolfers & Schneider, 2021). Therefore, more longitudinal studies are needed to examine these possibilities (Gonzalez-Bueso et al., 2018).

Cross-sectional analyses of the ABCD data have associated various patterns of SMA with structural brain characteristics (Paulus et al., 2019). In addition, cortical-subcortical structural covariation among regions in a thalamus-prefrontal-cortex (PFC)-brainstem circuit has been related to SMA and externalizing behaviors in children (Zhao et al., 2022). Interestingly, a virtually identical thalamus-PFC-brainstem circuitry had been linked previously in adults to early onset of alcohol use (Zhao, Constable, Hien, Chung, & Potenza, 2021), which opens the possibility that potential risk factors for extensive SMA share common structural neural substrates with those for substance-use disorders (SUDs) (Zhao et al., 2022). Other data linking online social networks to gray-matter (GM) density in the amygdala (Kanai et al., 2012; Von Der Heide et al., 2014) suggest that popular non-gaming forms of SMA (e.g., social media use, a possible concern particularly for girls and women (Su et al., 2020)) may impact developing brains (Crone & Konijn, 2018). Certain types and patterns of SMA (e.g., high-frequency gaming that is typical of IGD) have been linked to psychopathology (Gonzalez-Bueso et al., 2018) as well as more positive measures of cognitive functioning (Chaarani et al., 2022; Sauce et al., 2022). While research criteria exist for IGD in DSM-5 and gaming disorder is included in the ICD-11 (Billieux et al., 2017; King & Potenza, 2019; Potenza, 2018; Raffin et al., 2021; Saunders et al., 2017; Yao et al., 2017), other internet behaviors relating to other online behaviors (social networking, pornography viewing and buying/shopping) have been considered as the bases for possible disorders (Brand et al., 2020). Together, further study is needed of SMA and its links to brain structure and function, as well as other developmental outcomes, in large-scale longitudinal studies.

Individual variations in associations between certain behaviors and structural brain characteristics may reflect individual differences in brain organization (i.e., how different parts of the brain work in conjunction). From a developmental perspective, the brain is characterized by more synapses in infancy and early childhood, followed by decreases related to active synaptic pruning during later childhood, adolescence, and early adulthood (Johnson, Blum, & Giedd, 2009; Lenroot & Giedd, 2006). Synaptic pruning is a process of eliminating less-used synapses and strengthening frequently used connections. Despite multiple factors (e.g., genetics, nutrition, socioeconomic status) contributing to brain development, it has been suggested that synaptic pruning occurring between early childhood and adulthood is largely activity-/experience-dependent and influenced by gene–environment interactions (Tierney & Nelson, 2009). Behaviorally, across different developmental stages, excessive SMA has been associated with negative health measures including obesity (Robinson et al., 2017), depression (Boers et al., 2019; Madhav, Sherchand, & Sherchan, 2017), poor academic performance (Adelantado-Renau et al., 2019), and delays in achieving important developmental milestones in language, communication, and other domains (Madigan et al., 2019). Thus, there is a need to investigate whether and how high-frequency SMA may directly impact brain development and potentially result in worse health outcomes using longitudinal data.

This investigation analyzed longitudinal data from the Adolescent Brain Cognitive Development study (Volkow et al., 2018) to investigate whether covariation patterns of changes in cortical and subcortical morphological measures (i.e., brain co-development patterns) were related to SMA, internalizing problems, and externalizing problems at baseline. Based on the identification of such a covariation, we next tested whether the brain co-development pattern mediated the relationship between baseline total screen time and future psychopathological (internalizing, externalizing) concerns. We hypothesized that high-frequency SMA would relate to changes in cortical-subcortical co-development involving regions in a thalamus-PFC-brainstem circuit (Zhao et al., 2021), which in turn would lead to more internalizing and externalizing problems two years later. We further explored gender-related differences related to brain structural covariation patterns and SMA and internalizing and externalizing behaviors in these domains given the relevance of sex as a biological variable and gender-related differences in brain structure (Kaczkurkin, Raznahan, & Satterthwaite, 2019), SMA (Su et al., 2020) and internalizing and externalizing behaviors (Gutman & Codiroli McMaster, 2020; Hicks et al., 2007).

METHODS

Data source

This investigation used data from the ABCD study (Release 3.0) (Volkow et al., 2018), an ongoing large-scale longitudinal

cohort study following more than 11,000 participants aged 9–10 years at baseline, recruited from 21 sites across the US. Data from both baseline (T0) and two-year follow-up (T2) were analyzed. Participants without passing structural imaging quality control (QC) measures at both time points and with missing age, sex/gender, race, screen time, and psychopathology measures were excluded from the main analyses, resulting in a final sample size of 5,166 participants (2,385 girls).

Imaging preprocessing

The structural MRI (sMRI) data of all participants were collected on one of three types of 3T scanners (Siemens Prisma, General Electric 750, and Philips) (Casey et al., 2018). The raw brain imaging data were pre-processed by the ABCD investigative team using FreeSurfer with pipelines specifically designed to address several known challenges (e.g., head motion, distortion, and intensity inhomogeneity) in MRI data pre-processing (Hagler et al., 2019). For example, prospective motion correction (Tisdall et al., 2012; White et al., 2010) has been implemented to reduce motion-related image degradation (an issue particularly significant in image data acquisition with children). In the post-pre-processing quality control (QC) step, for each cortical surface reconstruction, trained technicians reviewed cortical surface reconstruction and assigned a value ranging from 0 (i.e., absent) to 3 (i.e., severe) to indicate the accuracy of reconstruction in terms of motion, intensity inhomogeneity, white-matter underestimation, pial overestimation, and magnetic-susceptibility artifacts. Participants were excluded from analyses if their sMRI data at T0 and/or T2 were rated as 'severe' in any of the aforementioned QC criteria (Hagler et al., 2019). Structural brain features, including surface area, thickness, and gray-matter volume (GMV), were measured for 68 cortical regions based on the Desikan-Killiany atlas (Desikan et al., 2006). Subcortical GMV (including bilateral amygdala, caudate, hippocampus, nucleus accumbens, putamen, pallidum, thalamus proper, ventral diencephalon, and brainstem) were also included in analyses.

Measures

SMA The primary SMA measure was baseline youth self-reported total number of hours spent on non-school-related SMAs on typical weekdays (i.e., Mondays through Fridays) and weekends (i.e., Saturday and Sunday) in the past year. Main types of SMA activities included watching TV shows/movies, watching videos, playing video games, texting on an electronic device, visiting social networking sites, and video-chatting. Data from the parent screentime survey at T2 were used to provide a general view of types of devices participants owned, most frequently used screen media, and parental perceptions of their children's SMA.

Psychopathology measures were based on internalizing and externalizing symptoms from the parent-reported Child Behavior Checklist (CBCL) (Achenbach, 2009). Specifically, the CBCL measures include 118 item-level questions about children's behaviors in the past six months. Parents were asked to mark on a three-point Likert scale, with items rated in terms of how much the behavior is "true" for the respondent (0 = not true, 1 = somewhat true, and 2 = very true). Data were aggregated into eight empirically based syndrome scales including withdrawn/depressed, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. The internalizing problem score was the average of the first four subscale scores, and the externalizing problem score was the average of the rule-breaking and aggressive behavior subscales. The CBCL has been widely used to measure youth general mental illness/psychopathology in both clinical and research settings (Ebesutani et al., 2010). It has high test-retest reliability and excellent internal consistency (Achenbach, 2009). The Cronbach's alphas for the CBCL syndrome scales range from 0.78 to 0.94. In this study, the Cronbach's alphas were 0.89 and 0.90 for the internalizing and externalizing behaviors, respectively. Raw scores were used, with higher scores reflecting more severe psychopathology.

Statistical analyses

Prior to statistical modeling, group differences on demographic characteristics and parental perception of participants' SMA behaviors were assessed by ANOVAs for continuous measures, Chi-square tests for categorical measures, and Cochran-Armitage trend tests for binary measures, respectively. Tests were adjusted for multiple comparison problems by setting the False Discovery Rate at a 0.05 level.

Cortical and subcortical structural co-development patterns were characterized by the Joint and Individual Variance Explained (JIVE) approach (Lock et al., 2013). JIVE extends principal component analysis to detect common and distinct covariation patterns among multiple data sources. This method has been previously used to detect robust brain structural covariation patterns across different developmental stages (Zhao, Klein, Castellanos, & Milham, 2019), and detected cross-sectional structural covariation patterns have been linked in adults to alcohol initiation prior to age 21 (Zhao et al., 2021) and in children to SMA (Zhao et al., 2022). In this investigation, brain development measures were defined as differences in structural features between T2 and T0. JIVE analyses were performed using brain development measures from different morphological features including cortical and subcortical GM volume, thickness, and surface area. The joint components estimated by the JIVE stand for brain co-development patterns. Here, the optimal numbers of joint and individual components were determined via permutation tests (Lock et al., 2013). Here, we aimed to understand the effects of baseline SMA on coordinated brain co-development and their associations with subsequent internalizing and externalizing behaviors.

Toward these goals, linear mixed models (LMMs) with study site and family as random effects were used to assess whether: 1) SMA as measured by total screen time was associated with psychopathology two years later, and 2) the

effects of SMA were mediated by the identified brain co-development pattern (i.e., the JIVE component). Analyses were performed in R using functions from the lme4 package. Site and family were included as random effects. All mixed effects models included age, sex/gender, race (a four-level variable), parental highest education level, family income, handedness, and the whole brain volume as covariates. R^2 reported in this study was the marginal R^2 (Nakagawa & Schielzeth, 2013), representing the proportion of variance explained by the variable of interest. A small portion of participants had missing family income and/or parental education level. The missing data were imputed using the predictive mean matching method implemented in the R package MICE (Zhang, 2016). Results from analyses of samples with listwise deletion agreed with the results using imputed data.

Ethics

The current study involved analyses of deidentified data from the ABCD study and was exempted by the Yale IRB, the Yale Human Investigation Committee. Thus, the study is in accordance with the principles of the Declaration of Helsinki.

RESULTS

Sample characteristics and parental perceptions of participants' SMA

Demographic information of the 5,166 participants, among them 2,385 (46.17%) were female, showed no significant effects of sex/gender on age, race/ethnicity, household income, or parental education (Table 1). In terms of parental perceptions of participants' SMA (Table 2), on average, boys reported more SMA (27.33 ± 21.04 h) than girls (23.04 ± 19.81 h; P-value < 0.001). The top three most popular electronic devices owned by participants were cell phones (n = 3,024, 62.0%), tablets (n = 2,335, 45.2%), and laptops (n = 1,650, 32.0%). The top three most frequently used screen media included televisions (n = 3,093, 59.9%), cell phones (n = 2,867, 55.5%), and video games (n = 2,437, 47.2%). Lastly, most parents worried, to some extent, that their children spent too much time online (59.0%) and would view inappropriate things online (61.0%), but only a small portion of parents worried that their children would post inappropriate things online (17.7%). Finally, we note that basic demographic information between participants being analyzed in this study were significantly different from these whose brain imaging data have yet to be released (Table A1 in Appendix).

Structural co-development patterns in early adolescence

JIVE analysis of changes in brain features between two years following baseline (T2) and baseline (T0) identified one joint component that explained 11.9% of the total variation across all 221 brain features (Fig. 1). The components derived from boys and girls correlated highly with those derived from the entire sample (r = 0.98–0.99). Specifically, this global brain co-development pattern accounted for around 20% of variation in both cortical thickness and GMV, 5% of variation in subcortical GMV, and 1% of variation in surface area.

Figure 2A highlights the top 10% of brain structures with the largest loading magnitudes in the joint component. These regions included GMV of the brainstem, left putamen, and bilateral rostral middle frontal, superior frontal, inferior and superior parietal, inferior and middle temporal, left precentral and left superior temporal cortices, and cortical thickness of the bilateral entorhinal region and frontal and temporal poles. Pairwise correlations among brain features with large magnitudes (mean = 0.23, SD = 0.12) were

Table 1. Demographic characteristics

Variable	Girls	Boys	Test Statistics[1]	P-value[2]
Sample size (n, %)	2,385 (46.17%)	2,781 (53.83%)		
Age (Months; mean ± SD)	119.01 ± 7.30	119.57 ± 7.45	2.744	0.075
Race (n, %)			10.109	1,000
White	1,607 (67.41%)	1,988 (71.49%)		
Black	309 (12.96%)	314 (11.29%)		
Asian	56 (2.35%)	56 (2.01%)		
Other/Mixed	412 (17.28%)	423 (15.21%)		
Parental highest education level (n, %)			0.789	1,000
Up to HS graduation/GED	274 (11.50%)	306 (11.02%)		
Some College	621 (26.07%)	710 (25.57%)		
Bachelor's Degree	655 (27.50%)	762 (27.44%)		
Post-Graduate Degree	832 (34.93%)	999 (35.97%)		
Household Income (n, %)			2.623	1,000
[<$50,000]	610 (27.38%)	676 (26.18%)		
[≥$50,000 & <$100,000]	691 (31.01%)	772 (29.90%)		
[≥$100,000]	927 (41.61%)	1,134 (43.92%)		

[1]: T-statistic was reported for continuous measure, and Chi-square test statistic was reported for categorical outcomes.
[2]: FDR adjusted P-values were reported.

Table 2. Parental reports of children's screen media activity

Variable	Girls	Boys	Test Statistics[1]	*P*-value[2]
Sample size (*n*, %)	2,385 (46.17%)	2,781 (53.83%)		
Baseline total screen time (Hours; mean ± SD)	23.04 ± 19.81	27.33 ± 21.04	7.510	<0.001
Internalizing scores at two-year follow-up (mean ± SD)	5.17 ± 5.82	4.75 ± 5.48	−2.708	0.075
Externalizing scores at two-year follow-up (mean ± SD)	3.47 ± 5.18	4.42 ± 5.74	6.196	<0.001
Number of devices owned (*n*, %)			25.334	0.002
0	218 (9.14%)	333 (11.97%)		
1	942 (39.51%)	1,187 (42.68%)		
2	788 (33.05%)	853 (30.67%)		
3	436 (18.29%)	408 (14.67%)		
Number of frequently visited social media sites (*n*, %)			115.688	<0.001
0	17 (0.71%)	13 (0.47%)		
1	796 (33.39%)	662 (23.80%)		
2	673 (28.23%)	650 (23.37%)		
≥3	898 (37.67%)	1,456 (52.36%)		
Parental concerns regarding their children (*n*, %)				
spends too much time online	1,372 (57.65%)	1,669 (60.19%)	3.313	1,000
will view inappropriate things online	1,374 (57.83%)	1,762 (63.68%)	18.745	0.003
will post inappropriate things online	392 (16.47%)	522 (18.81%)	4.651	1,000
Devices owned (n, %)				
Cellular Phone	1,594 (66.86%)	1,610 (57.89%)	43.468	<0.001
Tablet	1,096 (45.97%)	1,239 (44.55%)	0.990	1,000
Laptop computer	779 (32.68%)	871 (31.32%)	1.025	1,000
Frequently used screen media (*n*, %)				
Television	1,478 (62.00%)	1,615 (58.07%)	8.065	0.451
Video games	514 (21.56%)	1,923 (69.15%)	1164.5	<0.001
Cellular phone	1,498 (62.84%)	1,369 (49.23%)	95.706	<0.001
Tablet	913 (38.30%)	962 (34.59%)	7.461	0.511
Handheld video game devices	130 (5.45%)	440 (15.82%)	139.51	<0.001
Computer/laptop	846 (35.49%)	1,038 (37.32%)	1.793	1,000

[1]: T-statistic was reported for continuous measure, and Chi-square test statistic was reported for categorical outcomes.
[2]: FDR adjusted *P*-values were reported.

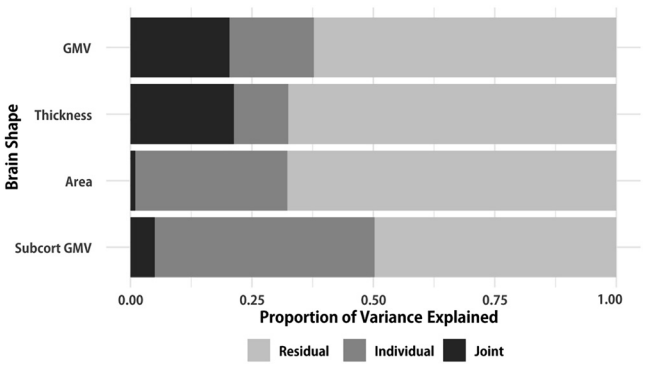

Fig. 1. Proportion of the variance of brain-feature change scores explained by JIVE components. The brain co-development pattern accounted for around 20% of variation in both cortical thickness and GMV, 5% of variation in subcortical GMV, and 1% of variation in surface area. A large portion of total variation was explained by the residuals, indicating significant individual variations in brain development. Subcort = subcortical

stronger than those among features with small loading magnitudes (mean = 0.08, SD = 0.13) in the joint component (Fig. 3), indicating brain features with large magnitudes in the joint component co-develop together more closely than the other brain features. JIVE analyses supported the covariation of brain development among key regions in our hypothesized thalamus-PFC-brainstem circuitry that has been previously linked in adults to early initiation of alcohol use (Zhao et al., 2021) and in children to SMA (Zhao et al., 2022) in cross-sectional studies, albeit perhaps with less loading from the thalamus. In bivariate association analyses, this brain co-development pattern correlated with baseline total screen time and internalizing behavior at two-year follow-up with Pearson correlations of 0.04 each (Table A2 in Appendix).

Controlling for potentially confounding variables, higher baseline total screen time was associated with larger joint component scores ($\beta = 0.015, SE = 0.007, P = 0.029$), and baseline total screen time explained 0.1% of variation in the

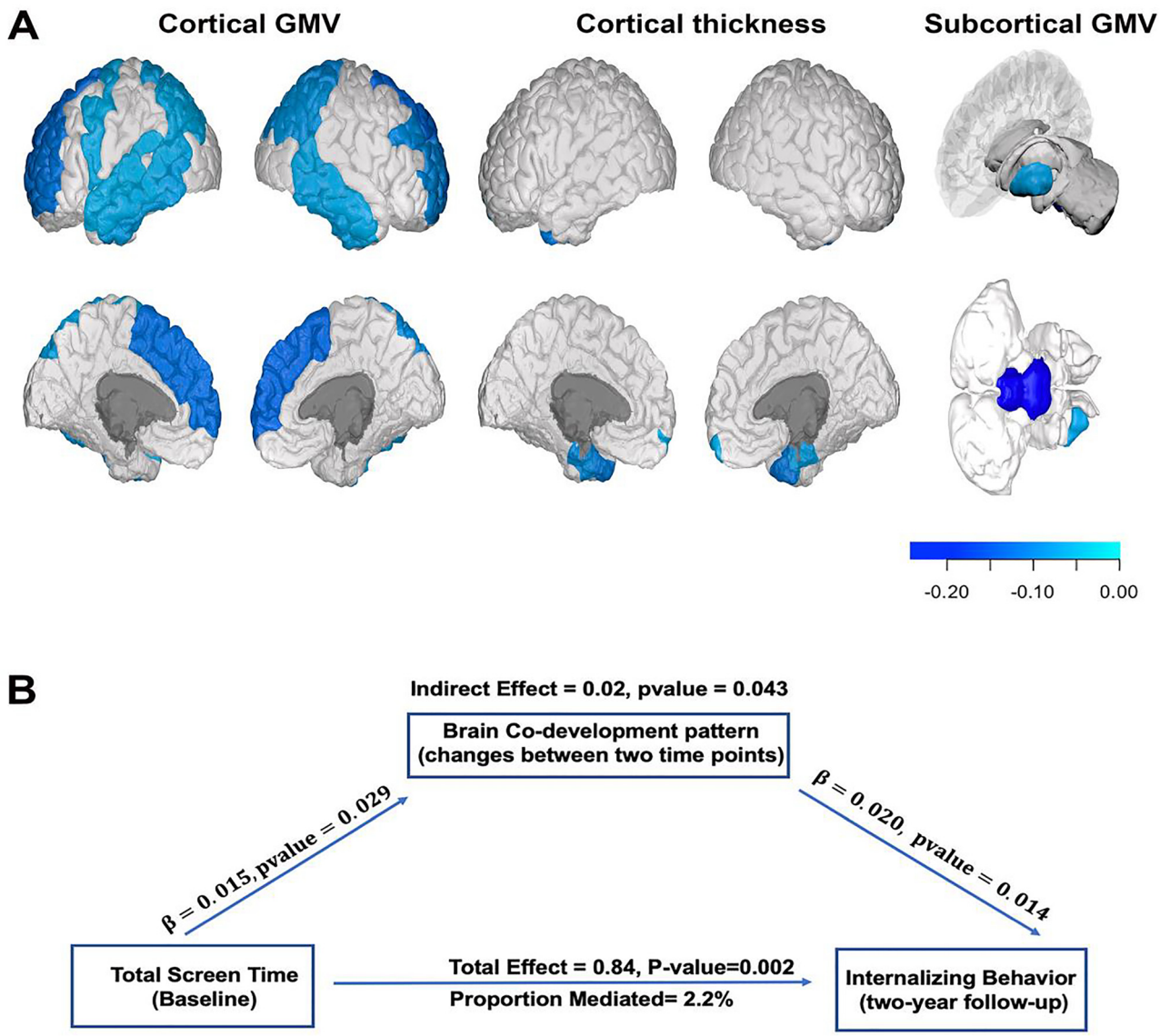

Fig. 2 (A) Plots are shown of brain regions in the brain co-development pattern with loadings larger than 0.105 (approximately corresponding to the top 10% of regions with the largest loading magnitudes). This JIVE component was related to both baseline screen time (β = 0.015, P = 0.029) and internalizing behaviors at two-year follow-up (β = 0.020, P = 0.014). (B) The brain co-developmental pattern partially mediated the effects of baseline screen time on internalizing behavior at two-year follow-up, explaining approximately 2.2% of the SMA effects on future internalizing behavior. The direct effect of baseline total screen time on internalizing behavior two years later was estimated to be 0.82

joint component. To facilitate the interpretation, percentage of brain changes in regions with large magnitudes in the joint component are presented in Table A3. We divided participants into those with low-frequency (≤1 h/day), moderate-frequency (>1 h/day and ≤ 7 h/day), or high-frequency screen use (> 7 h/day) based on findings from a large-scale study (Twenge & Campbell, 2018). Those with high-frequency SMA were reported to have at least twice the likelihood of experiencing a diverse range of psychological problems including anxiety and depression compared to those with no more than one hour/day SMA (Twenge & Campbell, 2018). In this study, compared to individuals with low-frequency and moderate-frequency SMA, those with high-frequency SMA demonstrated slower expansion in subcortical regions (e.g., brainstem, left putamen). Mean (SD) percentage of change in these regions was 2.11% (0.035) for high-frequency and 2.67% (0.036) for low-frequency SMA (P-value = 0.01). In contrast, individuals with high-frequency SMA had greater GMV reduction (−2.00% (0.034)) as opposed to −1.52% (0.027) for those with low-frequency SMA (P-value = 0.02) in key regions (e.g., superior frontal and rostral middle frontal cortices) in the hypothesized thalamus-PFC-brainstem circuitry. This global structural co-development pattern provided a proxy measure of imbalanced brain structural development (mainly in GMV and cortical thickness) among cortical and subcortical regions. Baseline

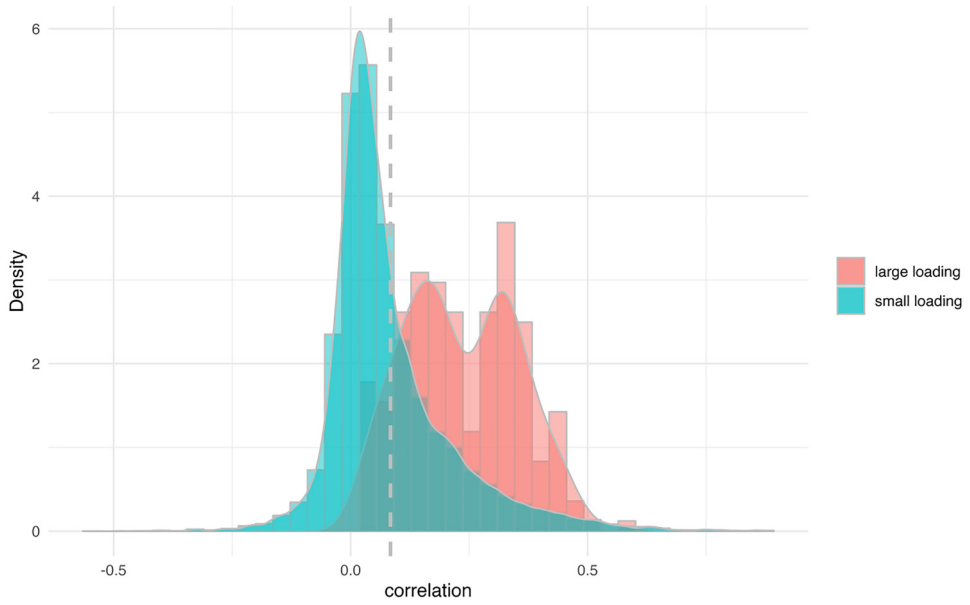

Fig. 3 Compared to features with small loading magnitudes, pairwise correlation of brain change scores were much larger among features with large loading magnitudes in the JIVE joint component. The dotted line stands for the mean correlation coefficient across all pairwise correlations

internalizing ($\beta = 0.008, SE = 0.025, P = 0.74$) and externalizing ($\beta = -0.004, SE = 0.023, P = 0.88$) scores were not associated with the joint component score.

Mediation models investigating baseline SMA relationships with internalizing and externalizing behaviors two years later

Higher baseline total SMA was associated with higher internalizing ($\beta = 0.013, SE = 0.004, P = 0.002$) and externalizing ($\beta = 0.024, SE = 0.004, P<0.001$) behaviors two-years later, suggesting that an increase in screen time by one hour/day corresponded to an increase of internalizing scores by 0.093 points and externalizing scores by 0.16 points two years later. Controlling for baseline total screen time, higher joint component scores were associated with higher internalizing scores two years later ($\beta = 0.020, SE = 0.008, P = 0.014$, Fig. 2B) but not with externalizing scores ($\beta = 0.009, SE = 0.008, P = 0.26$). Subsequent mediation analysis showed that the joint component partially mediated the effects of total screen time on internalizing behavior two years later (indirect effect = 0.020, 95% CI: (0.0003, 0.05), *P*-value = 0.043, proportion mediated: 2.24%, Fig. 2B) but not externalizing behavior (indirect effect = 0.009, 95% CI: (−0.007, 0.03), *P*-value = 0.29, proportion mediated: 0.51%).

Gender-related differences

Tables 1 and 2 summarize differences in boys and girls. Boys showed more externalizing behaviors than girls (boys: 4.42 ± 5.74, girls: 3.47 ± 5.18; *P*-value < 0.001), SMA involving videogames (boys: 69.15%, girls: 21.56%; *P*-value < 0.001) and visitation of social media sites (boys: 52.36% frequently visited at least three sites, girls: 37.67%; *P*-value < 0.001). Girls reported more engagement with cellular phones (boys: 49.23%, girls: 62.84%; *P*-value < 0.001). Boys and girls did not differ on internalizing scores (boys: 4.75 ± 5.48, girls: 5.17 ± 5.82; *P*-value = 0.075). Parents were more likely to have concerns that boys more so than girls would view inappropriate material online (boys: 63.68%, girls: 57.83%; *P*-value = 0.003). The extent to which this may apply to certain forms of SMA more prevalent in males (e.g., pornography viewing) or other factors requires further study.

We note there were no significant differences between boys and girls on SMA/future-psychopathology relationships and on brain co-development-pattern/future-psychopathology relationships, respectively. SMA explained a small amount of variation on future internalizing (R^2 = 0.30% in boys vs R^2 = 0.10% in girls) and externalizing (R^2 = 0.88% in boys vs R^2 = 0.54% in girls) behaviors. A small (R^2 = 0.13% in boys vs R^2 = 0.14% in girls) but significant brain co-development pattern effect on future internalizing behavior was observed in both boys and girls.

DISCUSSION

This investigation, which examined in youth 9–10 years of age, the relationships among baseline SMA, brain structural co-development, and psychopathological problems two years later, yielded three main results. First, more extensive baseline SMA was related to greater internalizing and externalizing behaviors two years later. Second, there was a pattern of structural brain co-development indicating that brain features within a medial PFC-brainstem circuit (Siciliano et al., 2019) previously linked to early alcohol use in

adult humans and SMA in children shared similar structural features. Third, this pattern of structural brain co-development was associated with baseline SMA and mediated relationships with subsequent internalizing but not externalizing behaviors two years later.

This investigation focused on cortical and subcortical covariation patterns among brain structural changes from baseline (T0 at ages 9–10 years) to a two-year follow-up (T2 at ages 11–12 years). The data showed that in general subcortical GMV and surface area continued to expand from baseline to two-year follow-up, while thickness and GMV in the cortical regions on average started to decline (Table A1). The observed structural expansion/reduction pattern was in line with neurodevelopmental milestones (Bethlehem et al., 2022) in late childhood and early adolescence. Our JIVE analyses indicated that 61.8% of total variation (Fig. 1) in brain structural changes cannot be explained by any systematic variation patterns among the tested regions, suggesting that there exists extensive individual variability in brain structural development. Despite these individual differences, JIVE analyses identified a brain structural co-development pattern across various structural features and brain regions. This structural co-development pattern suggested that participants with high-frequency SMA had a greater level of brain development imbalance among cortical and subcortical regions, especially those implicated in a medial-PFC-brainstem circuit (Siciliano et al., 2019) and key regions in a thalamus-PFC-brainstem circuit (Zhao et al., 2021, 2022). This finding is important because these circuits have been linked to compulsive drinking in mice (Siciliano et al., 2019), early initiation of alcohol use in young adult humans (Zhao et al., 2021), and SMA in human children (Zhao et al., 2022) in cross-sectional studies. Our data suggest abnormal imbalance in brain development (i.e., slower subcortical GMV expansion and greater cortical GMV reduction in individuals with high versus low SMA) in key regions involved in the aforementioned neural circuits. This finding is in line prior data linking risky behavior with imbalances in brain development. Based on previous studies (Casey, Getz, & Galvan, 2008; Constantinidis & Luna, 2019; Kuss, Pontes, & Griffiths, 2018; Luna & Wright, 2016; Somerville, Jones, & Casey, 2010), neurodevelopmental changes during the second decade of life are characterized by greater cortical control over subcortical circuits. These changes are accompanied by pruning of cortical neurons leading to thinning of cortical GM. Thus, alterations in these processes may lead to less cognitive control over subcortical circuits, which has been proposed to be a basis for an imbalance in brain development related to risk behaviors and psychopathology.

Using the ABCD longitudinal data, our findings demonstrated that extensive SMA (i.e., more than seven hours per day) may impact brain development processes, leading to imbalanced brain development of specific cortical and subcortical regions. Given that baseline SMA, but not internalizing and externalizing behaviors, was associated with the global structural co-development pattern, along with the results from the mediation analyses, our findings suggest that imbalanced brain structural co-development among cortical and subcortical regions may consequently lead to heightened internalizing behavior, and not vice versa. This result is not necessarily surprising given that brain development is a complex process including genetics, environmental and lifestyle factors, sleep disturbances, and mental health issues that may contribute to and shape brain development in children and adolescents. For example, in cross-sectional studies, smaller brainstem GMVs among participants with mild traumatic brain injuries (Kim et al., 2021) and among children with autism (Hashimoto et al., 1992) have been reported. In addition, higher levels of physical activity have been associated with increased cortical thickness in older adults (Lee et al., 2016; Raffin et al., 2021). However, in children and adolescents, cortical thickness and/or GMV reduction have been associated with both higher physical activity and better academic achievement (Chaddock-Heyman et al., 2015), childhood abuse (Gold et al., 2016), and impulsive choice in adolescents (Pehlivanova et al., 2018). In short, multiple findings suggest that brain structures change dynamically across the life course (Sowell et al., 1999) in response to environmental demands (Spear, 2000).

Children and adolescents experience critical developmental brain changes. According to the selective-elimination hypothesis (Changeux & Danchin, 1976), synaptic pruning during adolescence is highly specific and activity-dependent. Brain connections that are rarely used will be selectively pruned to make the brain work more efficiently, and connections that are frequently used will become strengthened. Therefore, children and adolescents have opportunities to make their brains healthier by spending their time wisely on activities that promote good cognitive and mental health outcomes. The extent to which SMA may promote positive or negative outcomes during development has been debated. However, high-frequency or excessive SMA has been more consistently linked to negative health measures, and the current investigation suggests a possible brain mechanism accounting for some of this relationship.

In partial support of our hypothesis, we found that the brain structural co-variation pattern mediated the relationship between SMA in 9-10-year-old children and internalizing but not externalizing psychopathology two years later. However, SMA at baseline was linked to both internalizing and externalizing psychopathology two years later. These findings suggest that the relationship between SMA and externalizing behaviors may be linked through independent brain mechanisms at this developmental period, and future studies should seek to identify such mechanisms. Nonetheless, the finding of this link with subsequent internalizing psychopathology may be particularly clinically relevant given links between high-frequency SMA or internet addiction and internalizing disorders like depression (Liu et al., 2022; Lozano-Blasco & Cortés-Pascual, 2020). Taken together, individuals who engage in high-frequency SMA (i.e., >7 h a day) also showed cortical and subcortical developmental patterns that were associated with future internalizing behaviors. We acknowledge that the strength of

the SMA and brain co-development relationship was relatively weak, and the size of the mediation effect was small. Therefore, our results should be interpreted with caution.

This investigation has limitations. First, SMA data were based on youth self-report. Objective screentime data have advantages, as the self-report data could be influenced by individual differences in psychological and contextual factors (Hodes & Thomas, 2021), resulting in overestimation or underestimation of actual screentime. Importantly, the amount of screentime is not equivalent to the extent of problematic use (Twenge & Farley, 2021), especially in children and adolescents who may not have full control over their access to media (e.g., related to different parenting approaches or school rules). Some types of screen time may be more problematic and disruptive and carry greater potential for future disordered use. Thus, it is important to consider different screen modalities beyond total screen use and additional potential influences in future studies. Second, whether SMA-related brain co-development pattern in this investigation can be generalized to other age groups or to the full ABCD or other samples needs to be further investigated. The ABCD participants whose data have yet to be released at the time of this study were in general younger and had a higher portion of non-White and lower-income-family participants (Table A1). Thus, future study of the ABCD data appears indicated. Additionally, the impact of screen exposure on brain co-development pattern may be age-dependent, as synaptic pruning in different brain regions occurs at different age periods (Kolb & Gibb, 2011), also suggesting the need for additional studies. Third, in cross-sectional analyses, we have found that GMV of the thalamus proper covaries with GMV of the brainstem and prefrontal regions across different ages (Zhao et al., 2021, 2022). It is currently unclear why the rates of change in thalamic GMV deviate from those in the brainstem and superior and rostral middle frontal regions, and this should be further explored in future studies. Fourth, we only explored the impact of SMA on future psychopathological problems. How SMA may interact with other potential risk factors, such as family conflict (Mathiesen, Sanson, Stoolmiller, & Karevold, 2009), harsh parenting style (Pinquart, 2017), and adverse childhood events (Bolger & Patterson, 2001) that may influence the development of internalizing behaviors, warrants further investigation. In addition, bidirectional relationships between SMA and psychopathology may exist (Gamez-Guadix, 2014; Jeong et al., 2019), and these should be investigated using data from future releases. Fifth, considerable gender-/sex-related differences in types of SMA were identified in this study and have been reported elsewhere (Twenge & Farley, 2021). However, the SMA-psychopathology and the SMA-brain co-development pattern relationships did not differ significantly between boys and girls. The ABCD data included participants aged 9–10 years at baseline; however, as reported elsewhere, significant changes in SMA occur during the second decade of life (Orben et al., 2022). It is possible that sex differences may emerge in the ABCD data set as participants age and experience pubertal changes. Thus, brain correlates of gender-/sex-related differences by types of SMA warrant further investigation.

In conclusion, our findings provide a deeper understanding of how SMA may affect brain development with respect to the development of internalizing psychopathology. While providing a potential brain mechanism underlying some of the relationship between SMA and subsequent internalizing problems, more effort is needed to identify other sources promoting both internalizing and externalizing psychopathology, particularly those amenable to interventions that will serve to prevent or ameliorate mental health concerns related to SMA.

Funding sources: This study was supported by grants from Children and Screens (CSDMB001) and the NIH (RF1 MH128614, R01 AA029611). The views presented in this manuscript represent those of the authors and not necessarily those of the funding agencies.

Authors' contribution: Y.Z. performed data analyses and wrote the original draft. Y.Z. and M.N.P obtained funding and conceptualized the study. M.N.P. and M.P. provided critical revisions and intellectual input. All authors have read and agreed to the published version of the manuscript. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: The authors declare no conflicts of interest. Dr. Potenza has consulted for Opiant Therapeutics, Game Day Data, Baria-Tek, the Addiction Policy Forum, AXA and Idorsia Pharmaceuticals; has been involved in a patent application with Yale University and Novartis; has received research support from Mohegan Sun Casino and the National Center for Responsible Gaming; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for and/or advised gambling and legal entities on issues related to impulse-control/addictive disorders; has provided clinical care in a problem gambling services program; has performed grant reviews for research-funding agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. Dr. Potenza is an associate editor of the Journal of Behavioral Addictions. The other authors do not report disclosures.

Acknowledgement: Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children age 9–10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA05 1016, U01DA041022, U01DA051018, U01DA051037,

U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from the NDA collection #2573 (DOI: 10.15154/1527880).

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Appendix

Table A1. Baseline demographic differences between the data currently analyzed and these to be released in the future*

Variable	Data Available (n = 5,166)	Data Not Available (n = 6,691)
Age (Months; mean ± SD)	119.31 ± 7.38	118.73 ± 7.57
Total screen time (Baseline hours; mean ± SD)	25.35 ± 20.59	27.47 ± 22.15
Internalizing score (Baseline; mean ± SD)	5.09 ± 5.48	5.00 ± 5.56
Externalizing score (Baseline; mean ± SD)	4.44 ± 5.82	4.45 ± 5.89
Gender/sex (Female; *n*, %)	2,385 (46.17%)	3,289 (49.16%)
Race (*n*, %)		
White	3,596 (69.61%)	3,914 (58.50%)
Black	623 (12.06%)	1,243 (18.58%)
Asian	112 (2.17%)	163 (2.44%)
Other/Mixed	835 (16.16%)	1,371 (20.49%)
Education Level (*n*, %)		
Up to HS graduation/GED	580 (11.24%)	1,138 (17.03%)
Some College	1,331 (25.79%)	1,742 (26.06%)
Bachelor's Degree	1,417 (27.46%)	1,595 (23.86%)
Post-Graduate Degree	1,832 (35.50%)	2,209 (33.05%)
Family Income (*n*, %)		
[<$50,000]	1,286 (26.73%)	1,944 (32.11%)
[≥$50,000 & <$100,000]	1,463 (30.41%)	1,612 (26.63%)
[≥$100,000]	2,062 (42.86%)	2,498 (41.26%)

* Samples being analyzed in this study are statistically different from these whose data yet to be released on all key baseline demographic information listed in the table.

Table A2. Bivariate associations among SMA, brain co-development pattern, and psychopathology measures

	Baseline Total Screen Time	Brain Co-development Pattern	Internalizing Problem at Baseline	Externalizing Problem at Baseline	Internalizing Problem at Two Year Follow Up
Baseline Total Screen Time					
Brain Co-development Pattern	0.04*				
Internalizing Problems at Baseline	0.07****	<0.01			
Externalizing Problems at Baseline	0.16****	−0.01	0.59****		
Internalizing Problems at Two-Year Follow-Up	0.04**	0.04**	0.65****	0.39****	
Externalizing Problems at Two-Year Follow-Up	0.14****	0.01	0.43****	0.69****	0.57****

1) FDR-adjusted *P*-values were reported here.
2) $^{****}P < 0.0001$, $^{**}P < 0.01$, $^{*}P < 0.05$

Table A3. Mean percentages of changes in brain features between baseline and two-year follow-up by total screen time usage. Participants in Low, Moderate, and High use groups on average had up to one hour per day, between one hour and less than seven hours per day, and at least seven hours per day screen time, respectively

Feature	Loading	Low (n = 632)	Moderate (n = 3,914)	High (n = 620)
GMV_brain.stem	−0.24	4.4	4.0	3.9
GMV_superiorfrontal.rh	−0.19	−1.0	−1.2	−1.5
GMV_superiorfrontal.lh	−0.18	−0.9	−1.2	−1.7
GMV_rostralmiddlefrontal.lh	−0.17	−1.6	−1.9	−2.3
Thick_temporalpole.rh	−0.17	0.2	−0.1	−0.4
Thick_temporalpole.lh	−0.17	−0.3	−0.4	−0.7
GMV_rostralmiddlefrontal.rh	−0.15	−2.0	−2.2	−2.6
GMV_superiorparietal.rh	−0.15	−3.0	−3.0	−3.5
Thick_entorhinal.lh	−0.14	0.6	−0.2	−0.4
GMV_inferiorparietal.rh	−0.14	−2.5	−2.6	−2.8
GMV_putamen.lh	−0.13	0.9	0.6	0.3
GMV_inferiortemporal.lh	−0.13	−1.0	−1.3	−1.3
Thick_entorhinal.rh	−0.13	1.0	0.9	−0.1
GMV_superiorparietal.lh	−0.12	−2.6	−2.9	−3.4
GMV_inferiortemporal.rh	−0.12	−1.0	−1.3	−1.2
GMV_middletemporal.rh	−0.12	−1.1	−1.1	−1.4
GMV_middletemporal.lh	−0.11	−0.6	−0.9	−1.2
GMV_inferiorparietal.lh	−0.11	−2.6	−2.7	−3.0
Thick_frontalpole.rh	−0.11	−2.1	−1.6	−2.0
GMV_precentral.lh	−0.11	−0.2	−0.3	−0.4
Thick_frontalpole.lh	−0.11	−2.0	−1.7	−1.9
GMV_superiortemporal.lh	−0.11	−1.1	−1.4	−1.8
GMV_thalamus.proper.lh	−0.07	3.1	2.9	3.0
GMV_thalamus.proper.rh	−0.05	1.9	1.7	1.5

**Note:* Both left and right Thalamus Proper GMV were not ranked as top features in the co-development pattern and are included here given their hypothesized involvement. Other listed measures include the brain regions contributing most substantially to the identified brain co-development pattern.