NEW RESEARCH

Multisystem Environmental Factors Elucidate Shared and Distinct Associations With Brain and Behavior in Adolescents

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Objective: Environmental factors have long been shown to influence brain structure and adolescent psychopathology. However, almost no research has included environmental factors spanning micro-to-macro-systems, brain structure, and psychopathology in an integrated framework. Here, we assessed the ways and degree to which multisystem environmental factors during late childhood are associated with subcortical volume and psychopathology during early adolescence.

Method: We used baseline, 2-year follow-up, and 3-year follow-up data from the Adolescent Brain Cognitive Development℠ Study (n = 2,766). A Bayesian latent profile analysis was applied to obtain distinct multisystem environmental profiles during late childhood. The profiles were used in a path analysis to derive their direct and indirect effects on subcortical volume and psychopathology during early adolescence.

Results: Bayesian latent profile analysis revealed 9 environmental profiles. Two distinct profiles were directly associated with greater externalizing psychopathology in adolescents: (1) adversity across family, school, and neighborhood systems, and (2) family conflict and low school involvement. In contrast, a profile of family and neighborhood affluence was directly associated with lower externalizing psychopathology. Furthermore, family/neighborhood affluence was associated with higher subcortical volume, which in turn was associated with lower externalizing and internalizing psychopathology; conversely, a family economic and neighborhood adversity profile was associated with lower subcortical volume, which in turn was associated with higher externalizing and internalizing psychopathology.

Conclusion: We identified environmental and brain-related equifinal pathways associated with externalizing and internalizing psychopathology. This work highlights the importance of considering the role of multiple systems and factors in the conceptualization and treatment of adolescent psychopathology.

Diversity & Inclusion Statement: One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented racial and/or ethnic groups in science. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented sexual and/or gender groups in science. One or more of the authors of this paper received support from a program designed to increase minority representation in science. We actively worked to promote sex and gender balance in our author group. We actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our author group. While citing references scientifically relevant for this work, we also actively worked to promote sex and gender balance in our reference list. While citing references scientifically relevant for this work, we also actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our reference list. The author list of this paper includes contributors from the location and/or community where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.

Key words: adolescence; environment; subcortical brain volume; psychopathology; externalizing

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An extensive body of research establishes that adolescent psychopathology relates to experiences in the environment and changes in brain development. However, much of this work is siloed into research specifying the environmental or neurobiological factors related to psychopathology in adolescence.

On one hand, decades of research documents that environmental systems influence the development of psychopathology (ie, externalizing and internalizing).[1-5] Meta-analyses report medium-to-large effects between adversity in adolescents' families (eg, conflict, caregiver nonacceptance) and neighborhoods (eg, experiencing violence or disadvantage) and adolescent psychopathology.[6,7] Externalizing psychopathology is associated with adverse experiences in the form of family poverty, harsh parenting, association with deviant peers, concentrated disadvantage, and exposure to community violence.[2] Similarly, internalizing psychopathology is linked to maternal depression, maltreatment by a caregiver, peer victimization, and exposure to community violence, which can exacerbate internalizing psychopathology in youth.[3-5] The vast majority of studies examine externalizing and internalizing psychopathology separately and show the influence of environmental systems on these outcomes.[2-5] However, others explore externalizing and internalizing psychopathology in the same models and highlight that certain environmental risks are common in their association with psychopathology.[6,8] For example, socioeconomic disadvantage is associated with increased risk for psychopathology, including externalizing (eg, aggression and delinquency) and internalizing (eg, anxiety and depression).[8] Similarly, exposure to childhood maltreatment and exposure to community violence are associated with externalizing (eg, risk-taking/violent behavior) and internalizing (eg, depression and anxiety).[6] Taken together, these findings underscore the importance of environmental experiences on externalizing and/or internalizing psychopathology in adolescence.

On the other hand, neurobiological theories of adolescent psychopathology emphasize that general brain health influences the development of externalizing and internalizing psychopathology. In particular, there is evidence that the size of subcortical brain volumes located across the hippocampus, amygdala, thalamus, caudate, putamen, globus pallidum, and nucleus accumbens relate to the development of externalizing and internalizing psychopathology in adolescence.[9-11] These subcortical brain regions may be particularly important for understanding adolescent psychopathology because they support self-regulation and affective processing.[9-11] Existing work shows that smaller amygdala volumes relate to elevated internalizing psychopathology during adolescence.[12] Similarly, smaller volume and reduced volumetric growth of the hippocampus across school-age and adolescent development mediate associations with elevated psychopathology outcomes during late adolescence.[12,13] Although there is a general pattern of smaller subcortical volumes being associated with increased risk of psychopathology,[11] there also are inconsistencies that have been reported, perhaps because most previous work takes a region-of-interest approach (ie, looking exclusively at the amygdala or hippocampus).[9-12] Therefore, examining the subcortex in its entirety instead of selecting regions of interest is a needed step in developing a more complete understanding of how subcortical brain development relates to adolescent psychopathology.

Moving beyond research that examines environmental experiences and neurobiology in isolation, environmental risk factors in youth have been linked to structural brain development.[14] Non-human animal models show that hippocampal and amygdala development is sensitive to environmental experiences.[15] In human research, adverse experiences—such as low household income, harsh parenting, maltreatment, peer victimization, neighborhood disadvantage, and community violence—relate to reduced subcortical volumes.[16-21] For example, children from lower-income families and those exposed to community violence show smaller hippocampal and amygdala volumes.[16-19] In addition, experiences of maternal harsh parenting relate to smaller amygdala volume,[20] and childhood maltreatment is associated with smaller hippocampal volume.[21] Researchers have also demonstrated that anti-poverty policies in the United States mitigate socioeconomic-related brain differences, such that in high–cost-of-living states with generous anti-poverty programs, the association between family income and hippocampal volume resembled that of lower–cost-of-living states.[17] However, there are several limitations of previous research: (1) the majority of previous studies focus on the influences of single environmental systems on brain structures, and not the combined influence of family, school, neighborhood, and policy factors; (2) many of the previous studies are plagued by small sample sizes; (3) other studies use restricted sociodemographic samples (eg, all low income, all high income, all maltreatment, all disadvantaged neighborhood); and (4) most studies, as noted above, focus on selective subcortical regions (eg, only hippocampus or amygdala)—in part because deep subcortical regions have limited signal-to-noise ratio and are susceptible to sources of physiological noise without adequate scanning protocols.

Research on the influence of environmental experiences on adolescent psychopathology, brain on psychopathology, and their interactions (albeit in limited ways) has laid a strong foundation for understanding how psychopathology may unfold in different contexts for different youth. Consistent with foundational theories of development (eg, Bronfenbrenner's Ecological Systems Theory, Life History Theory, Transactional Model of Development)[22-25] that emphasize the importance of examining multiple contexts at different levels of proximity to youth,[26-29] there has been a recent increase in studies using various methods beyond multiple regression to represent the interplay among more than one or two environmental systems and the relation to adolescent psychopathology.[30-34] For example, in a study using the Adolescent Brain Cognitive Development℠ Study (ABCD Study®), 4 distinct profiles of perceived threat were derived using latent profile analysis with family, school, and neighborhood systems.[31] Youth in the elevated threat across all systems profile had poorer mental health outcomes, but youth in the family threat profile uniquely showed more disruptive behavior symptoms, and youth in the elevated neighborhood threat profile displayed increased sleep problems. Another study using latent profile analysis from the Future Families and Child Well-Being Study found distinct groups of youth who experienced high maternal depression, low adversity across family and neighborhood systems, medium adversity, or high adversity.[32] Youth in the high maternal depression profile or high adversity profile reported the highest number of psychopathology symptoms. These examples of using profile analyses to test foundational theories of development are a great step in identifying the interplay among environmental systems as well as their impact on psychopathology. However, work is still needed to use an integrated approach[26,27] that captures environmental experiences that span multiple experiences within a youth's microsystem (eg, family, school, neighborhood)[28] and broader macrosystem (eg, policies, law).[29] Furthermore, we need to understand how interconnected environmental experiences, directly or indirectly, relate to subcortical brain structure and psychopathology. This is an important step to advance the science of biosocial transactions related to the development and maintenance of psychopathology in adolescence.

In the present study, we tested the relationships among multiple environmental systems, subcortical gray matter (GM) volume, and psychopathology using the ABCD Study.[35] First, we aimed to identify distinct profiles of youth during late childhood that capture their life experiences across family, school, neighborhood, and policy systems, by using a novel Bayesian latent profile analysis (LPA)[36] method. We chose environmental factors that were representative across micro-to-macro systems instead of relying solely on experiences within a single system. Furthermore, we built on previous research using LPA that derives profiles of individuals who exhibit similar environmental experiences as a way to examine environmental interplay. However, we used a new Bayesian LPA method to identify profiles of multisystem environmental experiences. Briefly, conventional LPA fits a series of models with different number of profiles, and the best model solution is chosen based on objective and subjective criteria; these criteria may not agree with each other, making it challenging to decide on the optimal number of meaningful profiles.[37] A small number of profiles often reflects having many participants in profiles that show less variation (eg, low, medium, and high levels), whereas a large number of profiles often reflects having fewer participants in profiles that show more variation (but may not be meaningful).[37] By contrast, we recently showed that a Bayesian LPA method overcomes the limitations of conventional LPA in 2 ways[36]: (1) automatic profile selection without making judgments based on objective and subjective criteria, and (2) detection of more nuanced and more certain profiles (details in Methods section and in Supplement 1, available online). The Bayesian LPA method provides an opportunity to detect potentially meaningful variations in adversities spanning environmental systems without *a priori* specifying the optimal number of profiles. Based on previous research, it is expected that latent profiles characterized by adversities within specific environmental systems (eg, family/neighborhood) and across systems (eg, all/most variables) will be evident (quantified by the deviations from the sample average).[6,31,38] Given the novelty of combining multisystem environments in the Bayesian LPA method, we did not have hypotheses about the specific combinations of variables within the latent profiles.

Second, we aimed to assess the ways and degree to which the multisystem environmental profiles during late childhood associate with subcortical GM volume and psychopathology (ie, externalizing, internalizing) during early adolescence. Based on prior research,[1-21] we hypothesized that profiles describing adverse family and neighborhood environments would be associated with smaller subcortical GM volume and greater externalizing and internalizing psychopathology. Following evidence that brain structures can mediate the associations between poverty and externalizing and internalizing during adolescence,[18,19,39] we also expected indirect relationships between adverse multisystem environments, that included evidence of lower income within profile, and externalizing/internalizing via subcortical GM volume.

METHOD

Participants

The ABCD Study is a 10-year longitudinal study that tracks the development of children and adolescents across 21 research sites in the United States.[35] The ABCD Study obtained approval from a centralized Institutional Review Board (IRB) located at the University of California, San Diego in addition to obtaining local IRB approval from each of the imaging sites. Written assent was provided by the youth, and written informed consent was obtained by their parents or guardians.

We used the demographic, environmental (baseline), imaging (2-year follow-up), and behavioral (3-year follow-up) data from the ABCD Study Release 5.1 (N = 11,865) (https://abcdstudy.org/). Our ABCD sample reflects the minimally processed data that are publicly available from the NDA (https://nda.nih.gov/abcd). Only participants who had complete demographic, environmental, psychopathology, and imaging data in addition to successfully passing the MRI data quality control criteria described by the ABCD Data Analysis and Informatics Center (DAIC)[40] (https://wiki.abcdstudy.org/release-notes/imaging/quality-control.html) were included in the study. A total of 2,766 youth were included in the present study (Table 1).

Environmental Data

The environmental factors were obtained at baseline from the ABCD Study Culture and Environment,[41] Linked External Data,[42] and Adolescent Neural Urbanome[43] batteries. We focused on selecting environmental factors that have shown relationships with subcortical GM volume and youth psychopathology in previous literature.[1-21] Furthermore, the Bayesian LPA method can handle correlated factors (Figure 1B), but this method currently requires that the factors follow a normal distribution.[36] Therefore, environmental factors that had binary outcomes were not included in this study. Policy data available in the ABCD Study, such as Medicaid expansion, naloxone policies, and Good Samaritan laws were binary outcomes and had no variability in their distributions[42] (Figure S1, available online). By contrast, the marijuana laws variable was not binary, and it displayed sufficient variability within the ABCD Study sample.

Family Conflict

The Family Conflict subscale from the Family Environment Scale (FES) was used to measure participants' family climate based on the amount of conflict and anger expressed among family members. The FES Conflict subscale consists of 9 items, whereby the youth indicates whether each statement is true or false for most family members (eg, we fight a lot in our family). The subscale shows moderate internal consistency ($\alpha = 0.66$) and test–retest reliability (intraclass correlation coefficient [ICC] = 0.46) within the ABCD Study. The 9 items were summed and reverse scored to obtain a measure of family conflict for each youth. A higher value on the FES Conflict subscale indicates less family conflict perceived by the youth.

Positive Parenting

The Acceptance Scale from the Children's Reports of Parental Behavior Inventory (CRPBI) was used to measure participants' perceptions of their caregivers' parenting behaviors in terms of warmth, acceptance, and responsiveness. The CRPBI Acceptance Scale consists of 5 items, whereby the youth describe their caregivers' positive parenting behavior on a 3-point scale (eg, makes me feel better after talking over my worries with him/her). The scale shows moderate internal consistency ($\alpha = 0.71$) and test–retest reliability (ICC = 0.47) within the ABCD Study. The mean score from the 5 items was used as a measure of positive parenting for each youth. A higher value on the CRPBI Acceptance Scale indicates more positive parenting perceived by the youth.

Income-to-Needs Ratio

The income-to-needs ratio was calculated as the median of the income band described by the ABCD Study divided by the federal poverty level based on the respective household size. The income band reflects the combined household income where the youth reside. The median of the first income band was set at $5,000 and the median for the last income band was set at $200,000. The federal poverty level was obtained from the Department of Health and Human Services (https://www.healthcare.gov/glossary/federal-poverty-level-fpl/). An income-to-needs ratio of 1 indicates living at the poverty threshold, a ratio greater than 1 denotes living above the poverty threshold, and a ratio less than 1 denotes living below the poverty threshold.

School Involvement

The School Involvement subscale from the School Risk and Protective Factors (SRPF) questionnaire was used to measure youth perceptions of the amount of school involvement. The SRPF School Involvement subscale contains 4 items as indicators of positive involvement in school (eg, I like school because I do well in class). The subscale shows moderate internal consistency ($\alpha = 0.65$) and test–retest reliability (ICC = 0.48) within the ABCD Study. The scores from the 4 items were summed to obtain a measure of school involvement for each youth. A higher value on the SRPF School Involvement subscale indicates more school involvement perceived by the youth.

Neighborhood Deprivation

The area deprivation index (ADI) reflects the weighted sum of 17 composite scores related to employment, education, income and poverty, and housing at the census-tract level using the home address of the youth from the 2011-2015 American Community Survey (Table S1, available online). For each youth, the weighted sum was computed, where each composite measure was multiplied by its weighted score and then added together (Table S2, available online). The code used by the ABCD Study to compute the ADI is provided at https://github.com/ABCD-STUDY/geocoding/blob/master/Gen_data_proc.R. We reverse coded the ADI scores, with higher ADI values indicating lower neighborhood disadvantage.

TABLE 1 Demographic, Environmental, and Behavioral Characteristics Derived From the ABCD Study NIMH Data Archive Release 5.0

ABCD Study	n	%	Mean (SD)	Range
Sample size	2,766	100	—	—
Race				
White	1,685	60.9	—	—
Black	247	8.9	—	—
Asian	68	2.5	—	—
AIAN	30	1.1	—	—
NHPI	5	0.2	—	—
Mixed	57	2.1	—	—
Other[a]	57	2.1	—	—
Unspecified	208	7.5	—	—
Ethnicity				
Hispanic or Latino	409	14.8	—	—
Sex[b]				
Male	1,380	49.9	—	—
Female	1,386	50.1	—	—
Education[c]				
Less than HS diploma	105	3.8	—	—
HS diploma/GED	232	8.4	—	—
Some college	486	17.6	—	—
Associate degree	387	14.0	—	—
Bachelor degree	907	32.8	—	—
Postgraduate degree	649	23.5	—	—
Family income[d]				
Band 1: < $5,000	54	2.0	—	—
Band 2: $5,000-$11,999	72	2.6	—	—
Band 3: $12,000-$15,999	61	2.2	—	—
Band 4: $16,000-$24,999	120	4.3	—	—
Band 5: $25,000-$34,999	186	6.7	—	—
Band 6: $35,000-$49,999	276	10.0	—	—
Band 7: $50,000-$74,999	427	15.4	—	—
Band 8: $75,000-$99,999	538	19.5	—	—
Band 9: $100,000-$199,999	1,032	37.3	—	—
Band 10: > $200,000	0	0	—	—
Household size[e]				
1	6	0.2	—	—
2	100	3.6	—	—
3	340	12.3	—	—
4	912	33.0	—	—
5	674	24.4	—	—
6	425	15.4	—	—
7	168	6.1	—	—
8	79	2.9	—	—
9	24	0.9	—	—
10	20	0.7	—	—
>10	18	0.7	—	—
Environmental factors				
Family conflict (FES)[f]	2,766	—	2.45 (1.95)	0-9
Positive parenting (CRPBI)[f]	2,766	—	2.79 (0.29)	1-3
Income-to-needs ratio[f]	2,766	—	3.21 (2.27)	0.12-9.92
School involvement (SRPF)[g]	2,766	—	13.22 (2.22)	5-16

(continued)

TABLE 1 Continued

ABCD Study	n	%	Mean (SD)	Range
Neighborhood deprivation (ADI)[h]	2,766	—	96.78 (16.21)	3.73-124.52
Neighborhood safety and crime (PhenX)[h]	2,766	—	15.87 (3.09)	4-20
Residential segregation (ICE)[j]	2,766	—	0.15 (0.27)	−0.73 to 0.86
Marijuana laws[i]	2,766	—	2.29 (0.73)	1-4
Psychopathology				
CBCL-Externalizing[j]	2,766	—	44.04 (9.28)	33-80
CBCL-Internalizing[j]	2,766	—	48.07 (10.57)	33-87

Note: ABCD Study = Adolescent Brain Cognitive Development Study; ADI = area deprivation index; AIAN = American Indian and Alaska Native; CBCL = Child Behavior Checklist; CRPBI = Children's Reports of Parental Behavior Inventory; FES = Family Environment Scale; HS = high school; ICE = index of concentration at the extremes; NHPI = Native Hawaiian and Pacific Islander; NIMH = National Institute of Mental Health; SRPF = School Risk and Protective Factors questionnaire.

[a]*Other race/ethnicity corresponds to Eastern and Western European, Afro-Carribean/Indo-Carribbean/West Indian, Middle Eastern/North African in addition to parents who selected "Other race" to indicate that the predefined groups did not apply to them.*

[b]*Participant sex denotes youth's sex assigned at birth.*

[c]*Education refers to the highest grade or level of school a parent has completed or the highest degree they have received.*

[d]*Family income refers to the total income in a household (income bands are provided by the ABCD Study).*

[e]*Household size describes the total number of people living in the same household. Income-to-needs ratio is computed by dividing the median of the family income band with the household size.*

[f]*Family-related environmental factors describe family conflict, positive parenting, and income-to-needs ratio at baseline.*

[g]*School-related environmental factor describes school involvement at baseline.*

[h]*Neighborhood-related environmental factors describe neighborhood deprivation, neighborhood crime and safety, and residential segregation at baseline.*

[i]*Policy-related environmental factor refers to marijuana laws with regards to cannabis legalization in the United States at baseline.*

[j]*Child Behavior Checklist indexing externalizing and internalizing psychopathology at 3-year follow-up. Note that the CBCL externalizing and internalizing scores were T standardized. The participants had no missing scores (values) on the scales related to the environmental factors and psychopathology. We also compared the characteristics of our sample with the full ABCD Study sample to test for differences in demographics, multisystem environments, and psychopathology (Supplement 1, available online).*

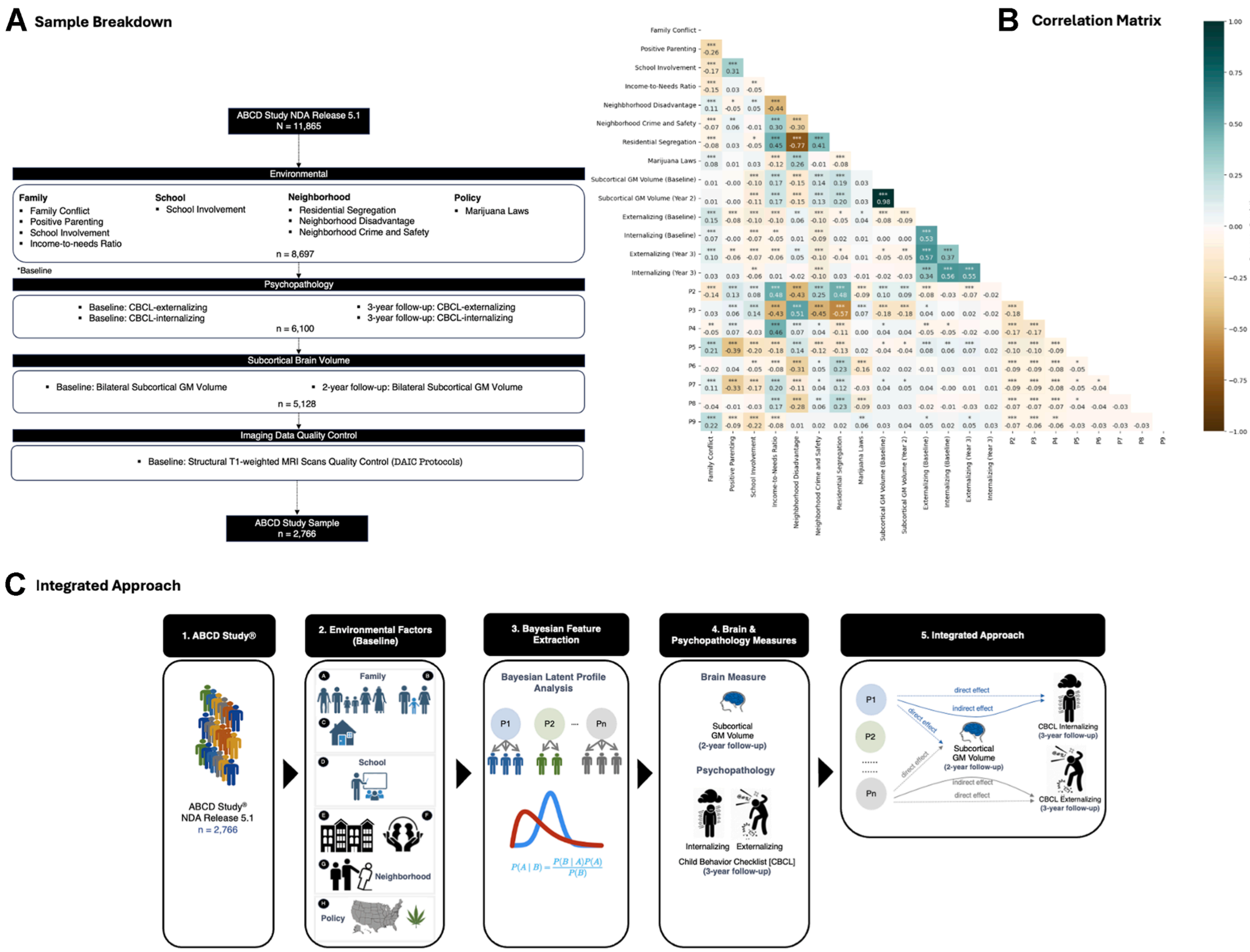
Neighborhood Safety and Crime

The Safety from Crime item scales from the PhenX Toolkit were used to measure neighborhood safety and crime. The Safety from Crime scales describe 3 statements administered to the parent related to feeling safe walking in their neighborhood, violence in their neighborhood, and crime in their neighborhood (eg, I feel safe walking in my neighborhood, day or night). Each item is rated on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"). Only one statement was administered to youth to assess their feelings about safety and crime in their neighborhood (ie, My neighborhood is safe from crime). The item scales show high internal consistency ($\alpha = 0.88$) and moderate test–retest reliability (ICC = 0.37) within the ABCD Study. The scores from the parent and youth item scales were summed to obtain a measure of neighborhood safety and crime for each youth. A higher value on the Safety from Crime item scales indicates a safer neighborhood perceived by the parent and youth.

Residential Segregation

The index of concentration at the extremes (ICE) was used to examine the extent to which a population in a specified area is concentrated into the wealthiest and most impoverished extremes of a specified social distribution. ICE measures the distributions of affluence and poverty at the census-tract level within racial or ethnic groups across the wealthiest and most impoverished areas of the community based on the 2014-2018 American Community Survey. It ranges from −1 to 1 such that a positive value indicates concentration of a racial/ethnic group in affluent areas, a negative value denotes concentration of a racial/ethnic group in impoverished areas, and a value closer to 0 indicates no concentration of a racial/ethnic group in either an affluent or poorer area of the community. The code used to compile and compute the residential segregation values is provided by the ABCD Study Adolescent Neural Urbanome (https://osf.io/8q6vb).

FIGURE 1 Integrated Approach Linking Multisystem Environmental Profiles, Subcortical Gray Matter Volume, and Externalizing/Internalizing Psychopathology



Note: *(A) Adolescent Brain Cognitive Development Study (ABCD Study) Sample Breakdown. (B) Correlations between multisystem environmental profiles (P2…P9), environmental factors, subcortical GM volume, and psychopathology using the Spearman correlation. Note that the profiles were dummy coded and Profile 1 was treated as the reference profile. (C) Integrated Approach. 1. The ABCD Study NDA Release 5.1 was used to obtain environmental, brain, and behavioral data from late childhood to early adolescence. 2. The environmental factors were obtained at baseline and they captured multiple systems including family, school, neighborhood, and policy. Family-related factors correspond to (A) family conflict, (B) positive parenting, and (C) income-to-needs ratio. School-related factor corresponds to (D) school involvement. Neighborhood-related factors correspond to (E) neighborhood disadvantage, (F) neighborhood safety and crime, and (G) residential segregation. Policy-related factor corresponds to (H) marijuana laws with regard to cannabis legalization in the United States. 3. The environmental factors were then used to generate distinct profiles (denoted by P1, P2, …., Pn) of youth automatically that share similar characteristics without* a priori *specifying the number of latent profiles using a Bayesian latent profile analysis framework. We assigned each participant to their most probable profile and then treated the profiles like an observed variable. 4. Subsequently, the subcortical gray matter (GM) volume was obtained at 2-year follow-up from the ABCD Study. The subcortical GM volume corresponds to 19 regions of interest (ROIs) including the bilateral nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, ventral diencephalon, cerebellum, and extending to the midline brainstem. The behavioral measures also were obtained from the Child Behavior Checklist (CBCL) that correspond to externalizing and internalizing psychopathology at 3-year follow-up. 5. The integrated approach represents a path analysis linking the multisystem environmental factors (denoted by P1, P2, …., Pn), subcortical GM volume, and externalizing and internalizing psychopathology. A direct effect captures either the relationship between a multisystem environmental profile and subcortical GM volume or between a multisystem environmental profile and externalizing/internalizing psychopathology. An indirect effect captures the relationship between a multisystem environmental profile and externalizing/internalizing psychopathology via the subcortical GM volume.*
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Marijuana Laws

Currently, there are 38 states that have legalized cannabis for medical use, 24 states that provide legal access to cannabis for recreational use, and 9 states that allow low–tetrahydrocannabinol (THC), high–cannabidiol (CBD) products either for medical purposes or as a legal defense in the United States (http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx). States that legalize either recreational or medical cannabis use reflect more liberal marijuana laws as opposed to those that forbid legal access to cannabis, therefore being more conservative. The impact of policy changes on marijuana use during adolescence is still in the early stages. There is some evidence showing that younger adolescents (7th- to 8th-graders) who report greater exposure to cannabis advertising (which is more common in states with more liberal marijuana laws) also report earlier and higher use, stronger intentions to use, and more negative consequences from use over time.[42] We obtained policy data representing marijuana laws at the state level in the United States, and reverse coded the categories for cannabis legalization. Cannabis legalization was categorized as follows: (1) no legal access to cannabis; 2: low-THC/CBD; 3: medical; and 4: recreational. A higher value in the cannabis legalization categories indicates a less conservative law.

Psychopathology Data

The Child Behavior Checklist (CBCL) is a parent-report assessment that was used to measure externalizing and internalizing psychopathology.[44] We used the parent-report, as youth self-report on externalizing and internalizing were not available for the 3-year follow-up. Externalizing reflects symptoms such as aggression and rule breaking, whereas internalizing captures anxiety and depression. The CBCL externalizing and internalizing scores were obtained from their respective syndrome scales that were subsequently T standardized. Internal consistency is excellent for CBCL externalizing and internalizing ($\alpha >$ 0.90) as well as their test–retest reliability (ICC $>$ 0.95) within the ABCD Study. The higher the CBCL externalizing and internalizing T scores, the greater the risk of experiencing behavioral and emotional problems.

MRI Data Acquisition

Structural T1- and T2-weighted MRI scans were acquired using Siemens Prisma, Philips, and GE 750 3T scanners with a 32-channel head coil.[35] Three-dimensional (3D) MPRAGE T1-weighted and 3D FSE T2-weighted volumes with spatial resolution $1 \times 1 \times 1$ mm^3 were obtained for each youth at 2-year follow-up. The structural MRI data were preprocessed using the DAIC standard processing pipeline.[40]

Subcortical Gray Matter Volume

For each participant, the subcortical GM structures were labeled using an automated, atlas-based, volumetric segmentation procedure from FreeSurfer.[40] These structures include 19 regions of interest (ROIs) corresponding to the bilateral nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, ventral diencephalon, cerebellum, and midline brainstem.

Bayesian Latent Profile Analysis

We performed a Bayesian latent profile analysis (LPA)[36] using the environmental factors. LPA explains a set of indicator variables by grouping participants into latent profiles, that is, categories of individuals with similar characteristics. The LPA model assumes that each participant belongs to a single latent profile, and that indicator variables have independent normal likelihoods with means that vary across profiles. Conventional methods for determining the optimal number of latent profiles often provide conflicting results for which number of profiles is best to select.[37] We used a Bayesian form of LPA based on the Dirichlet process mixture (DPM) model that automatically detects the optimal number of latent profiles.[36]

The Bayesian LPA model chooses the number of profiles in 2 fundamentally different ways from those of the conventional LPA and other clustering methods (eg, K-Means). First, in Bayesian statistics, parameter estimates are influenced by both the likelihood and the prior distribution. The prior distribution describes the inherent probability of different model solutions. The prior distribution in Bayesian inference leads to simpler solutions than those produced by maximum likelihood estimation alone (in conventional LPA). Because Bayesian models do not become more complex than necessary to explain the data, this simplifying effect of the prior distribution prevents the Bayesian LPA model from finding redundant and less nuanced profiles. Previously, we showed that the Bayesian LPA method produced more distinct profiles (with higher entropy reduction and low similarity) than conventional LPA using the ABCD Study.[36] Moreover, we found that the Bayesian LPA method was good at recovering the correct number of profiles using simulated data at small (n = 250) and large (n = 1,000) sample sizes.[36] Second, the Bayesian LPA model infers the optimal number of profiles automatically while estimating other model parameters (mathematical derivations in Supplement 1, available online). The model is fit by computing a probability distribution over the parameters (including participant-specific variables such as latent profile membership) rather than a single point estimate. A key guiding principle in this fit process is Bayesian Occam's Razor, which seeks to automatically find an LPA solution that balances model fit and complexity. In contrast, conventional LPA finds point estimates of model parameters by maximizing the likelihood of the data. As the conventional method fits a series of models with different number of profiles (1, 2, 3, 4…), the best model solution is chosen using a combination of subjective (eg, 5% participant membership in each profile, profile interpretability) and objective criteria (eg, Akaike information criterion [AIC], Bayesian information criterion [BIC]).[37]

Similar to conventional LPA, DPM-LPA assumes that all correlations between variables (ie, environmental factors) are explained by the profiles. Therefore, the residual matrix should be approximately diagonal (Table S3, available online). The Bayesian LPA method was implemented using the Python package vbayesfa.[36] We used proportional reduction in classification entropy to assess the distinctiveness of the profiles inferred. Entropy reduction values range from 0 (no confidence in classifying participants) to 1 (total confidence in classifying participants), with a high entropy reduction statistic $\geq$ 0.80 suggesting that the model can accurately assign participants to latent profiles. As a stability check, we varied the value of α (concentration parameter) to test whether changing the value of this parameter led to different priors and, as a result, a different number of profiles (Supplement 1, available online, provides more details about α). Finally, we computed the minimum and mean distances between profile pairs as indices of profile distinctiveness (Figure S2, available online).

Integrated Approach

We examined relationships among multisystem environmental profiles, subcortical GM volume, and externalizing and internalizing using a path analysis (Figure 1C). The path analysis was conducted by choosing randomly one sibling per family based on youth who share a similar family ID to limit family dependency confounds, with the lavaan package in R version 4.3.2. We tested the direct and indirect effects of the multisystem environmental profiles simultaneously: a direct effect represents a relationship between a multisystem environmental profile and subcortical GM volume or between a multisystem environmental profile and externalizing/internalizing, whereas an indirect effect represents a relationship between a multisystem environmental profile and externalizing/internalizing via the subcortical GM volume. For direct effects, the standardized coefficient estimates, standardized errors, and statistical significance were reported. For indirect effects, the standardized coefficient estimates and 95% confidence intervals, which were obtained from a bootstrapping procedure, were reported.

In the main analyses, we present the direct and indirect effects without including baseline subcortical GM volume, externalizing, and internalizing because baseline and 2-year follow-up subcortical GM volume are strongly correlated and baseline and 3-year-follow-up externalizing and internalizing are strongly correlated (Figure 1B). For completeness, we included baseline subcortical GM volume, externalizing, and internalizing in the path analysis in Supplement 1, available online (Figures S6-S8, available online)

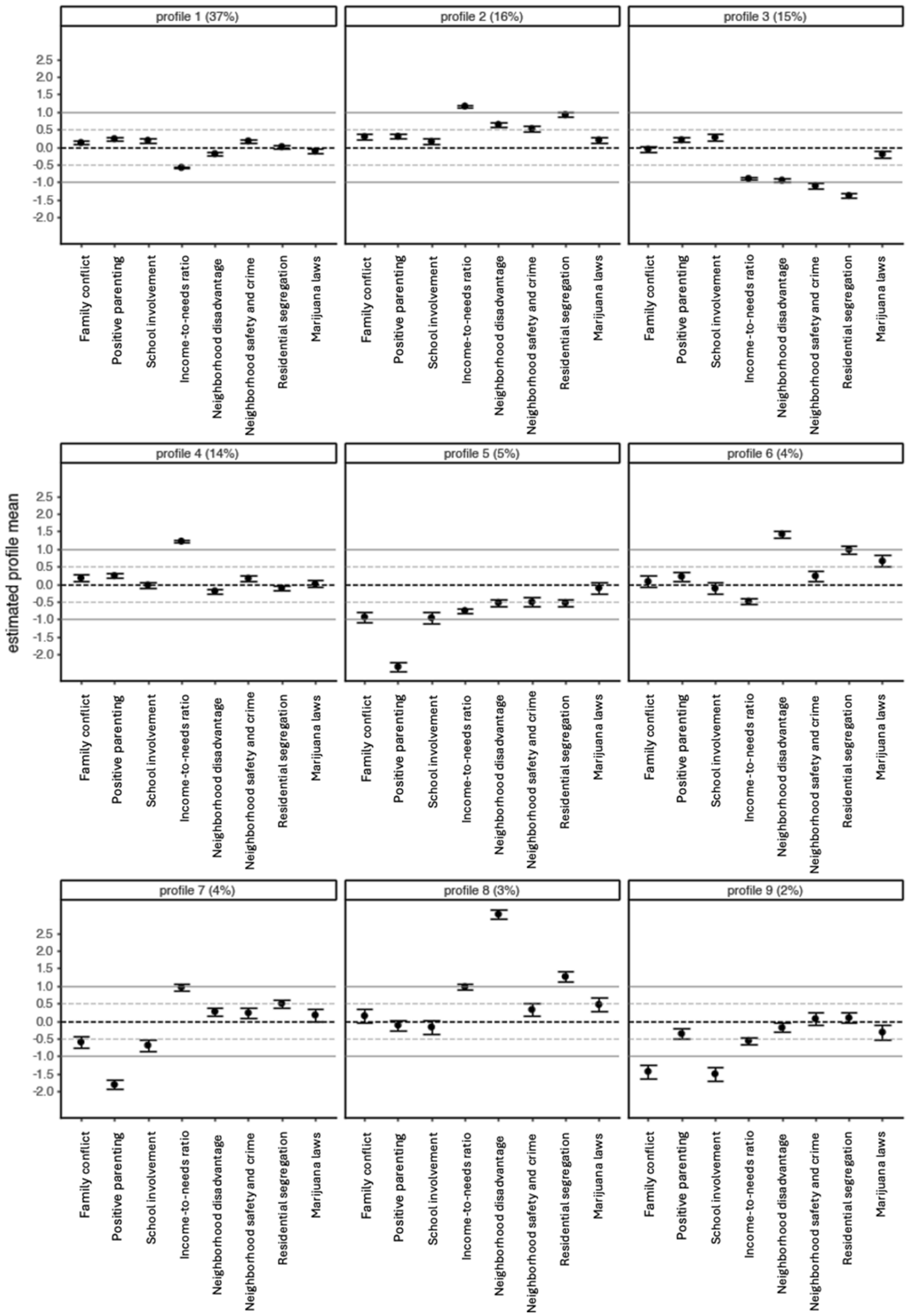
RESULTS

Description of the Multisystem Environmental Profiles

The Bayesian LPA model produced 9 distinct profiles with an excellent proportional reduction in entropy of 0.89 (Figure 2). The number of profiles did not change with different values of α (ie, 1, 2, 4, 8). We also described the results of conventional LPA using 4 comparison metrics (Figure S2, available online). In creating labels, we wanted to use judgment-free language and to avoid listing factors as positive or negative. Furthermore, given the array of factors representing environmental systems, it was difficult to come up with a labeling scheme that would apply appropriately to all factors. Therefore, we opted to use descriptive labels for each profile based on the factors that deviated at least 0.5 SD from the sample mean.[6,31,38] For each profile, the characteristics of all environmental factors are provided in Table 2.

Profile 1 was characterized by below-average family income (mean income band = 6) representing 37% of the sample. Profile 2 was characterized by family (mean income band = 9) and neighborhood affluence ($\overline{\text{ICE}}$ = 0.424; $\overline{\text{PhenX}}$ = 17.6; $\overline{\text{ADI}}$ = 85.5) representing 16% of the sample. Profile 3 was characterized by family economic (mean income band = 5) and neighborhood adversity ($\overline{\text{PhenX}}$ = 12.2; $\overline{\text{ICE}}$ = −0.246; $\overline{\text{ADI}}$ = 113) representing 15% of the sample. Profile 4 was characterized by family economic affluence (mean income band = 9) representing 14% of the sample. Profile 5 was characterized by adversity across family ($\overline{\text{CRPBI}}$ = 2.05; $\overline{\text{FES}}$ = 4.00; mean income band = 5), school ($\overline{\text{SRPF}}$ = 11.0), and somewhat in the neighborhood systems ($\overline{\text{PhenX}}$ = 14.1; $\overline{\text{ICE}}$ = −0.000004; $\overline{\text{ADI}}$ = 106) representing 5% of the sample. Profile 6 was characterized by neighborhood affluence ($\overline{\text{ICE}}$ = 0.441; $\overline{\text{ADI}}$ = 70.3) and liberal marijuana policy ($\overline{\text{mj}}$ = 1.74), but below average family income (mean income band = 6) representing 4% of the sample. Profile 7 was characterized by adverse family interactions ($\overline{\text{CRPBI}}$ = 2.21; $\overline{\text{FES}}$ = 3.12) and low school involvement ($\overline{\text{SRPF}}$ = 11.4), but family economic (mean income band = 8), and neighborhood affluence ($\overline{\text{ICE}}$ = 0.309) representing 4% of the sample. Profile 8 was characterized by neighborhood

FIGURE 2 Descriptions of the Multisystem Environmental Profiles Obtained From Family, School, Neighborhood, and Policy Factors



($\overline{\text{ICE}} = 0.534$; $\overline{\text{ADI}} = 40.8$) and family economic affluence (mean income band = 8), with somewhat liberal marijuana policy ($\overline{\text{mj}} = 1.91$) representing 3% of the sample. Profile 9 was characterized by family conflict ($\overline{\text{FES}} = 5.56$) and low school involvement ($\overline{\text{SRPF}} = 8.79$) representing 2% of the sample. The multisystem environmental profiles differed significantly in the distributions of participant race/ethnicity, US region, and sex assigned at birth (Figure S3, available online).

Integrated Approach

The 9 multisystem environmental profiles were dummy coded, and Profile 1 was treated as the reference profile, as youth recorded average responses for the majority of the environmental factors relative to the other 8 profiles (Figure 3). First, we observed direct effects of the multisystem environmental profiles on subcortical GM volume. Profile 2, that is, family and neighborhood affluence during late childhood, compared to Profile 1 was associated with higher subcortical GM volume during early adolescence (estimate [SE] = 0.20 [0.059], $P = .001$). Profile 3, that is, family economic and neighborhood adversity during late childhood, compared to Profile 1 was associated with lower subcortical GM volume during early adolescence (estimate [SE] = −0.43 [0.059], $P < .001$). Profile 5, that is, adversity across, family, school, and somewhat in the neighborhood systems during late childhood, compared to Profile 1 was associated with lower subcortical GM volume during early adolescence (estimate [SE] = −0.22 [0.094], $P = .018$).

Next, we observed direct effects of the multisystem environmental profiles on externalizing psychopathology. Profile 2, compared to Profile 1 was associated with lower externalizing during early adolescence (estimate [SE] = −0.15 [0.061], $P = .014$). Profile 5, compared to Profile 1, was associated with higher externalizing during early adolescence (estimate [SE] = 0.27 [0.095], $P = .004$). Profile 9, that is, family conflict and low school involvement during late childhood, compared to Profile 1 was associated with higher externalizing during early adolescence (estimate [SE] = 0.37 [0.14], $P = .008$).

We also observed indirect effects of the multisystem environmental factors on externalizing and internalizing psychopathology via subcortical GM volume. The respective paths Profile 2 → Subcortical 2y → Externalizing 3y and Profile 2 → Subcortical 2y → Internalizing 3y indicated that family and neighborhood affluence during late childhood was associated with higher subcortical GM volume during early adolescence, which in turn was associated with lower externalizing (estimate = −0.009, 95% bootstrap CI = [−0.020, −0.00035]) and internalizing (estimate = −0.009, 95% bootstrap CI = [−0.020, −0.00080]). In addition, the respective paths Profile 3 → Subcortical 2y → Externalizing 3y and Profile 3 → Subcortical 2y → Internalizing 3y indicated that family economic and neighborhood adversity during late childhood were associated with lower subcortical GM volume, which in turn was associated with higher externalizing (estimate = 0.018, 95% bootstrap CI = [0.0012, 0.038]) and internalizing (estimate = 0.020, 95% bootstrap CI = [0.0028, 0.039]) during early adolescence. Furthermore, examining the subcomponents of externalizing and internalizing, both subscales of externalizing (aggression and rule breaking) resulted from an indirect effect of multisystem environmental profiles via subcortical GM volume (Figure S4, available online). In addition, Profile 5 showed direct and indirect effects with the depression subscale for internalizing (Figure S5, available online). The Supplemental Material includes tests of robustness by treating baseline subcortical GM volume, externalizing, internalizing, and participant sex assigned at birth, respectively (Figures S3, S6-S8, available online).

DISCUSSION

The goal of the present study was to capture complex interactions among multiple environmental systems, and to examine the impact of these systems on the brain and behavior in youth as they transition from childhood to adolescence. To achieve this goal, we first applied a novel Bayesian LPA method to identify subgroups of children who have similar experiences within family, school, neighborhood, and policy systems. We then assessed the ways and degree to which the multisystem environmental profiles were associated with subcortical GM volume and externalizing and internalizing psychopathology during early adolescence. The Bayesian LPA method revealed 9 distinct profiles with excellent certainty and discrimination. The integrated approach also captured equifinal pathways

Note: Family factors correspond to family conflict, positive parenting, and income-to-needs ratio. The school factor corresponds to school involvement. Neighborhood factors correspond to neighborhood disadvantage, neighborhood safety and crime, and residential segregation. The policy factor corresponds to marijuana laws. The proportion of youth in each distinct profile also is displayed. Note that family conflict, neighborhood disadvantage, and marijuana laws have been reverse coded. The dotted black line denotes the mean of each profile. The dotted gray line denotes responses 0.50 ± SD from the mean of each profile. The profile averages on each indicator are relative to the sample average. The solid gray line denotes responses 1.0 ± SD from the mean of each profile. The black error bars denote the 95% credible intervals of each variable.

TABLE 2 Characteristics of the Multisystem Environmental Profiles

Profile	Mean household size	Mean income band	ABCD income range	Family conflict (FES)
1	5	6	$35,000-$49,000	1.74 (0-9)
2	5	9	$100,000-$199,999	1.38 (0-8)
3	5	5	$25,000-$34,999	2.10 (0-9)
4	4	9	$100,000-$199,999	1.69 (0-8)
5	5	5	$25,000-$34,999	4.00 (0-9)
6	5	6	$35,000-$49,999	1.88 (0-8)
7	5	8	$75,000-$99,999	3.12 (0-9)
8	4	8	$75,000-$99,999	1.59 (0-8)
9	6	6	$35,000-$49,999	5.56 (2-9)

Note: *For each profile, the mean and range of the environmental factors are shown. In this note, we highlight a few variables to help characterize the profiles. The ABCD income range reflects the mean income band for a given profile. Based on 2024 U.S. Federal Poverty Guidelines issued by the Department of Health and Human Services (https://aspe.hhs.gov/topics/poverty-economic-mobility/poverty-guidelines), income ranges for Profiles 3 and 5 fall below the federal poverty line ($36,580) for a household of 5 people. For the remaining profiles, the income ranges do not fall below the federal poverty line for their respective mean household sizes. The ADI measure is represented as weighted sum. Based on the profiles-specific weighted mean, people in Profile 3 are, on average, living in the national 74th percentile of disadvantage, and people in Profile 5 are, on average, living above the 51st percentile of disadvantage, whereas people living in Profiles 2, 6, and 8 are living below the 20th percentile of disadvantage. For the ICE score, Profile 2, Profile 6, and Profile 8 show more concentration of a racial/ethnic group in affluent areas, with Profile 2 fitting in a privileged quintile.[45] Profile 3 shows more concentration of a racial/ethnic group in impoverished areas, fitting in a less privileged quintile. ADI = area deprivation index; CRPBI = Children's Reports of Parental Behavior Inventory; FES = Family Environment Scale; ICE = index of concentration at the extremes; mj = marijuana laws; SRPF = School Risk and Protective Factors questionnaire.*

through which multisystem environmental profiles exerted both direct and indirect influences on subcortical GM volume and externalizing/internalizing psychopathology.

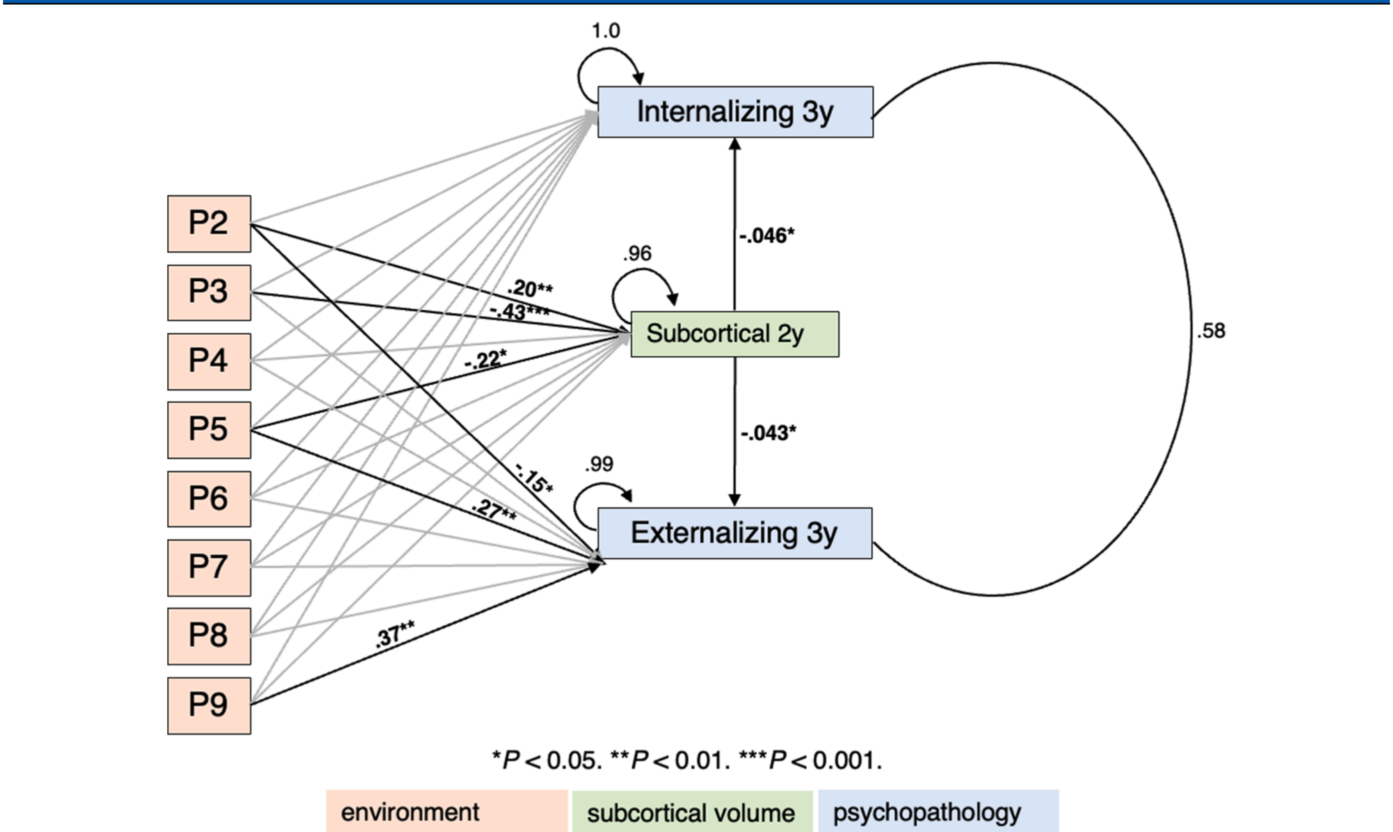
Several developmental theories highlight the importance of considering multiple environments at different levels of proximity to a youth.[22,24,25] Consistent with previous research[6,31,38] and in line with our hypothesis, we found distinct profiles that characterized above sample average adversities across multiple environmental systems. One profile (Profile 5) reflected adversities across all systems. It is important to acknowledge that the experience of adversity across family, school, neighborhood, and policy systems might reflect the insidious nature of structural racism, whereby access to resources at every level is limited. However, using the Bayesian LPA method, we also identified meaningful variations that highlighted a subset of influential environmental factors for some youth. For example, aligning with U.S. Census data,[46] Profile 2 reflected the youth and their family who reside in the West, where White families dominate higher-income levels, whereas Profile 3 reflects the youth and their family who live in the South, which has the highest childhood poverty and 1 in 5 Black women in poverty. Differences in these profiles—specifically, who is represented within each—highlight the unequal distribution of resources across the country, as structural and political factors influence access to quality education, financial stability, safe housing, health care services, political empowerment, and opportunities for growth.[47] Together, the Bayesian LPA method advances our understanding of how diverse environmental experiences interact, and offers a nuanced picture of risk and protective environmental factors in adolescent development.

We found 3 pathways from which late childhood multisystem environmental profiles directly associate with subcortical volume. First, youth experiencing family and neighborhood affluence were associated with larger subcortical volume compared to youth in a below-average family income profile. Generally, environments that provide more opportunities and quality resources can act as a buffer against stress for children, and relate to better physical health compared to those who belong to lower socioeconomic families and disadvantaged neighborhoods.[48] Second, youth experiencing family economic and neighborhood adversity had smaller subcortical volume compared to youth living in an environment with below-average family income. Third, adversity across, family, school, and neighborhood systems during late childhood was associated with smaller subcortical volume compared to lower family income alone. The latter 2 effects are consistent with non-human animal research showing that certain subcortical regions are susceptible to effects of early adversities.[15] Early-life adversity negatively affects neurogenesis (ie, the process of generating new neurons) in the hippocampus, and has been associated with increased dendritic arborization (ie,

TABLE 2 Continued

Positive parenting (CRPBI)	School involvement (SRPF)	Neighborhood disadvantage (ADI)	Neighborhood safety and crime (PhenX)	Residential segregation (ICE)	Marijuana laws (mj)
2.86 (2.2-3.0)	13.6 (6-16)	99.9 (72.2-116)	16.4 (6-20)	0.155 (−0.39 to 0.63)	2.38 (1-4)
2.89 (2.4-3.0)	13.6 (6-16)	85.5 (60.0-102)	17.6 (7-20)	0.424 (0.11-0.74)	2.13 (1-3)
2.86 (2.2-3.0)	13.9 (7-16)	113 (87.4-125)	12.2 (4-20)	−0.246 (−0.73 to 0.09)	2.44 (1-4)
2.86 (2.4-3.0)	13.1 (6-16)	101 (69.8-119)	16.3 (5-20)	0.095 (−0.44 to 0.41)	2.29 (1-4)
2.05 (1.0-2.4)	11.0 (4-16)	106 (68.0-125)	14.1 (5-20)	−0.000004 (−0.54 to 0.53)	2.37 (1-4)
2.86 (2.2-3.0)	12.8 (8-16)	70.3 (40.8-90.0)	16.6 (7-20)	0.441 (−0.21 to 0.74)	1.74 (1-3)
2.21 (1.0-2.6)	11.4 (4-16)	91.4 (55.3-115)	16.6 (11-20)	0.309 (−0.13 to 0.69)	2.15 (1-3)
2.77 (1.2-3.0)	12.9 (8-16)	40.8 (3.73-61.7)	17.0 (12-20)	0.534 (0.08-0.86)	1.91 (1-3)
2.69 (2.4-3.0)	8.79 (5-13)	99.8 (83.6-116)	16.3 (6-20)	0.183 (−0.31 to 0.54)	2.57 (1-3)

FIGURE 3 Integrated Approach Linking Multisystem Environmental Profiles, Subcortical Gray Matter Volume, and Externalizing/Internalizing Psychopathology



Note: The integrated approach was operationalized using a path analysis from structural equation modeling. The multisystem environmental profiles (denoted by P2, …., P9) are derived from family, school, neighborhood, and policy factors at baseline. The imaging measure corresponds to the subcortical gray matter (GM) volume at 2-year follow-up. Externalizing and internalizing psychopathology are derived from the Child Behavior Checklist (CBCL) at 3-year follow-up. Bold black arrows represent the significant relationships (direct and indirect) with their respective coefficient estimates. Gray arrows indicate the relationships between the multisystem environmental profiles and subcortical GM volume or externalizing/internalizing psychopathology that are not significant. Circle arrows capture the respective variances of subcortical GM volume, externalizing psychopathology, and internalizing psychopathology. Circular line denotes the correlation between externalizing and internalizing psychopathology. A bootstrapping procedure was performed to estimate the 95% confidence intervals of the indirect effects by selecting samples of youth randomly to perform the path analysis more than 10,000 times.
$^*p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.001$.

the process by which neurons create connections with other neurons) in the amygdala.[15] In human research, children living in or near poverty exhibit structural brain differences,[18,19] including smaller subcortical volumes. Combined with previous research, the present study documents the relative effect that access to fewer economic resources (at the family and neighborhood levels) has on brain health. This highlights the need to implement policies related to anti-poverty programs and neighborhood resources (eg, safety, amenities) to facilitate healthy developmental trajectories for youth.

The present analysis also revealed the unique ways in which different environmental systems may directly associate with adolescent externalizing psychopathology. Youth who experienced relative family and neighborhood affluence compared to youth living in families with lower income showed fewer externalizing symptoms. However, youth who experienced adversity across family, school, and neighborhood systems or who experienced family conflict and low school involvement during late childhood had more externalizing psychopathology in adolescence. It is well documented that youth who experience multisystem adversity show more externalizing psychopathology.[49,50] For instance, the family stress model posits that poverty, unsafe neighborhoods, and economic instability stress parents, undermining their emotional resources and leading to greater family conflict and eventually harsher parenting (and child externalizing). This model has been supported by a host of empirical studies,[51-53] highlighting that broader environments play a role in shaping the proximal environment for the developing youth. Notably, however, experiences of family conflict and low school involvement reflected another robust risk pathway for externalizing, suggesting that, for some youth, adversity localized to family and school interactions confer risk for externalizing. Parenting that is harsh and inconsistent has been linked robustly to the development of externalizing behaviors.[54,55] This type of parenting is thought to model aggression for young people and to undermine their ability to develop emotion regulation skills necessary for related constructs such as empathy, and inconsistency in parenting is thought to lead to reward contingencies that make aggression or breaking rules useful in some contexts. Furthermore, youth who experience conflict at home often bring this history to school, where they begin these types of cycles with peers and teachers, leading to trouble in school and often social rejection. These findings underscore the need for researchers and clinicians to assess risk across multiple systems. We already possess an array of relatively effective treatments and prevention strategies for externalizing psychopathology.[56-58] They may not work for all young people, but they can for some young people.[59] However, generally speaking, the interventions that work best take into account transactions that exist within and around the child. Thus, consideration of the multiple risk factors for a specific youth is needed during the selection and implementation of treatment.[56,60]

Critically, the integrated analysis highlighted key pathways whereby experiences within environmental systems were associated with externalizing and internalizing psychopathology via subcortical GM volume, aligning with our second hypothesis. Family and neighborhood affluence during late childhood was associated with higher subcortical GM volume during early adolescence, which in turn was associated with lower externalizing and internalizing. This pathway reveals how relative affluence buffers against externalizing and internalizing psychopathology via GM volume in brain regions responsible for reward, sensorimotor, cognitive, and emotion processing. In contrast, family economic and neighborhood adversity were associated with lower subcortical GM volume, which in turn was associated with higher externalizing and internalizing. This finding is consistent with a previous study showing that subcortical GM trajectories mediate the relationships between preschool socioeconomic status and high-risk behaviors.[18] Therefore, there is growing evidence to show that socioeconomic adversities can have a negative impact on structural brain development, which may increase the risk of mental health problems through stress and lack of experiences that enrich development.[17,19,61] However, it is notable that subcortical GM volume did not mediate the relationship between the profile that described the most adverse experiences across multiple systems (Profile 5) and externalizing/internalizing (although see Supplement 1, available online, for a specific effect with depression). When a child experiences multiple strong adversities, these adverse experiences provide a "push" to a given outcome such that the importance of biological factors in these environments might be diminished.[62] This is supported by the social push hypothesis[62]—namely, that when there are more and stronger environmental pushes (eg, harsh parenting in the context of neighborhood disadvantage and crime) toward psychopathology, biological risk for psychopathology may matter less. Our findings support the consideration of an integrated approach to parse the direct and indirect transactions among multiple environmental systems, subcortical GM volume, and externalizing/internalizing psychopathology.

Before concluding, it is important to note some limitations. First, there is sometimes criticism about the small effect sizes obtained from the ABCD Study. To address this criticism, there have been efforts to establish heuristics to describe the meaningfulness of these small effect sizes in a relatively larger sample such as those in most other studies.[63,64] For example, a recent study suggested that benchmarks such as below average ≈0.03, average ≈0.05, above average ≈ 0.09, and extremely above average ≈0.18 may be a heuristic for research for the ABCD Study.[63] Based on this heuristic, the magnitude of the direct effects (environment → subcortical GM volume and environment → externalizing) was extremely above average. The magnitude of the mediation effects in our study was small using this heuristic, although there is growing recognition that very small effects can accumulate meaningfully over time.[65] As small effect sizes are well powered in the ABCD Study, they do have the potential for practical and clinical significance.[64] Second, we focused on subcortical GM volume, as subcortical structures are sensitive to socioeconomic resources and psychopathology during childhood and adolescence.[1-21] However, other brain measures also have been associated with socioeconomic resources.[66,67] Future work could identify pathways that facilitate transactions between multiple environments, multi-modal brain measures (eg, cortical thickness and surface area, diffusion tractography, functional connectivity), and psychopathology. Given the large number of variables, this would require the use of multivariate methods such as canonical correlation analysis to identify all linear combinations of variables from 2 sets that are maximally correlated—which is challenging with traditional path analysis. Third, evidence of the relationship between the multisystem environmental profiles and internalizing was more inconsistent across effects than the externalizing effects. It is possible that this inconsistency relates to the reliance on parent reports for our youth sample. There is evidence of low-to-moderate agreement between parent- and youth-reported problem behaviors from the CBCL syndrome scales, with lower agreement for internalizing than for externalizing, which could add more noise to the relationships.[68-71] Fourth, the environmental data were obtained from scales that have moderate reliabilities over time. Although some of the environments may change for some youth as they grow up, others may not change as much.[72] Future research can examine the latent transitions of multisystem profiles over time. Furthermore, there is a possibility of bi-directional associations among multiple environmental factors, brain, and youth psychopathology. Ultimately, future work could extend the integrated approach by examining specific pathways through which these bi-directional associations may exist, fully testing the transactional nature of environment–brain–psychopathology relationships. Finally, using a subset of the ABCD Study may introduce sampling bias in deriving the multisystem environmental profiles, as the sample may not fully represent the target population, which in turn could affect the generalizability of the profiles.[73] Although our sample reflects the socioeconomic and psychopathology characteristics of the full ABCD Study, we observed differences in neighborhood deprivation and residential segregation (Supplement 1, available online). By extension, although the ABCD Study sample and the subsample used in the present study show sociodemographic variation, the ABCD Study/our sample may not capture the full spectrum of adversities that youth experience.

In conclusion, our integrated approach highlights multiple equifinal pathways to adolescent psychopathology, some directly via the environment and others via structural brain development. To advance research and clinical work, it is crucial to move beyond simplistic or siloed models and instead adopt frameworks that capture the interplay among diverse environmental contexts—ranging from proximal influences such as parenting to distal factors such as policy and structural inequality. By incorporating multilevel assessments of the environment, researchers can better identify the nuanced pathways through which risk and resilience emerge. Such complexity is necessary to develop more precise, personalized models of adolescent psychopathology, and to identify which youth are most likely to benefit from specific treatments, given the full ecological reality of their lives.

CRediT authorship contribution statement

Jivesh Ramduny: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Samuel Paskewitz:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Inti A. Brazil:** Writing – review & editing, Validation, Investigation. **Arielle Baskin-Sommers:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Data Sharing: Data used in the preparation of this article were obtained from the ABCD Study® (abcdstudy.org/), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children aged 9-10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health (NIH) and additional federal partners under award numbers: U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. The full list of federal supporters is available at https://abcdstudy.org/federal-partners.html. The complete lists of participating sites and study investigators can be found at https://abcdstudy.org/consortium_members/. The ABCD Consortium investigators designed and implemented the study and/or provided the 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.

Code Availability: The analysis code for the Bayesian LPA framework can be found at https://github.com/SamPaskewitz/dpm.lpa. The analysis code for the integrated approach can be found at https://github.com/JRam02/embeddedbrain.

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