Modeling Individualized Adolescent Mental Health through a Multifactorial Causal Framework to Identify Potential Intervention Strategies

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Abstract

Adolescence is a sensitive period for the emergence of psychopathology. During this time, physiological changes and environmental exposures jointly shape brain development and influence cognitive and personality maturation, collectively heightening vulnerability to mental disorders. However, the complexity of interactions between these factors has hindered a systems-level understanding of mental health and the causal roles of cognition and personality in psychopathology. In this study, we proposed a multifactorial causal framework integrating brain, pubertal, environmental, and behavioral factors to characterize heterogeneity in adolescent mental health trajectories at the individual level. We then investigated latent causal pathways linking cognition and personality to mental health outcomes and identified potential personalized intervention targets. Leveraging the Adolescent Brain Cognitive Development (ABCD) dataset ($N = 4{,}501$), we analyzed 165 behavioral pairs connecting cognition and personality traits to mental health symptoms. Using cross-sectional multivariate mediation and longitudinal interaction-inclusive analyses, we identified 68 behavioral pairs showing significant causal relationships, with brain and environmental exposures contributing to most pathways, while pubertal factors exhibited limited involvement. Individualized interpretive analyses further revealed 23 pairs suggesting potential interventions with response rates exceeding 50%. Among these, behavioral inhibition, negative urgency, and processing speed emerged as the most common intervention targets, whereas psychosis symptoms and attention problems were the most likely issues to improve. Overall, our study advances a comprehensive framework capturing the multifactorial and heterogeneous nature of adolescent mental health, delineates specific causal pathways from cognitive and personality traits to psychopathology, and provides a principled basis for potential individualized intervention strategies.

Introduction

Adolescence is a period of intense physiological and psychological development[1,2] that often contributes to increased individual vulnerability and a heightened risk for the onset of various mental health disorders[3,4]. Approximately 20% of adolescents suffer from a psychopathology persisting into adulthood[5] that results in substantial patient and healthcare burdens[6,7]. This highlights the importance of a systems-level understanding of mental health, the identification of causal factors contributing to psychopathology, and the development of targeted intervention strategies.

Understanding adolescent mental health involves two major challenges. Firstly, accounting for the complex interactions among multiple contributing factors remains challenging[8]. Theoretical frameworks, including the Scaffolding Theory of Aging and Cognition model[9] and heuristic conceptual models[3,10] have highlighted the crucial roles of brain development, environmental exposures, pubertal transitions, cognition and personality in shaping mental health. However, their joint contributions have not yet been extensively investigated. Secondly, adolescent mental health exhibits substantial inter-individual heterogeneity, encompassing differences in psychological development[11–14]. Variations in biological[15,16], behavioral[17,18], and environmental[19,20] profiles across individuals contribute to this heterogeneity and confer distinct vulnerabilities[21]. This multifactorial complexity and individual variability have prevented a full mechanistic understanding of mental health, consequently limiting the effectiveness and precision of current intervention strategies[7].

Existing interventions aimed at improving mental health have mostly focused on reducing risk exposure[22–25] and strengthening coping skills[26–28]. While these approaches have shown beneficial effects, alternative strategies have been largely overlooked. Few studies have examined whether regulating cognition and personality traits could enhance mental health, despite growing evidence of strong associations between behavioral factors and mental health[29,30]. Lower cognitive performance, for example, has been linked to higher risk of mood and anxiety disorders during adolescence[31]. Likewise, all Big Five personality traits have been associated with well-being at both behavioral and neural levels, with shared neural substrates that may explain variability seen in therapeutic outcomes[32–34]. Overall, the causal influence of cognition and personality on mental health remains underexplored, limiting the development of novel interventions targeting these potentially modifiable traits.

To address these gaps, we developed a computational framework designed to advance insights into the multifactorial and individualized nature of adolescent mental health, elucidate behavioral causality and generate data-driven suggestions for personalized interventions. Leveraging a large sample (N = 4,501) from the Adolescent Brain Cognitive Development (ABCD) study, we integrated comprehensive measures of brain structure, puberty, environmental exposures, cognitive abilities, personality, and mental health[35–38]. We initially used interpretable linear regression models[39] to assess key brain-behavior associations and applied exploratory factor analysis to identify latent constructs and reduce data redundancy among brain measures. We then conducted three main analyses. First, we performed a cross-sectional multivariate mediation analysis to delineate potential pathways linking cognition and personality to mental health. Second, we used a longitudinal interaction-inclusive model to examine causal effects along these pathways. Finally, to account for the heterogeneity of mental health trajectories, we conducted individualized interpretive analyses on the longitudinal model to propose personalized preventive strategies and inform the identification of target populations. An overview of the analytical pipeline is presented in **Fig. 1**.

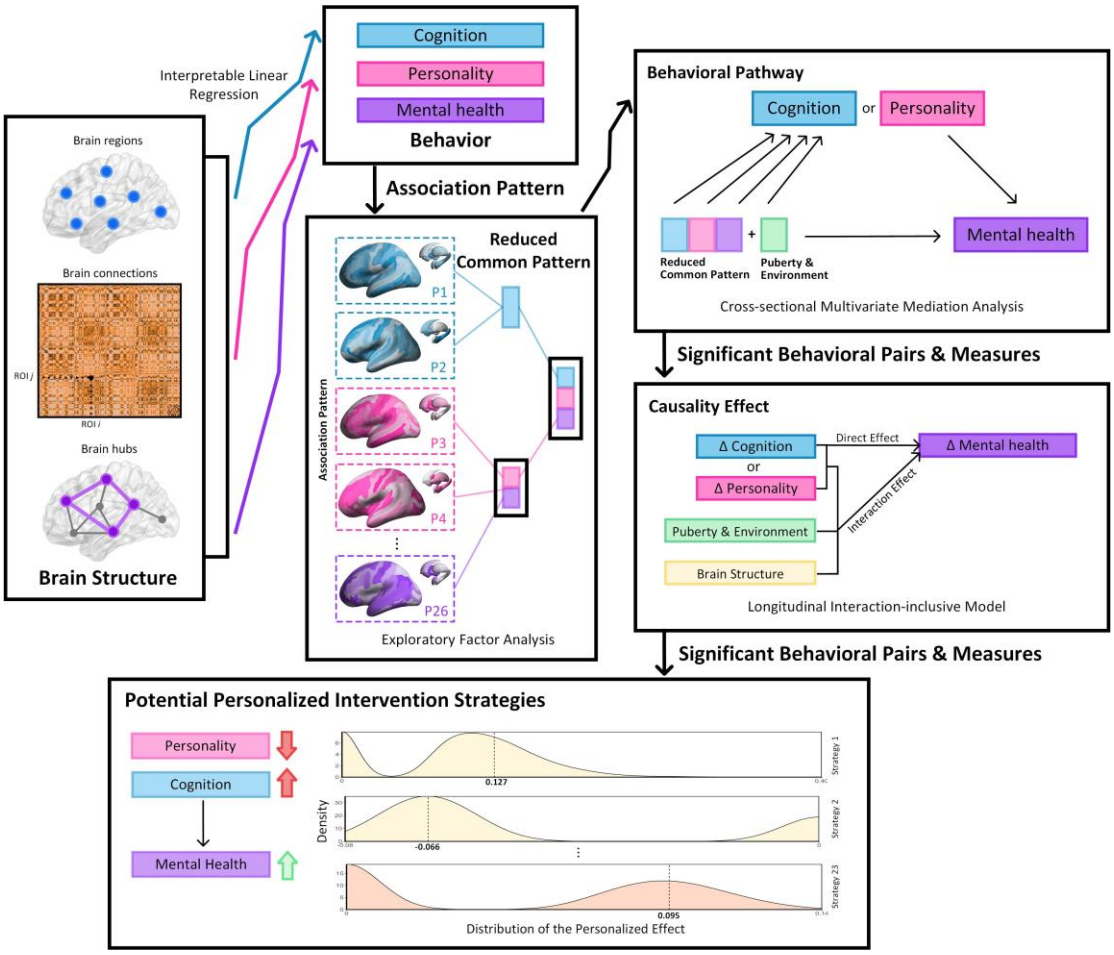

Fig. 1. Flowchart of the analysis. The study employed a multifactorial causal framework comprising five components: interpretable linear regression, exploratory factor analysis, cross-sectional multivariate mediation analysis, longitudinal interaction-inclusive model, and investigation of potential personalized intervention strategies.

Results

Hierarchical association of behaviors based on brain structure

To identify shared brain structural association patterns across cognition, personality, and mental health domains while reducing the dimensionality of brain measures (see Methods), we performed exploratory factor analysis (EFA) on the 26 brain-behavior association maps derived from the interpretable linear regression models[39]. This analysis allowed us to construct a hierarchical representation of the relationship between the 26 behavioral measures based on brain features. As shown in **Fig. 2**, all pairs of behaviors exhibited common brain structural association patterns that could be used for subsequent top-ranked brain measure selection. Importantly, the hierarchy derived from brain patterns was broadly consistent with that independently obtained from behavioral test scores, supporting the reliability of the EFA-based hierarchy. However, whereas behavioral domains were clearly delineated in the score-based results, these boundaries were less distinct in the brain-derived hierarchy. Specifically, based on brain association patterns, two measures of personality—lack of planning and lack of perseverance—showed stronger associations with mental health than with their own domain, while two mental health measures—total psychosis symptoms and psychosis severity—were more closely linked with personality. These shared brain association patterns were

subsequently used to reduce the dimensionality of brain measures for further analyses between behavioral pairs.

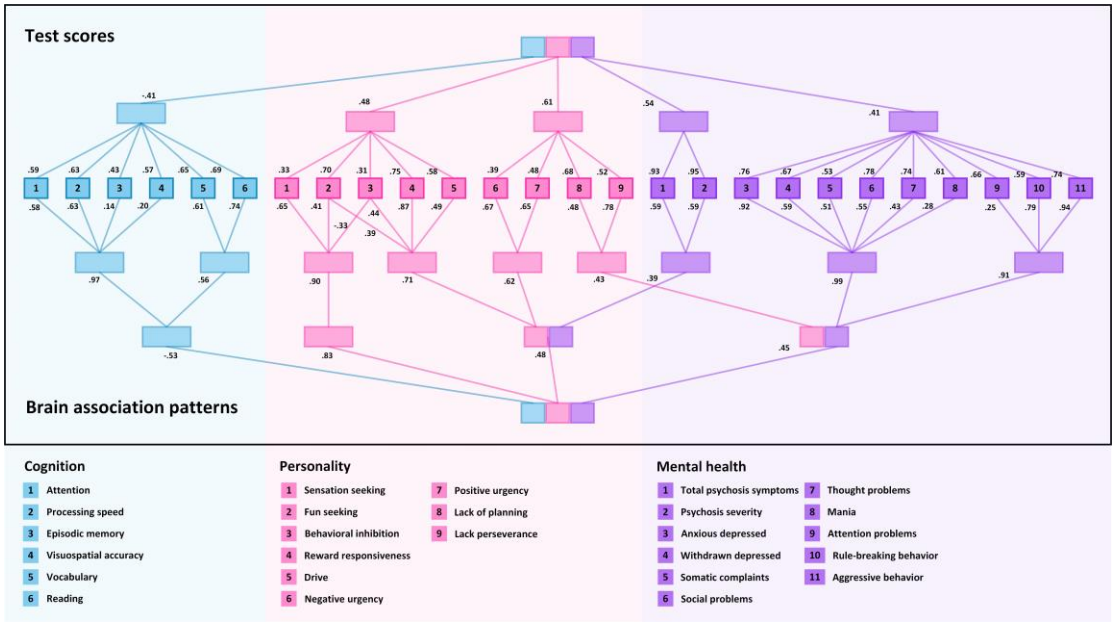

Fig. 2. Hierarchical association of cognition, personality, and mental health based on test scores and brain structural association patterns. The hierarchy derived from test scores comprised three layers, whereas the hierarchy from brain association patterns comprised four layers. The loading values obtained from EFA are represented in the graph. Blue indicates cognition, pink indicates personality, and purple indicates mental health. Combination of squares indicate latent factors integrating multiple subdomains (e.g. pink and purple combination squares indicate that this factor is constituted by subdomains stemming from both personality and mental health).

Mediation pathways linking cognition/personality to mental health

To identify pathways linking cognition and personality to mental health, we performed a cross-sectional multivariate mediation analysis leveraging previously reduced brain measures, pubertal measures, and environmental measures as model inputs. Among the 165 behavioral pairs tested, 95 exhibited significant mediation effects, with proportions mediated ranging from 3.27×10^{-11}% to 19.88% (**Fig. 3A**).

Personality showed greater involvement in these mediation pathways than cognition, particularly through, behavioral inhibition, and negative urgency. Crystallized cognitive abilities, such as vocabulary and reading, also contributed significantly. Among mental health outcomes, attention problems, rule-breaking behavior, and psychosis symptoms and severity were most frequently implicated.

Across the three categories of phenotypic measures (brain, pubertal, and environmental), environmental factors were significantly involved in all 95 pathways (**Fig. 3A**), with weekend screen time, family conflict, and school involvement and disengagement emerging as the most frequently implicated contributors (**Fig. 3C**). In contrast, pubertal measures played a limited role, with dehydroepiandrosterone (DHEA) showing relative prominence. Puberty was not implicated in pathways relating to episodic memory, drive, and lack of planning (**Fig. 3A**).

Moreover, brain structure contributed significantly to the majority of mediation pathways, except

for a subset related to attention, episodic memory, behavioral inhibition, psychosis severity, thought problems, and mania (**Fig. 3A**). Our analysis revealed that the left horizontal ramus of the anterior segment of the lateral sulcus, right parahippocampal gyrus, right medial orbital sulcus, right inferior temporal gyrus, and left medial occipito-temporal sulcus and lingual sulcus were the most frequently implicated regions (**Fig. 3B**). More detailed phenotypic results are shown in **Supplementary Fig. 1-2**.

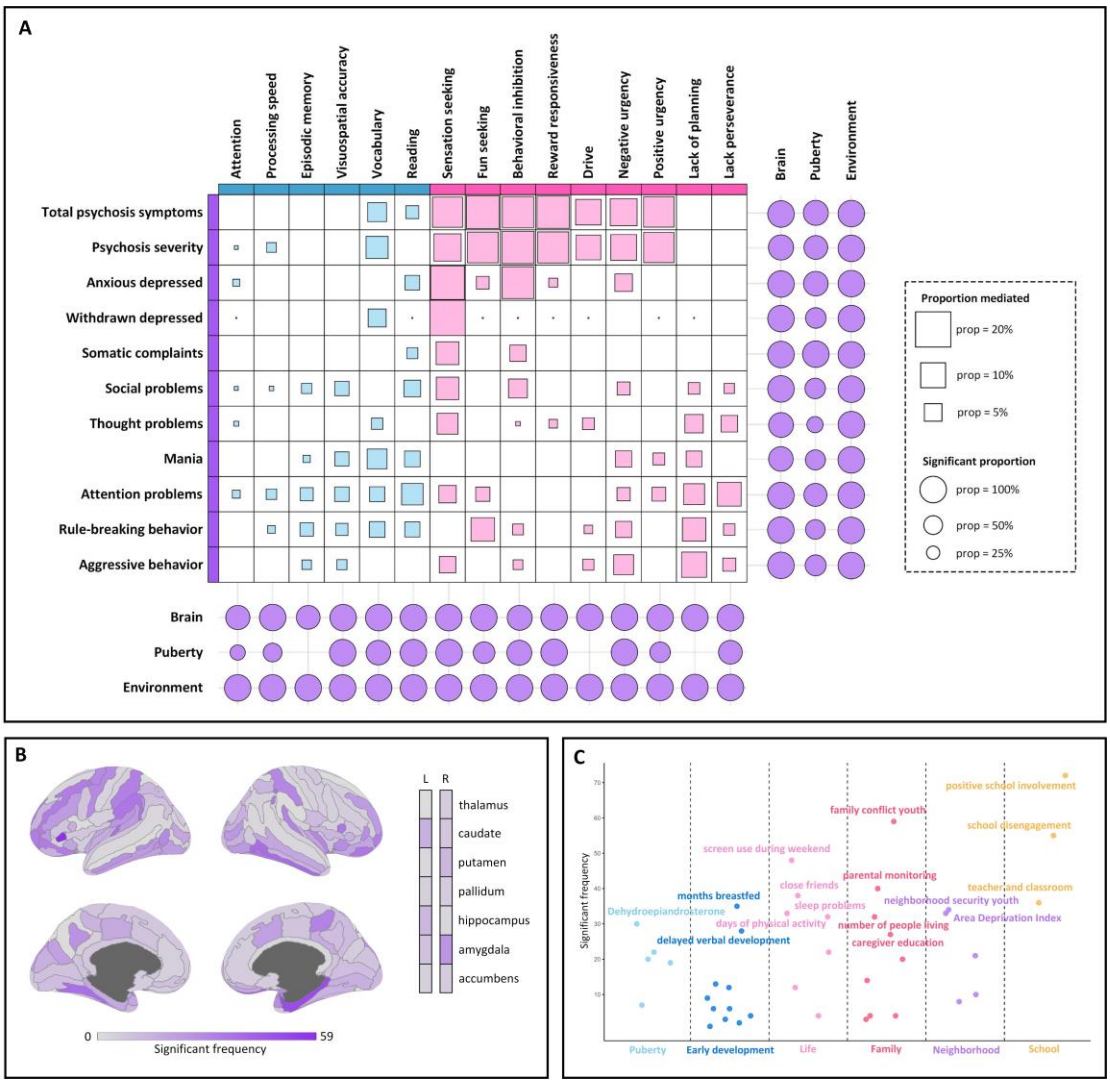

Fig. 3. Mediation pathways from cognition and personality to mental health, and the corresponding brain structural, pubertal, and environmental factors. (A) Proportion mediated for each behavioral pair and the significance of brain, pubertal, and environmental contributions. Square size represents the proportion mediated, with blue indicating cognition-related pairs and pink indicating personality-related pairs. The size of the purple circles denotes the proportion of significant input measures (brain, puberty, and environment), calculated as the ratio of behavioral pairs with a significant input measure to the total number of significant pairs within each row or column. (B) Summary of brain regions significantly implicated in the mediation pathways. Across all 95 significant behavioral pairs, significant brain regions, connections, and hubs were identified based on 162 ROIs; each connection was counted as two ROIs to reflect that each connection contributes to the involvement of both linked regions. (C) Summary of pubertal and environmental

factors contributing to the mediation pathways. For all 95 significant behavioral pairs, we quantified the frequency of significant pubertal and environmental measures, with the most prominent ones displayed.

Causal effects from cognition/personality to mental health

To examine causal effects linking cognition and personality to mental health, we applied a longitudinal interaction-inclusive model to the 95 significant behavioral pairs and their corresponding significant phenotypic measures. This analysis yielded 68 behavioral pairs showing significant causal effects (**Fig. 4A**). Consistent with the previous mediation findings, personality contributed more frequently than cognition to these causal relationships.

We examined four types of effects, as detailed in the Methods section: one behavioral direct effect and three interaction effects involving brain, pubertal, and the environmental measures. Results demonstrated substantial combinatorial heterogeneity among these four effect types across behavioral pairs, with 31 of the 68 pairs exhibiting at least two effect types. Direct effects from cognition or personality to mental health were observed in 30 of 68 pairs, whereas no direct effects emerged in pairs involving episodic memory, reward responsiveness, or withdrawn depressed.

Consistent with the previous pathway results, environmental interactions played a prominent role (**Fig. 4A**). However, environmental factors were not involved in pairs related to attention, processing speed, or somatic complaints. Compared with earlier mediation findings, the most significant environmental contributors shifted from school-related factors (*e.g.* school involvement) to life-event and family environment, including weekend screen time, sleep problems, and family conflict (**Fig. 4C**). Pubertal influences remained minimal, with DHEA no longer among the top contributors. In contrast, brain interactions continued to be widely implicated, occurring in 34 of the 68 behavioral pairs. The most frequently involved regions included the left transverse temporal sulcus, left fronto-marginal gyrus and sulcus, right sulcus intermedius primus, and right calcarine sulcus (**Fig. 4B**). Although these top regions differed from those identified in the mediation analysis, they were likewise concentrated in the frontal, temporal, and occipital lobes. Among subcortical structures, only the right amygdala showed consistent significance. More detailed phenotypic results are shown in **Supplementary Fig. 3-4**.

Additionally, when comparing the current 68 behavioral pairs (**Fig. 4A**) with the previous 95 pairs (**Fig. 3A**), we found that pairs that were no longer significant were primarily related to cognition, particularly attention, visuospatial accuracy, and reading. In terms of mental health outcomes, these dropped pairs were mostly associated with scores on the withdrawn depressed, social problems, and rule-breaking behavior scales. In contrast, pairs involving fun seeking, reward responsiveness, psychosis symptoms, anxious depression, and somatic complaints consistently showed significant effects. A split-half validation was conducted to evaluate the generalizability of the findings, showing an average stability of $r = 0.81 \pm 0.13$, indicating robust reproducibility. After applying multiple-comparison correction via Bonferroni adjustment (empirical permutation, adjusted $p \leq 0.05$), all 95 behavioral pairs remained significant. Results of the competitive permutation-based correction are provided in **Supplementary Materials S1**.

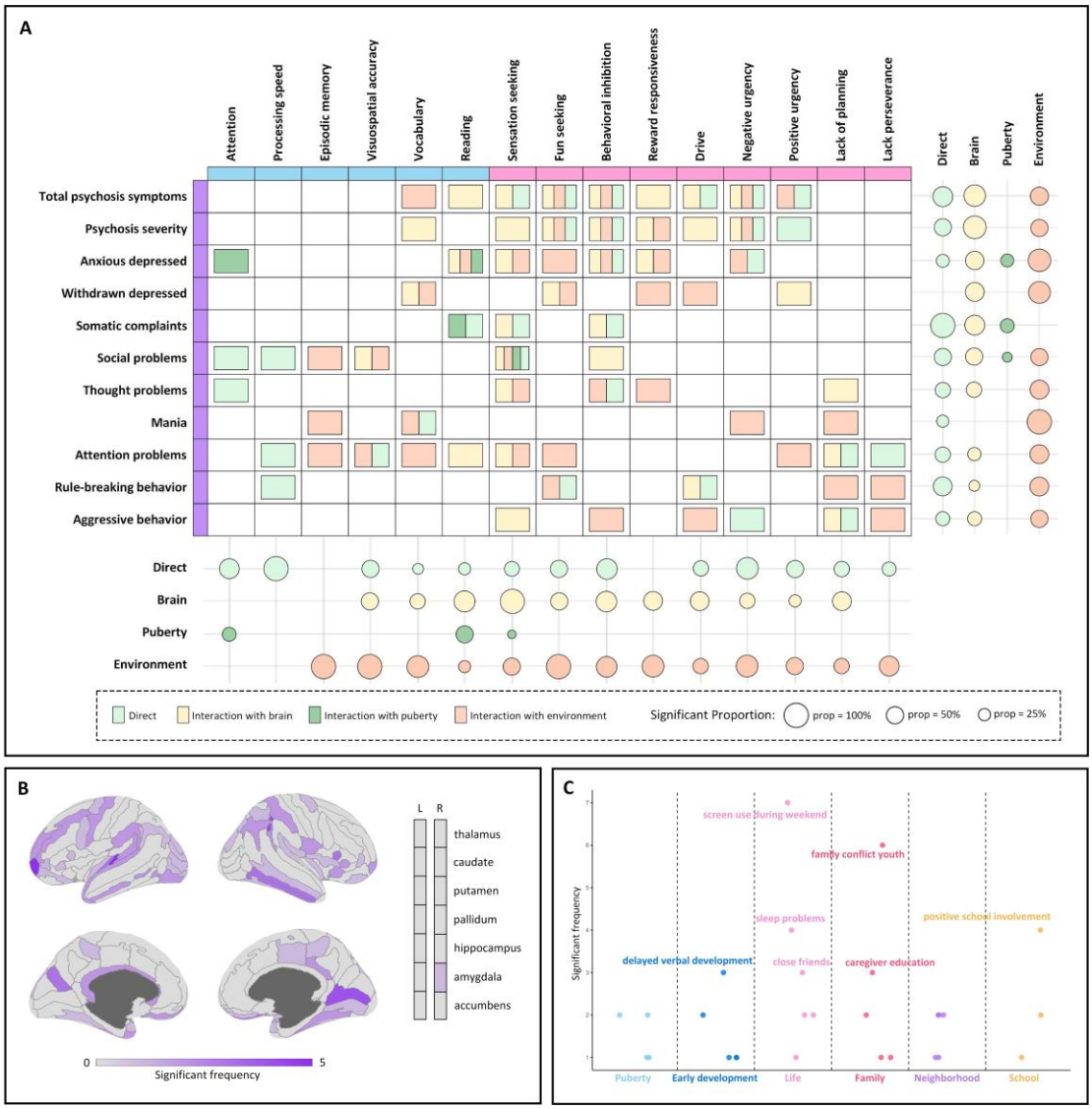

Fig. 4. Causal effects from cognition/personality to mental health and the corresponding brain structural, pubertal, and environmental factors. (A) Types of causal effects across behavioral pairs and significance of brain, pubertal, and environmental factors. Four effect types were examined: direct effects (light green), interactions with brain (yellow), puberty (green), and environment (orange). As in **Fig. 3A**, circle size indicates the significant proportion of input measures. (B) Summary of significant brain regions identified in the causal analyses. For all 68 significant behavioral pairs, significant brain regions, connections, and hubs were counted based on 162 ROIs; connections were counted as two ROIs to reflect that each connection contributes to the involvement of both linked regions. (C) Summary of significant pubertal and environmental factors identified in the causal analyses. For all 68 significant pairs, significant pubertal and environmental measures were quantified, with the most prominent ones displayed.

Potential personalized intervention strategies through regulation of cognition and personality

Building on previously established longitudinal models for the 68 behavioral pairs with significant causal relationships, we performed individualized interpretive analyses to identify potential personalized strategies for improving mental health via modulating cognition and personality factors. We identified 37 behavioral pairs that exhibited a non-zero response rate—defined as the proportion

of participants showing significant suggested intervention effects within the sample, **Fig. 5A**). Among these, behavioral inhibition and negative urgency emerged as the most effective personality-based regulators, while attention and processing speed were the leading cognition-based regulators. The most frequently modulated mental health symptoms included attention problems and psychosis-related symptoms and severity. Within these 37 pairs, 8 exhibited a 100% response rate (**Fig. 5B**), reflecting that all individuals demonstrated significant model-predicted intervention effects, not complete recovery. In contrast to previous results, cognitive traits, particularly processing speed and attention, were more frequently involved than personality traits in these highly responsive strategies. Nevertheless, among the 15 behavioral pairs that exhibited a response rate between 50% and 100% (**Fig. 5C** and **5D**), personality played a more prominent role.

Furthermore, all 23 behavioral pairs (comprising 5 cognition-based and 18 personality-based pairs) demonstrated absolute interventional mean effect sizes ranging from 0.059 to 0.192. Ten pairs showed mean effects greater than 0.1, with the strongest effects observed in the following strategies: reducing anxious-depressed symptoms via behavioral inhibition, reducing attention problems via lack of perseverance, and reducing psychosis severity via fun seeking. Consistently, all strategies indicated that enhancing cognitive abilities and reducing maladaptive personality traits improved mental health outcomes. Split-half validation on the corresponding longitudinal models of these 23 pairs demonstrated strong generalizability and reproducibility with an average stability of 0.84 ($r = 0.84 \pm 0.10$).

We randomly selected three moderately effective (50-70% response rate) behavioral pairs to illustrate suggested strategies for identifying individuals most likely to exhibit a therapeutic response (**Fig. 5E**). The first pair involved reducing aggressive behavior by decreasing lack of planning; individuals with stronger specific brain structural connections ($p < 0.001$) were more likely to respond. The second pair aimed to reduce somatic complaints by decreasing behavioral inhibition; individuals with higher FA in the right intraparietal sulcus and transverse parietal sulci ($p < 0.001$) tended to benefit from this potential intervention. The third pair targeted attention problems through increasing visuospatial accuracy; individuals with moderate weekend screen time ($p < 0.001$) were more likely to show a response.

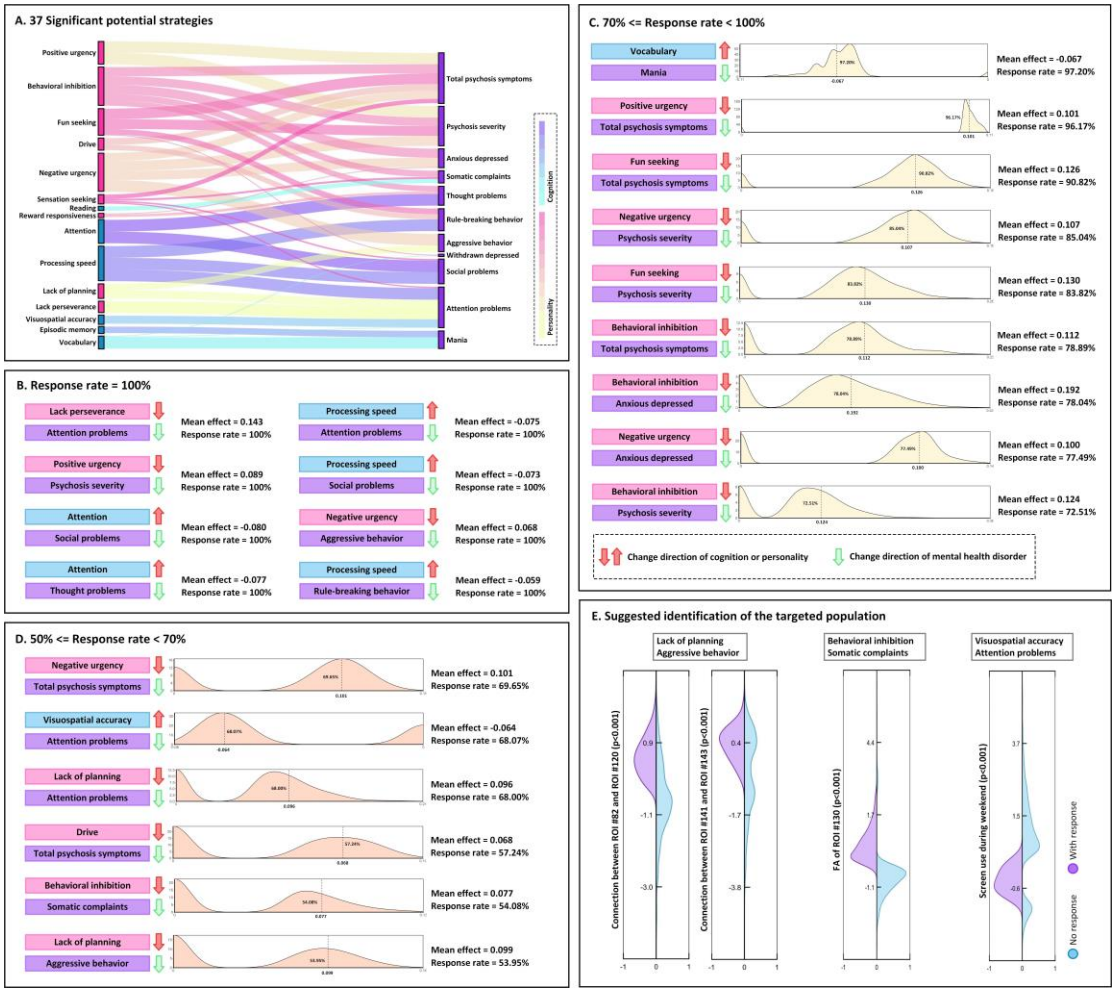

Fig. 5. Suggestions for personalized intervention strategies and identification of targeted populations. (A) We identified 37 significant behavioral pairs with a non-zero suggested response rate (proportion of participants showing significant suggested intervention effects), representing potential personalized intervention strategies. In the Sankey diagram, shades of blue represent cognition-related interventions, while shades of pink represent personality-related interventions. Ribbon width corresponds to the response rate across the tested population, with wider ribbons denoting higher response rates. (B) Eight behavioral pairs showed a suggested response rate of 100%. For each pair, we presented the mean effects (calculated based on the subjects with non-zero effects). Red arrows indicate the direction of change in cognition or personality, while green arrows indicate the corresponding direction of change in the targeted mental health outcome. Upward arrows denote increases, and downward arrows denote decreases. (C-D) To accommodate space limitations, behavioral pairs with response rates <100% were divided into two groups: 9 pairs with 70-100% response rates (C) and 6 pairs with 50-70% response rates (D). For each pair, we showed the distribution of suggested intervention effects across the population, together with the mean effect and response rate. (E) Examples of targeted population identification. For each of three behavioral pairs, participants were split into "response" and "no response" groups. Distributions of corresponding significant phenotypic measures are shown for both groups, all of which differed significantly ($p < 0.001$). ROI #82: right middle-posterior part of the cingulate gyrus and sulcus, ROI #120: right marginal branch of the cingulate sulcus, ROI #130: right intraparietal sulcus and transverse parietal sulci, ROI #141: right postcentral sulcus, ROI #143: right superior part of the

precentral sulcus.

Discussion

Adolescence is a particularly vulnerable period for mental health, shaped by ongoing maturation of cognition and personality, rapid brain development, dynamic pubertal hormone changes, and the cumulative effects of environmental exposures[7,27,29]. To our knowledge, the present study is among the first to systematically examine these complex and interacting phenotypes within a data-driven, multifactorial causal framework. Using this approach, we identify significant patterns of behavioral causality and delineate potential avenues for individualized intervention.

Causality linking cognition and personality with mental health

All behavioral factors examined in the current study participated in multiple significant causal pathways (**Fig. 4A**), with traits related to interpersonal engagement—particularly vocabulary, sensation seeking, and behavioral inhibition—emerging as the most frequently involved. Impairment of vocabulary ability during adolescence would cause lower engagement in education and employment, along with an increased risk of affective disorders[40]. Sensation seeking, in turn, directly links to increased sexual risk-taking and exposure to violence[41,42], and is positively associated with narcissistic, antisocial, and aggressive traits[43]. Early-life behavioral inhibition, particularly when interacting with parental influences, can influence long-term mental development[44,45], such as associations between higher levels of behavioral inhibition and greater difficulties in mentalizing ability[46]. Taken together, these behavioral traits may alter patterns of interpersonal engagement by increasing internalized stress while limiting access to externalized social support, thereby conferring heightened vulnerability to depression, social problems, and psychosis-related symptoms[44,45,47]. Causal relationships among other behavioral pairs appear to operate through more heterogeneous mechanisms, underscoring the need for future studies that integrate brain maturation, environmental exposures, and pubertal development to more precisely characterize the pathways linking cognition, personality, and mental health.

Impacts of brain in behavioral causality

Predominantly, significant effects in behavioral causality were observed in regions located within the frontal, temporal, and occipital lobes, with additional involvement of the insular cortex. These regions have been repeatedly implicated in prior research on personality disorders and cognitive impairments, particularly deficits in attention and cognitive control[48–50]. For instance, dysfunctions in prefrontal regions have been linked to impaired impulse control and attentional regulation in conditions such as borderline personality disorder and attention-deficit/hyperactivity disorder[48]. Abnormalities within the temporal lobe have similarly been associated with cognitive impairments and personality changes, including evidence from neurodegenerative conditions[49,51] and schizotypal personality disorder[52]. Altered activity in occipital regions, particularly in EEG-based resting-state alpha dynamics and emotional visual processing, has also been related to cognitive impairment[53] and affective dysregulation[50] in major depressive disorder. Notably, the insular cortex, which plays a central role in integrating cognitive control and emotional processing, has also been implicated in schizophrenia and personality disorders[54,55]. Collectively, these findings indicate that the regions participating in behavioral causality are consistently implicated in disorders characterized by impaired attention, cognitive control, and personality dysfunction.

Impacts of environment and puberty in behavioral causality

Compared to brain-derived metrics, environmental factors exhibited more widespread effects, with lifestyle-related exposures showing the strongest contribution. In particular, weekend screen use and sleep problems emerged as prominent factors. Excessive screen time has been consistently associated with poorer cognitive performance[47] as well as diminished well-being[56], while sleep problems, which are highly prevalent across mental disorders[57], have been linked to adverse personality traits[58] and reduced positive mood[59]. Together, these lifestyle-related exposures appear to exert sustained and pervasive influences on individual behavioral patterns, further influencing broader mental health systems. Family-related exposures also showed notable effects. For example, family conflict was significantly associated with poorer well-being, with prior work suggesting partial mediation by cognitive abilities such as cognitive flexibility[60], underscoring the importance of family support during adolescence.

In contrast, pubertal factors showed relatively limited effects. Hormonal measures were significant in only a small number of behavioral pairs, predominantly involving reading ability (**Fig. 4A**). This pattern is consistent with prior evidence indicating that testosterone influences brain regions implicated in verbal dominance[61]. At the same time, the restricted scope of pubertal effects aligns with recent findings reporting no clear causal links between estradiol exposure and brain structure or mental health outcomes[62]. Overall, these findings highlight the complex, multifactorial nature of mental health systems and the predominant role of environmental influences[3,7,9].

Prior research on mental health enhancement through cognition and personality regulation

Prior research has demonstrated evidence for reducing symptoms of psychiatric disorders through cognitive and personality modulation. For example, improving attention and focus have been shown to improve social and behavioural symptoms in children with neurodevelopmental disorders[63–66]. In patients with ADHD, improving attention through behavioural interventions or stimulant medication have also been linked to improved social functioning and decreased symptoms from comorbid psychopathologies[63], while in autism, joint-attentional interventions generalized to better social communication skills[64]. Likewise, our results indicate that modulating attention may represent a particularly effective target, specifically in improving thought-disorder symptoms and social functioning (**Fig. 5**). Indeed, many of our identified paired cognitive, personality, and behavioural traits align with patterns previously reported in the literature, such as the association between stronger speech ability and reduced manic symptoms[67], or the relationship between negative urgency and poorer depression and anxiety outcomes[68]. Nevertheless, not all identified pairs are currently supported with empirical evidence, necessitating further clinical investigation to validate and extend our findings. Given that neuropsychiatric treatments are typically multifactorial therapeutic strategies, developing targeted interventions using discrete cognitive and personality traits may prove useful complements to established gold-standard approaches like cognitive behavioural therapy, which predominantly focuses on regulating higher-order cognitive processes[69]. Overall, our findings provide data-driven, theoretical guidance on the cognitive and personality traits most relevant to different mental-health domains, offering a foundation for future clinical validation and development of personalized therapies.

A real-world design for investigating novel personalized intervention strategies

Building on our results, we propose an experimental framework to assess the real-world intervention effects of potential strategies and expected outcomes suggested in our study. First, a representative sample for the target population should be recruited. Based on the expected Type I Error and statistical power, the required sample size can be estimated using G*Power software[70]. Next, validated measurements should be selected to assess both the targeted cognitive/personality traits and relevant mental health outcomes[7,71]. An effective intervention for regulating the targeted cognitive/personality should be concomitantly identified, either drawing from prior literature or pilot experiments[72,73]. Ideally, a longitudinal placebo-controlled intervention should be conducted, during which repeated assessments are collected, including brain MRI, pubertal, environmental and behavioral observations[4,9]. Then unpaired t-tests can be used to compare mental health outcomes between the intervention and placebo groups. Within the intervention group, individuals can be categorized into responders and non-responders. Responders and non-responders can also be compared to further delineate the most important phenotypic measures (brain, pubertal, and environmental) that distinguish those who respond to the intervention. Ultimately, this proposed investigation framework can validate the effectiveness of our suggested potential intervention strategies. We present an example testing processing speed for reducing attention problems, social problems, and rule-breaking behavior (**Table 1**).

Table 1. Investigation process of reducing social problems, attention problems, and rule-breaking behavior by improving processing speed ability.

Participants: Recruit 1204 participants with representative demography, aiming for around 93.41% statistical power of intervention effectiveness investigation and around 68.78% power of targeted phenotype identification at 5% Types I Error.
Measurements: Use NIH Toolbox[74] to measure processing speed ability and CBCL scale[75] to measure social problems, attention problems, and rule-breaking behavior. Additional measurements should also include brain MRI, pubertal, and environmental data.
Intervention: Speed of processing training (SPT) is performed to improve processing speed ability[76], consisting of ten 60- to 75-min sessions for 6 weeks[77]. The first 5 sessions are standardized, and the last 5 ones can be determined by the certified trainer.
Experiment: Divide the participants into 3 groups randomly[77]: SPT group (n = 602), active control group (perform memory training, n = 301), no-contact control group (n = 301). Baseline observations, performance interventions, and follow-up observations should be recorded.
Analysis: Investigate the effectiveness of SPT for improving processing speed ability. Perform the unpaired t-test to investigate the effectiveness of improving processing speed ability for reducing social problems, attention deficits, and rule-breaking behavior. Finally, identify the participants with/without response after the SPT intervention, and then perform the unpaired t-test to determine the phenotypes (such as morphometry of frontal cortex and insula) which help identify the responders with positive effects.

Strengths and limitations

To our knowledge, the present study is among the first to address the multifactorial nature and heterogeneity of the adolescent mental health system within a data-driven causal framework. We developed a generalizable analytical structure that integrates multilevel developmental factors, constrains behavioral causal inference through longitudinal modeling, and enables individualized

estimation of mental-health-relevant effects, rather than being limited to a disorder-specific or dataset-bound model. Results from individualized analyses support the potential for personalized intervention strategies and provide a principled approach for identifying individuals most likely to benefit from such interventions, thereby contributing to the precision medicine in adolescent mental health.

Nevertheless, there are several limitations in the current study. First, the ABCD dataset does not include data from participants undergoing mental health interventions, and we are unable to directly assess the actual intervention effects. Second, participant recruitment bias may limit generalizability of our results as most individuals belong to high-income countries. Derived associations between mental health factors and suggested interventions may not be applicable to those in lower to middle income countries that tend to report a heavier burden of mental illness[7,26].

Methods

Participants

We adopted the full ABCD 5.1 release cohort, including 27595 observations of 11868 participants ranged from 9 to 15 years old across 22 sites[37]. We first excluded brain scans which failed in quality control or were defined as clinically abnormal[38]. We then excluded any observation with missing phenotypic measures studied here, while retaining other time points from the same participant when complete data were available. This process yielded a final cohort including 6255 observations of 4501 participants, which were adopted for the cross-sectional analysis. Within these 6255 observations, we selected all the 1644 pairs of longitudinal observations of 1437 participants, which were adopted for the longitudinal analysis. The detailed participant characteristics are described in **Supplementary Table 1**.

Behavioral measures

Behavioral measures comprised scores from cognitive, personality, and mental health assessments. Cognitive assessments included 6 measures: Attention, Processing speed, Episodic memory, Vocabulary, and Reading from the NIH Toolbox[74] and Visuospatial accuracy from the Little Man Test[78]. Other cognitive measures in ABCD were missing at some time points and were thus not utilized in the current study. As for personality, we adopted 9 impulsivity-related personality measures: Negative urgency, Positive urgency, Lack of planning, Lack of perseverance, and Sensation seeking from the Modified UPPS-P for Children[79] and Behavioral inhibition, Reward responsiveness, Drive, and Fun seeking from the Behavioral Inhibition and Activation scales[80]. These were the only personality measures available in the ABCD dataset, which does not include traditional Big Five traits. In terms of mental health, we used 11 measures: Anxious depressed, Withdrawn depressed, Somatic complaints, Social problems, Thought problems, Attention problems, Rule-breaking behavior, and Aggressive behavior from the Achenbach Child Behavior Check List (CBCL)[75], Mania from the Parent General Behavior Inventory[81], and Total psychosis symptoms and Psychosis severity from the Pediatric Psychosis Questionnaire[82]. These behavioral measures have been widely used in prior research as they effectively capture individual variability in cognitive ability, personality profile, and mental health status[30,39,83,84].

Brain structural, pubertal, and environmental measures

We adopted a comprehensive set of brain structural measures, as in a previous study[39]. The imaging

data included T1w density (T1w), T2w density (T2w), and diffusion Magnetic Resonance Imaging (dMRI) images[37], which were preprocessed by the ABCD group[38]. The Destrieux atlas[85] with 148 regions of interest (ROIs) and ASEG atlas[86] with 14 ROIs were adopted for brain cortex and subcortex parcellation, respectively. Each brain cortical region had 6 Structural Magnetic Resonance Imaging (SMRI) measures (cortical area, cortical thickness, sulci depth, volume, T1w density, and T2w density), 4 Diffusion Tensor Imaging (DTI) measures (Fractional Anisotropy, Mean Diffusivity, Longitudinal Diffusivity, and Transverse Diffusivity), and 6 Restriction Spectrum Imaging (RSI) measures (Hindered Normalized Directional, Hindered Normalized Isotropic, Hindered Normalized Total, Restricted Normalized Directional, Restricted Normalized Isotropic, and Restricted Normalized Total)[87]. Each subcortical region had the same measures except for cortical area, cortical thickness, and sulcal depth. This led to a total of 2550 region-wise structural measures (*i.e.* 148×16 + 14×13 = 2550). We then applied the advanced morphometric similarity networks (MSNs) method[88] to characterize the structural connections between each pair of ROIs, yielding a total of 13041 connection-wise measures (*i.e.* 162×(162 - 1)/2 = 13041). We further calculated 6 graphical measures (strength, clustering coefficient, local efficiency, betweenness centrality, within-module degree, and participation coefficient)[89] for each brain ROI within the constructed MSNs to obtain a total of 972 hub-wise measures (*i.e.* 162×6 = 972). In total, we extracted 16563 brain structural measures (*i.e.* 2550 + 13041 + 972 = 16563, **Fig. 1**) to characterize individual brain structure, similarly to one of our previous studies[39]. More details are described in **Supplementary Materials S2**.

For puberty, we adopted 8 measures that showed significant influences on adolescent behavior[3]. We utilized 4 measures derived from the Pubertal Development Scale (PDS)[35,90] to capture puberty stage, including the overall average PDS score, adrenal-related average score, gonadal-related average score, and puberty category score. Additionally, we used Body Mass Index (BMI) as a puberty-related indicator of physical maturation. We also used 3 measures to capture hormone levels[90,91], including dehydroepiandrosterone (DHEA), testosterone (T), and estradiol (E2). E2 was only available for females. More details about these measures are described in **Supplementary Materials S3**.

Moreover, we adopted 39 environmental measures from 5 distinct categories[29]. The first category was perinatal events and early development (13 measures), including maternal and paternal age at childbirth, twin birth, planned pregnancy, maternal medication use during pregnancy, maternal substance use during pregnancy, maternal medication conditions during pregnancy, Prematurity status, caesarian delivery, birth complication, months breasted, delayed motor development, and delayed verbal development. The second category was life events and lifestyle (7 measures), including traumatic events, religious beliefs, close friends, days of physical activity, screen use during weekdays, screen use during weekends, and sleep problems. The third category was family environment (10 measures), including family conflict reported by parents and youth, parental monitoring, caregiver employment, number of people living, caregiver marital status, severe financial difficulty[92], parental psychopathology, caregiver education, and family income. The fourth category was neighborhood environment (6 measures), including neighborhood security reported by parents and youth, area deprivation index, pollution, crime, and lead risk. The fifth category was school environment (3 measures), including teacher and classroom environment, positive school involvement, and school disengagement. More details can be found in a previous study[29].

Interpretable linear regression and exploratory factor analysis

Given that the number of brain measures substantially exceeded the number of subjects, we reduced the brain measures to avoid N/P ratio issues for machine learning methods[93]. For each of the 26 behaviors (*i.e.* 6 cognition + 9 personality + 11 mental health = 26), we fitted a separate interpretable linear regression to examine corresponding brain-behavior association patterns (**Fig. 1**). Specifically, as in a previous study[39], the interpretable linear regression was implemented via an optimized LASSO model to provide reliable association results. This method yielded 26 association patterns, each with 16563 associations, corresponding to each brain structural measure detailed in the previous section (further methodological details are provided in **Supplementary Materials S4**). We then conducted an exploratory factor analysis (EFA)[94], which helped identify latent factors by grouping together brain-behavior associations that share common variance. Specifically, we performed EFA 3 times, resulting in a 4-layer hierarchical structure that ultimately converged to a single factor. The common pattern for each of the 165 behavioral pairs (*i.e.* (6 cognition + 9 personality)×11 mental health = 165 pairs) was the first latent factor where the two corresponding patterns (one from the cognitive/personality and one from the mental health) converged in the EFA hierarchy. Independently, we also conducted EFA on the 26 behavioral test scores to evaluate the reliability of the EFA-based hierarchy. In terms of the prior assumption validation and settings for EFA, all our inputs passed KMO and Bartlett's test of sphericity. We utilized principal axis factoring and Promax rotation combined with Kaiser normalization[94], and set 0.3 as the golden loading threshold to determine significant latent factors[95].

After identifying the common latent brain-behavior association patterns for each of the 165 behavioral pairs, we extracted the most informative subset of brain measures based on their absolute loading strengths on the corresponding common patterns. This procedure effectively reduced the original 16,563 brain measures to a smaller subset, thereby mitigating N/P ratio issues and improving the interpretability and stability of subsequent machine learning models. Specifically, we first selected the top-ranked hub-wise measures over a range of numbers (2, 3, 4, and 5-30, 5 intervals) and then proportionally selected region-wise and connection-wise measures, yielding 9 sets of brain measures with varying total feature counts (113, 147, 181, 214, 382, 551, 719, 887, and 1055, including hub-, region-, and connection-wise features). Accordingly, we constructed 9 sets of brain inputs and performed our further analysis 9 times to fully leverage the brain structural features. More details can be found in **Supplementary Materials S5**.

Cross-sectional multivariate mediation analysis

We performed a multivariate mediation analysis on cross-sectional data to identify behavioral pairs that exhibited significant pathways from cognition or personality to mental health outcomes (**Fig. 1**). Each mediation model incorporated one of nine sets of reduced brain measures, together with eight pubertal and 39 environmental measures, as predictors (x) in Equations (1) - (3). In these equations, M and Y represent the single targeted cognition/personality measure and the corresponding mental health outcome, respectively. Linear regression models were estimated with 1,000 bootstrap iterations, and coefficients c_k and mediation products $a_k b$ were deemed significant when their two-sided 5–95% confidence intervals excluded zero[96–99]. Traditional mediation analysis involves three variables (x, M, and Y); here, we expanded the predictor x into multiple variables similarly to prior studies[100] to better capture the multifactorial nature of mental health. We computed total, indirect, and mediated effects according to Equations (4) - (6). For each

behavioral pair, nine mediation analyses were performed using the nine distinct input sets, and the model yielding the best proportion mediated was retained as the final result. Pathways were considered present only when the final proportion mediated was significantly different from zero. Brain, pubertal, and environmental variables exhibiting significant $a_k b$ effects were interpreted as mediators contributing to the observed pathways. Only behavioral pairs with significant mediation effects were included in subsequent analyses. Additional details are provided in **Supplementary Materials S5**.

$$M = a_1x_1 + a_2x_2 + \cdots + a_nx_n + Intercept_1 \quad (1)$$
$$Y = c'_1x_1 + c'_2x_2 + \cdots + c'_nx_n + bM + Intercept_2 \quad (2)$$
$$Y = c_1x_1 + c_2x_2 + \cdots + c_nx_n + Intercept_3 \quad (3)$$
$$Total\ effect = \sum_{k=1}^{n} |significant\ c_k| \quad (4)$$
$$Indirect\ effect = \sum_{k=1}^{n} |significant\ a_k b| \quad (5)$$
$$Proportion\ mediated = Indirect\ effect\ /\ Total\ effect \quad (6)$$

In Equation (1), M denotes the mediator (a single cognition or personality measure), and a_k represents the effect of each predictor x_k (brain, pubertal, or environmental measure) on the mediator. In Equation (2), b represents the path coefficient from M to the outcome Y (a single mental health measure), while c'_k denotes the direct effects of each predictor after accounting for the mediator. Equation (3) models the total effects c_k of predictors on Y without including M. Equations (4) - (6) define the total, indirect, and mediated effects, where only coefficients whose bootstrap confidence intervals excluded zero were considered significant.

Longitudinal interaction-inclusive model and the investigation of potential personalized intervention strategies

Because mediation analysis identifies statistical pathways rather than causal effects, we next applied a longitudinal interaction-inclusive model to determine behavioral pairs exhibiting significant potential causal relationships, based on the previously identified significant behavioral pairs and phenotypic measures (brain structure, puberty, and environment). Specifically, we decomposed the causal effects into two components: (1) the direct effects of changes in the targeted cognition/personality measure (hereafter referred to as targeted behavior) on changes in the corresponding mental health outcome, and (2) the interaction effects between changes in the targeted behavior changes and baseline phenotypic measures (**Fig. 1**). For each behavioral pair, the longitudinal interaction-inclusive model was specified as follows:

$$\Delta MH \sim \Delta TB + \Delta TB * BS_0 + \Delta TB * P_0 + \Delta TB * E_0 + BS_0 + P_0 + E_0 + \Delta BS + \Delta P + \Delta E + \epsilon \quad (7)$$

Where MH denotes the targeted mental health measure, TB the targeted behavior, BS the brain structural measure, P the pubertal measure, and E the environmental measure. The Δ symbol indicates change in value between two longitudinal timepoints for a given variable, while the subscript 0 represents the baseline value of the variable. Beyond the direct effects (ΔTB), and interaction effects ($\Delta TB * BS_0$, $\Delta TB * P_0$, $\Delta TB * E_0$), baseline and change terms (BS_0, P_0, E_0, ΔBS, ΔP, ΔE) were included as covariates for strict control. The interaction-inclusive model was estimated using 1,000 bootstrap iterations. Two-sided 5-95% CIs were calculated for all to identify

significant direct and interaction effects, thereby determining behavioral pairs showing significant causal associations with phenotypic measures. Only these significant behavioral pairs and phenotypic variables were retained for subsequent analyses.

Although previous group-wise results cannot be applied to individual level, the interaction terms in Formula (7) allow us to address the heterogeneity of mental health systems. We therefore conducted an individualized interpretive analysis based on these interaction terms. Specifically, as shown in Formula (8), we calculated each individual's effect from ΔTB to ΔMH by inputting their significant individualized phenotypic measures and summing up all the parameters multiplied by ΔTB. The resulting value represents the change (in standard deviation) in ΔMH corresponding to a one standard deviation change in ΔTB, reflecting the individualized intervention potential of improving mental health through modulation of cognition or personality.

$$\Delta TB + \Delta TB * significant\ BS_0 + \Delta TB * significant\ P_0 + \Delta TB * significant\ E_0 \rightarrow \Delta MH \quad (8)$$

Because 1000 longitudinal interaction-inclusive models were fitted across 1000 bootstrap samples, we obtained 1000 individualized effect estimates for each participant. Two-sided 5-95% CIs were then computed for these effects to identify subjects exhibiting a significant response – that is, those whose individual effects were significantly different from zero. The response rate was then quantified across the entire sample (1644 observations from 1437 participants) and the mean effect was calculated among participants with significant non-zero effects to estimate the potential effectiveness of the modeled intervention strategies. Finally, after classifying participants as responders or non-responders, we examined differences in the significant phenotypic measures involved in Formula (8) between the two groups. This comparison allowed us to identify phenotypic profiles associated with a higher likelihood of response, thereby providing potential guidance for tailoring future intervention strategies.

Collinearity removal strategy and significance selection strategy

We employed two key methodological strategies to ensure the reliability of the results: a collinearity removal strategy and a significance-based selection strategy. Both the multivariate mediation analysis and the longitudinal interaction-inclusive models relied on multivariate linear regressions, which are susceptible to collinearity when used for interpretability. Specifically, regression models may depend on a subset of predictors (inputs) for fitting, overlooking collinear variables that also influence the outcome, thereby introducing bias into the interpretation of results. To mitigate this issue, we implemented a collinearity removal strategy, as shown in Equations (9) and (10). Before inputting the original predictors X into linear regression model, we performed a principal component analysis (PCA) that mapped the original predictors into an orthogonal feature space by multiplying the $Mapping\ Matrix$. Note that this PCA was not used to reduce dimensionality, but solely to orthogonalize the predictors and eliminate inter-feature correlations. As a result, the shared variance among correlated predictors was distributed evenly, allowing the subsequent linear regressions to treat each input feature equitably for interpretability. The orthogonalized inputs were then normalized using the $New\ Mean$ and $New\ SD$ (New Standard Deviation), after which parameters W and intercept b were estimated by linear regression. Mathematically, the new parameters $New\ W$ corresponding to the original input features were derived by (10), which were subsequently used to interpret the contribution of each input feature.

$$((X * Mapping\ Matrix - New\ Mean)./New\ SD) * W + b = Y \quad (9)$$

$$New\ W = Mapping\ Matrix * W./New\ SD \quad (10)$$

Another key methodological component was the significance-based selection strategy, which followed the same principle adopted by various previous studies[39,96–99]. For each linear regression model in the current study, we performed 1000 bootstrap iterations, yielding 1000 observations for each model parameter. Parameters were considered significant when their two-sided 5-95% bootstrap-derived CIs excluded zero. The mean effect of each corresponding significant input feature was then calculated by averaging its 1000 parameter estimates. Because the core causal testing was conducted in Formula (7) and multiple models were constructed to evaluate distinct behavioral pairs, multiple comparison correction was applied across these models. This step was essential to determine which behavioral pairs exhibited statistically significant causal relationships, whereas correction was unnecessary within each model, as all input coefficients were jointly estimated within a single linear regression framework[96]. To accomplish this, we employed two complementary correction strategies[101]: empirical permutation (based on null distributions generated by shuffling output correspondence) and competitive permutation (in which input features were replaced by non-significant brain, environmental, and pubertal measures identified in the previous mediation analyses). Both procedures involved 10,000 iterations to ensure high-resolution estimation of the adjusted p value.

Covariate control

Age, sex, handedness, ethnicity, study site, and a proxy measure of brain volume (PBV) were included as covariates in all analyses. PBV refers to the whole brain volume excluding the specific cortical or subcortical metric examined in each analysis. PBV was used instead of total brain volume to avoid over-correcting for effects of interest[102]. For the longitudinal analyses, we controlled for age and PBV at both baseline and follow-up timepoints, as well as sex, handedness, ethnicity, and study site at baseline, which remained unchanged at follow-up. Subject and family confounds were further mitigated by improving the bootstrap procedure for each computational model, following a previous study[39]. Specifically, in each bootstrap iteration, we first randomly selected one observation per participant or family, and then performed bootstrap resampling across these observations. This procedure yielded 3,987 participants for cross-sectional analyses and 1,328 participants for longitudinal analyses, free from subject and family confounds.

Split-half validation

A split-half validation was performed to assess model generalizability. As the longitudinal interaction-inclusive models yielded the principal findings on behavioral causality and potential intervention effects, validation was limited to these models. For each of the 95 behavioral pairs, samples were randomly divided into two equal subsets, and the same longitudinal modeling procedure was applied to each subset. Significant parameter estimates from both models were correlated using the Pearson Correlation Coefficient (PCC). This random-split procedure was repeated 100 times, and the mean PCC across repetitions was used as the final indicator of generalizability.

Data availability

The data used in this study were obtained from the ABCD Study (release 5.1) under the terms of a data use agreement. The raw data cannot be shared directly by the authors but are accessible through application to the NIMH Data Archive (NDA). Researchers with approved access can use the analysis scripts provided by the authors to reproduce the results.

Code availability

All analysis code is accessible online: https://github.com/JDYan/Behavioral-Causality.

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Jiadong Yan: Methodology, Software, Formal analysis, Investigation, Writing–original draft, Writing–review & editing, Visualization. Bin Wan: Methodology, Investigation, Writing–original draft. Paule Joanne Toussaint: Methodology, Investigation, Writing–review & editing. Judy Chen: Investigation, Validation, Writing–original draft, Writing–review & editing. Gleb Bezgin: Visualization, Validation, Writing–review & editing. Yasser Iturria-Medina: Conceptualization, Methodology, Software, Formal analysis, Validation. Danilo Bzdok: Methodology, Validation, Writing–review & editing. Alan Evans: Conceptualization, Funding acquisition, Supervision. Sherif Karama: Conceptualization, Methodology, Writing–original draft, Writing–review & editing, Funding acquisition, Supervision.

Competing interests
The authors declare no competing interests.