Developmental timing of associations among parenting, brain architecture, and mental health

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Key Points

Question Are there sensitive periods when parenting during childhood has stronger associations with functional brain architecture during adolescence, and in turn mental health during early adulthood?

Findings This longitudinal cohort study of 173 youth demonstrated that associations between harsh parenting and brain architecture were widespread in early childhood, but localized to cortico-limbic circuitry in late childhood. Associations with warm parenting were localized to cortico-limbic regions in middle childhood, which related to lower internalizing symptoms in early adulthood during the COVID-19 pandemic.

Meaning Identifying sensitive periods for the neurodevelopmental associations of parenting can inform the type and timing of preventive interventions.

Abstract

Importance Parenting relates to brain development and long-term health outcomes, though whether these associations depend on the developmental timing of exposure remains understudied. Identifying these sensitive periods can inform when and how parenting is associated with neurodevelopment and risk for mental illness.

Objective To characterize how harsh and warm parenting during early, middle, and late childhood relate to brain architecture during adolescence and, in turn, psychiatric symptoms in early adulthood during the COVID-19 pandemic.

Design 21-year observational, longitudinal birth-cohort study from the Future of Families and Child Wellbeing Study. Data were collected from February 1998-June 2021. Analyses were conducted from May-October 2023.

Setting Population-based.

Participants 173 low-income youth from Detroit, Michigan; Toledo, Ohio; and Chicago, Illinois.

Exposures Parent-reported harsh parenting (psychological aggression, physical aggression), and observer-rated warm parenting (responsiveness), at ages 3, 5, and 9 years.

Main Outcomes and Measures Brain-wide (segregation, integration, small-worldness), circuit (prefrontal-amygdala connectivity), and regional (betweenness centrality of amygdala and prefrontal cortex) architecture at age 15 using functional magnetic resonance imaging. Youth-reported anxiety and depression symptoms at age 21.

Results 173 youth (mean[SD] age = 15.88[0.53] years; 95[55%] female; 138[80%] Black) were included. Parental psychological aggression during early childhood was positively associated with brain-wide segregation ($\beta = 0.30$, 95% CI 0.14 to 0.45) and small-worldness ($\beta = 0.17$, 95% CI 0.03 to 0.28), whereas parental psychological aggression during late childhood was negatively associated with prefrontal-amygdala connectivity ($\beta = -0.37$, 95% CI -0.55 to -0.12). Warm parenting during middle childhood was positively associated with amygdala centrality ($\beta = 0.23$, 95% CI 0.06 to 0.38) and negatively associated with prefrontal centrality ($\beta = -0.18$, 95% CI -0.31 to -0.03). Warmer parenting during middle childhood related to reduced anxiety (95% CI -0.10 to -0.01) and depression (95% CI -0.10 to -0.003) during early adulthood via greater adolescent amygdala centrality.

Conclusions and Relevance Neural associations with harsh parenting were widespread across the brain in early, but localized in late, childhood. Neural associations with warm parenting were localized in middle childhood, in turn relating to mental health during future stress. These developmentally-contingent associations can inform the type and timing of interventions.

Introduction

Cross-species evidence demonstrates that parenting promotes or undermines children's health, emotional wellbeing, and adaptive functioning across the lifespan, partly through alterations in brain development.[1-5] Across animal and human studies, parenting has been associated with the structure, function, and connectivity of cognitive and affective systems across the entire brain, with consistent associations reported in the cortico-limbic circuit that underlies processing of salience, threat, and emotion.[5-8] As the developing brain calibrates to current environmental demands, children adapt their emotional learning and regulation to navigate their immediate context, with consequences for future mental health.[4] Accordingly, characterizing how modifiable parenting behaviors relate to brain development and emotional wellbeing is critical for targeted treatment and prevention to reduce the substantial, cascading burden of mental illness.

Key theories in pediatric and developmental sciences posit *sensitive periods* of brain development, which represent windows of elevated neuroplasticity during which both positive and negative experiences can have more potent and lasting associations with brain and behavior.[9-12] In particular, the environment is theorized to more powerfully relate to brain systems that are developing most rapidly – and may thus be especially malleable – during the period of exposure.[12-14] Consistent with theory, emerging investigations suggest developmental specificity in how experiences relate to the structure and function of cortico-limbic circuitry.[15-22] However, limited research has tested this notion in humans with the ability to parse timing-specific from cumulative associations, especially with both adverse (e.g., harsh parenting) and supportive (e.g., warm parenting) contexts.

The brain is a complex network of regions that interact to shape behavior,[23] prompting the need for computational techniques that can capture the functional architecture of the brain across spatial scales,[24] rather than only specific regions or circuits of interest. Furthermore, how the neurobiological associations of parenting during sensitive periods relate to mental health remains unknown, especially during developmental (adolescence, early adulthood) and contextual (stressful) periods of heightened vulnerability.[25,26] Prospective, longitudinal, and network analytic designs that span multiple developmental stages are required to elucidate these complex, dynamic pathways. Delineating how different parenting behaviors exhibit timing-dependent neurobiological associations linked to mental health has critical public health implications to inform developmentally tailored preventive interventions.

The present study examined how harsh and warm parenting during early, middle, and late childhood relate to functional brain architecture within a longitudinal, population-based sample of predominantly low-income, racially minoritized adolescents. We applied connectivity and graph theoretic analyses to characterize functional architecture across the brain, in cortico-limbic circuitry, and in key cortical and limbic regions. Leveraging recent statistical innovations (structured life-course modeling approach; SLCMA),[27,28] we disentangled timing-dependent from cumulative associations between parenting and neural architecture to identify sensitive periods in the neurobiological embedding of parenting. We used multi-method (observational, parent-reported) measures of parenting, assessing harshness and warmth separately given their distinct associations with neurobehavioral development.[29,30] Finally, we tested whether neural architecture in adolescence was associated with anxiety and depression six years later in early adulthood during a widespread stressor (the COVID-19 pandemic).

Methods

Participants

Participants included 173 youth from the Future of Families and Child Wellbeing Study, a population-based cohort of 4,898 children born in large US cities oversampled (3:1) for non-marital births, resulting in a strong and generalizable sampling frame with high representation of low-income, racially minoritized families.[31] Data were collected at birth (starting on February 1, 1998) and ages 1, 3, 5, 9, and 15 years through phone and home visits. In a follow-up sub-study, the Study of Adolescent Neural Development (SAND), 237 youth (15-17 years) from Detroit (MI), Toledo (OH), and Chicago (IL) completed neuroimaging. Six years later (21 years), participants self-reported symptoms of anxiety and depression via online and phone interviews during the peak of the COVID-19 pandemic (April 30, 2020-June 26, 2021). Sixty-four participants were excluded due to MRI contraindications, refusing to scan, insufficient neuroimaging data, and coverage/signal issues (**eMethods**), but did not differ from included participants on major sociodemographic variables (**eTable1**). Parents provided written informed consent and youth provided oral assent across waves. FFCWS and SAND were approved by the Institutional Review Boards of Princeton University and the University of Michigan. This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Parenting Behaviors

We measured harsh and warm parenting from biological mothers during early (3 years), middle (5 years), and late (9 years) childhood (**eMethods, eTable2**). Harsh parenting was

measured using the Psychological Aggression and the Physical Aggression subscales from the parent-reported Parent-Child Conflict Tactics Scale.[18,32] Warm parenting was measured using in-home observer ratings on the Responsiveness Subscale from the Home Observation for Measurement of the Environment.[33]

MR Acquisition

Neuroimaging data were acquired on a GE Discovery MR750 3T scanner with an 8-channel head coil (**eMethods**). Acquisition included a T1-weighted structural scan, an 8-minute resting-state scan,[34] a socioemotional face processing task-based scan,[17] and a reward processing task-based scan.[35] We concatenated resting-state and task-based scans (with task effects regressed out), generating ~20 minutes of "pseudo-rest" neuroimaging data per participant to describe overall, intrinsic functional brain architecture with higher reliability.[36–38] We corrected motion artifacts using a conservative, multi-step procedure (**eMethods)**.[39]

Functional Connectivity and Graph Theoretical Analyses

We parcellated the brain into 333 cortical and 54 subcortical regions of interest (ROIs) from established atlases[40,41] to generate functional connectivity matrices using BOLD timeseries.

Circuit-Level. To investigate cortico-limbic circuitry (**Figure 1**), we constructed bilateral masks for the amygdala (4 ROIs) and regulatory regions of prefrontal cortex (PFC; 46 ROIs)[42–44] (**eTable3**). We then Fisher *r*-to-*z* transformed each matrix and calculated average PFC-amygdala connectivity.

Graph Analyses. In graph theoretic analyses probing brain architecture, we removed negative connections and Fisher *r*-to-*z* transformed each matrix.[45] We generated weighted, undirected graphs[45] to investigate *brain-wide* and *regional* architecture (**Figure 1**).

Brain-Wide. We characterized three metrics of brain-wide architecture: (1) modularity (network segregation) estimates the degree to which the brain organizes into distinct, specialized networks;[46] (2) global efficiency (network integration) estimates how efficiently information can flow across the brain;[47] and (3) small-world propensity measures the balance between segregation and integration, which represents an "optimal" architecture.[48]

Regional. At the regional level, we calculated the betweenness centrality of the amygdala and PFC.[49] Regions with higher betweenness centrality can exert a stronger influence on global neural communication. See **eMethods, eTable2**, and **eTable4**.

Mental Health

Anxiety and depressive symptoms during early adulthood (21 years) were self-reported using sum scores from the 21-item Beck Anxiety Inventory[50] and 20-item Beck Depression Inventory[51] during the COVID-19 pandemic (**eTable2**).[52]

Statistical Analyses

Analyses were conducted in R (v4.2.2) and accounted for missing parenting, covariate, or mental health data using multiple imputation (20 imputations, 25 iterations, *mice* package).[53] To examine how parenting relates to brain architecture, we leveraged SLCMA,[27,28] a two-stage approach that models associations with timing (continuous parenting scores during early/middle/late childhood) versus accumulation (sum of parenting scores across waves).

SLCMA has recently been applied to epigenetic, psychiatric, and behavioral, but not neural, outcomes,[54–57] and is similar to developmental science studies using time-varying exposures to investigate plasticity of resilience-related processes among adversity-exposed youth.[58] In the first stage, SLCMA implements least-angle regression to select a model containing the sensitive period, cumulative score, or combination thereof with the greatest explanatory power until additional model complexity contributes negligible incremental variance, determined by elbow plots of variance explained (**eFigure1**). In the second stage, effect estimates are calculated for each selected model pooled across imputed datasets using Rubin's rules. We used post-selective inference to calculate *P*-values and confidence intervals adjusted for the selective process in the first stage. We tested each parenting dimension and brain outcome separately, correcting for multiple comparisons based on the selected models within each parenting dimension using the false discovery rate (FDR). P_{fdr}-values <.05 indicated statistical significance.

When significant associations between parenting and brain architecture were detected, we tested for "indirect effects" to anxiety and depressive symptoms (i.e., brain architecture as a mechanism linking parenting to mental health). We used the PROCESS macro to calculate bias-corrected confidence intervals with 10,000 bootstraps within each imputed dataset and generated an average 95% confidence interval across imputations. Direct paths were estimated from regression models pooled across imputed datasets using Rubin's rules.

To address potential confounds during the neuroimaging wave (**eMethods**), analyses controlled for sex assigned at birth, ethnoracial identity (youth-reported at age 15), pubertal development (primarily youth-reported at age 15), poverty ratio (age 15), parental education (age 15), and in-scanner head motion (mean framewise displacement). Graph theoretic analyses also controlled for mean functional connectivity. Analyses with psychiatric symptoms additionally

controlled for pre-pandemic levels of anxiety and depression (age 15) to examine whether brain architecture relates to *changes* in psychiatric symptoms.

Results

Of the 237 participants, 173 (mean[SD] age = 15.88y[0.53y]; range = 15.03y-17.60y; 95[55%] female, 78[45%] male; 138[80%] Black, 9[5%] Hispanic, 9[5%] Other/Multiple, 17[10%] White; median family income = $36,555) were included following exclusion for neuroimaging analyses (**eMethods**). Harsh and warm parenting were weakly correlated with each other (**eTable5**). Correlations within parenting dimensions across waves ranged from weak to strong (|*r*| = .06 to .58; **eTable5**). These findings may partly reflect measurement unreliability and/or suggest that parenting environments are dynamic across childhood,[59] which facilitates delineation of potential sensitive periods in their neuropsychiatric associations.

Sensitive Periods for Neurobiological Associations of Harsh Parenting

In the first stage of model selection, timing-dependent associations were favored over cumulative associations for both psychologically and physically aggressive parenting (**eFigure1**). In the second stage (**Table; Figures 2-3**), greater psychological aggression during *early childhood* was associated with greater *brain-wide* modularity (β = 0.30, 95% CI [0.14, 0.45]) and small-world propensity (β = 0.17, 95% CI [0.03, 0.28]), but more negative PFC-amygdala *circuit* connectivity during *late childhood* (β = -0.37, 95% CI [-0.55, -0.12]). No other timing-dependent or cumulative associations survived FDR correction.

Sensitive Periods for Neurobiological Associations of Warm Parenting

For warm parenting, timing-dependent associations were similarly favored over cumulative associations (**eFigure1**). In the second stage (**Table; Figures 2-3**), warmer parenting

during *middle childhood* was associated with greater *regional* betweenness centrality of the amygdala (β = 0.23, 95% CI [0.06, 0.38]) and lower *regional* betweenness centrality of PFC (β = -0.18, 95% CI [-0.31, -0.03]). No other timing-dependent or cumulative associations survived FDR correction.

Longitudinal Associations with Mental Health

We next tested associations between adolescent brain architecture and psychiatric symptoms during early adulthood, controlling for psychiatric symptoms during adolescence (**Figure 4; eFigure2**). Greater *regional* amygdala betweenness centrality was significantly associated with lower anxiety (β = -0.20, 95% CI [-0.37, -0.03]). In "indirect effect" models, warmer parenting in middle childhood was significantly associated with reduced anxiety (95% CI [-0.10, -0.01]) and depression (95% CI [-0.10, -0.003]) in early adulthood via greater amygdala centrality during adolescence.

Sensitivity Analyses

Baseline models without covariates revealed similar associations among parenting, brain architecture, and mental health (**eTable6; eFigure3**). Additionally, since warm parenting scores skewed high, we repeated analyses after dichotomizing our warmth variable, and found similar associations (**eMethods**). Finally, we repeated our graph theoretic analyses with metrics generated from two null networks that randomized brain architecture at different levels of conservativeness (**eMethods**). These randomly permuted brain architectures were not significantly associated with parenting or internalizing symptoms (**eFigure4**), confirming the specificity and robustness of our findings.

Discussion

Leveraging a population-based sample enriched for adversity exposure and followed longitudinally across 20+ years, together with statistical innovations that parse timing-dependent from cumulative associations,[27,28] we investigated the developmental specificity of associations among parenting during childhood, functional brain architecture during adolescence, and mental health during early adulthood. We found that associations between harsh parenting and neural architecture were both widespread across the brain, and localized to cortico-limbic circuitry, depending on the timing of exposure. The associations between warm parenting and neural architecture were localized to cortico-limbic regions during middle childhood, in turn relating to future anxiety and depression during a major stressor (the COVID-19 pandemic). This prospective longitudinal study demarcates neurodevelopmental windows of vulnerability and opportunity, consistent with the notion that the developing brain may be associated with parenting and other experiences during sensitive periods of enhanced plasticity to relate to the emergence of psychiatric illness. Such precision can inform the environments and mechanisms targeted by interventions that focus on developmental stage, history, and psychosocial context.

Functional brain architecture develops at distinct rates across spatial scales. The overall architecture of the brain develops rapidly early in life, resulting in heightened plasticity globally throughout the brain during early childhood.[60,61] Across development, overall plasticity declines but specific brain circuits continue to mature, resulting in more localized, system-specific enhancements in plasticity during late childhood.[13,60,62] This heterochronous neurodevelopmental program suggests that environmental experiences may exhibit widespread associations early in development, but localized associations later on. Consistent with this hypothesis, we found that parental psychological aggression in early childhood was positively related to *brain-wide*

segregation and small-worldness, whereas psychological aggression in late childhood was negatively related to cortico-limbic *circuit* connectivity. These divergent associations suggest that *early* parental adversity may relate to the entire brain, spanning multiple cognitive, socioemotional, and sensorimotor systems. Conversely, *later* parental adversity may relate to localized communication within brain systems underlying emotional learning and regulation. The observation that harsh parenting during early childhood exhibited more widespread neural associations dovetails with literature indicating that earlier adversity exhibits more potent and lasting relationships with psychosocial and neuroendocrine functioning,[56,63] and that associations between adversity and cortico-limbic activity are timing-dependent.[17,18,20]

These developmentally-contingent associations have critical implications for prevention. These findings identify early childhood as a period when the developing brain may be more broadly associated with exposure to, and potentially prevention of, harsh parenting and other adversities. Several evidence-based interventions can lead to enduring reductions in harsh parenting, including Parent Management Training and Parent-Child Interaction Therapy,[64] Attachment and Biobehavioral Catch-Up,[65] and tiered approaches implementing primary-care prevention and home-based secondary/tertiary prevention, such as Smart Beginnings.[66] This developmental specificity further raises promise for biologically informed interventions to target distinct neural circuits, and cognitive-affective processes, depending on the timing of adversity exposure.[12]

The associations between warm parenting and neural architecture were localized to cortico-limbic regions only during middle childhood. Following warmer parenting, neural communication was influenced more strongly by bottom-up subcortical regions (amygdala) and less strongly by top-down cortical regions (PFC). The finding that warmth had more localized

neural associations than harshness accords with evolutionary theory by indicating that the developing brain may be more attuned to adversity over nurturance, given its salience for survival.[67] Warm parenting may relate to prefrontal and limbic architecture specifically during middle childhood, which involves high cortico-limbic plasticity while children rely on parental support to regulate their emotions and navigate novel transitions to school and peer contexts.[6]

A strength of this work is examining both an adverse (harsh parenting) and promotive exposure (warm parenting). Despite notable exceptions,[21,68] this is an important innovation in pediatric neuroscience, which has disproportionately adopted deficit-based perspectives (focusing on adversity) over strength-based perspectives, especially among youth marginalized via racialized identity or socioeconomic status.[69] Incorporating both adverse and promotive experiences allowed us to characterize how brain development may differentially adapt to different contexts depending on parental behavior, spatial scale, and developmental period of exposure.

Importantly, warmer parenting during middle childhood was associated with lower anxiety and depression in early adulthood during a global, naturally occurring stressor (COVID-19 pandemic), via greater amygdala centrality during adolescence. This pathway was observed while statistically controlling for these psychiatric symptoms during adolescence, indicating that limbic architecture uniquely relates to future wellbeing, especially resilience during stress.[52] These observations suggest that warmth-related variation in limbic architecture may reflect a protective neural phenotype through which warm parenting in childhood promotes emotional wellbeing 15 years later. Parental warmth begins to normatively decline during this period.[59] Thus, these findings have important translational implications. Specifically, our findings suggest that fostering parental warmth in middle childhood[64–66] may scaffold the development of neural

circuitry that supports the capacity and tendency to mobilize adaptive coping strategies during future stress,[70] mitigating psychiatric symptoms later in life.

While our study has several strengths, including prospective longitudinal assessments of harsh and warm parenting, computational measures of neural architecture across spatial scales, confirming our findings with random permutations, parsing timing-dependent versus cumulative associations, and examining populations that have been historically excluded from pediatric biological research, a few limitations warrant consideration. First, longitudinal neuroimaging data are required to characterize how these neural alterations unfold over time. Moreover, as this work used "pseudo-rest" neuroimaging data, future studies should examine whether these findings are affected by task demands or the type of functional neuroimaging data used. We also collected neuroimaging data using an 8-channel head coil, which has lower signal-to-noise ratio than recent acquisitions. Second, neurobiological associations with harsh parenting were specific to psychological rather than physical aggression, potentially because our measure of physical aggression (e.g., spanking) may not tap harshness in culturally sensitive ways.[71] Third, only warm parenting related to mental health via neural architecture, likely due to measurement differences between warmth (observer-rated) versus harshness (parent-reported). Future studies should replicate these results using other, potentially more sensitive parenting measures, such as structured laboratory observations. Fourth, future research must identify timing-dependent associations with parenting beyond biological mothers. Fifth, while psychiatric symptoms were examined using validated measures,[50,51] future research should implement gold-standard assessments such as diagnostic interviews. Finally, the effect sizes of parenting on neurobiology were relatively modest, which may not be surprising since parenting behaviors emerge from complex ecological systems, such as social/economic inequities that are associated with parental

stress.[72] Despite controlling for proxies of these exposures, additional work should examine how the timing of these broader experiences relates to neurodevelopment and health.

In summary, parenting during childhood may have timing-dependent associations with adolescent functional brain architecture and psychiatric symptoms in early adulthood. By integrating theoretically-informed and data-driven methods, we identified potential sensitive periods during which harsh and warm parenting may differentially relate to neural organization (at different spatial scales), and in turn psychiatric vulnerability or resilience when encountering future stress. Such developmentally-dependent associations could inform the type and timing of preventive interventions by targeting the biological state of the developing brain.[4,12] Our findings may also encourage reform of policies that enhance or constrain caregivers' ability to express behaviors that promote or undermine children's brain development and psychological wellbeing across the lifespan (e.g., home visits, income supplements, reducing concentrated disadvantage).[5,16,72,73]

Author Contributions: Mr Michael and Dr Hyde had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Michael, Gard, Tillem, Hardi, Mitchell, Monk, Hyde.

Acquisition, analysis, or interpretation of data: Michael, Gard, Tillem, Hardi, Mitchell, Brooks-Gunn, Monk, Hyde.

Drafting of the manuscript: Michael, Hyde.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Michael, Gard, Tillem, Hardi.

Obtained funding: Mitchell, Monk, Hyde.

Administrative, technical, or material support: All authors.

Supervision: Mitchell, Monk, Hyde.

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Figure 1. Description of brain-wide, circuit-level, and regional metrics of functional brain architecture. Modularity is a brain-wide, graph theoretic metric that characterizes network segregation. Global efficiency is a brain-wide, graph theoretic metric that characterizes network integration. Small-world propensity is a brain-wide, graph theoretic metric that characterizes the balance between segregation and integration. Average functional connectivity is a circuit-level metric that characterizes the strength of communication between two regions of interest (i.e., prefrontal cortex and amygdala). Betweenness centrality is a regional, graph theoretic metric that characterizes the importance, or centrality, of a brain region (i.e., prefrontal cortex and amygdala) in a system.

Figure 2. Summary of timing-dependent associations between harsh/warm parenting during childhood and functional brain architecture during adolescence. Structured life-course modeling approach (SLCMA) analyses demonstrated that harsh parenting during early childhood was associated with the architecture of the overall brain (segregation, small-worldness) during adolescence. Harsh parenting during late childhood was associated with the architecture of cortico-limbic circuitry (prefrontal cortex-amygdala connectivity) during adolescence. Warm parenting during middle childhood was associated with the architecture of cortical (prefrontal cortex) and limbic (amygdala) regions (betweenness centrality) during adolescence. All associations of harsh and warm parenting were explained by the developmental timing of exposure. There were no instances when parenting was associated with functional brain architecture via accumulation. PFC = prefrontal cortex.

Figure 3. Associations between harsh/warm parenting during early, middle, and late childhood with brain architecture during adolescence. Psychological aggression during early childhood was positively associated with brain-wide (A) segregation (modularity) and (B) small-worldness (small-world propensity). (C) Psychological aggression during late childhood was negatively associated with functional connectivity between prefrontal cortex and the amygdala. Warm parenting during middle childhood was (D) negatively associated with the betweenness centrality of prefrontal cortex and (E) positively associated with the betweenness centrality of the amygdala. All analyses controlled for sex assigned at birth, race/ethnicity, pubertal development, poverty ratio, parental education, and head motion. Graph theoretical analyses further controlled for average functional connectivity.

Figure 4. Longitudinal associations among warm parenting, functional brain architecture, and mental health during the COVID-19 pandemic. Warmer parenting during middle childhood was associated with greater betweenness centrality of the amygdala during adolescence, which was in turn associated with lower levels of (A-B) anxiety and (C-D) depression during early adulthood. Paths among warm parenting, amygdala betweenness centrality, and internalizing symptoms represent standardized regression coefficients and 95% confidence intervals derived from standard errors pooled across imputed datasets using Rubin's rules. Indirect effects were assessed from estimates and bias-corrected 95% confidence intervals with 10,000 bootstraps averaged across imputed datasets (Panel B for anxiety; Panel D for depression). All analyses controlled for sex assigned at birth, race/ethnicity, pubertal development, poverty ratio, parental education, head motion, average functional connectivity, and anxiety or depression during adolescence.

Table. Structured life-course modeling approach (SLCMA) results relating the accumulation of, versus the developmental timing of exposure to, harsh and warm parenting during childhood to functional brain architecture during adolescence.

SLCMA Model	Selected Variables	R^2 Change	Coefficient	95% CI	P_{orig}	P_{fdr}
Psychological Aggression						
Modularity	Early Childhood	4.14%	0.30	0.14 to 0.45	<.001	.003
	Middle Childhood	4.24%	-0.18	-0.32 to -0.01	.03	.07
Global Efficiency	Middle Childhood	2.10%	-0.05	-0.09 to 0.02	.06	.10
	Early Childhood	0.44%	0.02	-0.10 to 0.06	.46	.51
Small-World Propensity	Early Childhood	2.89%	0.17	0.03 to 0.28	.005	.02
	Late Childhood	1.68%	-0.10	-0.20 to 0.22	.18	.22
Prefrontal Cortex - Amygdala Connectivity	Late Childhood	2.70%	-0.37	-0.55 to -0.12	.002	.01
	Middle Childhood	3.29%	0.29	-0.10 to 0.46	.05	.09
Betweenness Centrality of Prefrontal Cortex	Late Childhood	2.31%	-0.14	-0.28 to 0.05	.04	.09
Betweenness Centrality of Amygdala	Late Childhood	0.48%	-0.13	-0.28 to 1.29	.16	.22
	Middle Childhood	0.17%	0.08	-2.27 to 0.20	.96	.96
Physical Aggression						
Modularity	Early Childhood	3.17%	0.24	-0.18 to 0.40	.23	.66
	Middle Childhood	0.83%	-0.13	-0.28 to 0.64	.60	.81
Global Efficiency	Early Childhood	0.23%	-0.02	-0.06 to 0.20	.62	.81
	Middle Childhood	0.07%	0.01	-0.39 to 0.05	.81	.81
Small-World Propensity	Early Childhood	1.93%	0.16	-0.05 to 0.27	.25	.66

SLCMA Model	Selected Variables	R^2 Change	Coefficient	95% CI	P_{orig}	P_{fdr}
	Late Childhood	1.00%	-0.10	-0.20 to 0.49	.71	.81
Prefrontal Cortex - Amygdala Connectivity	Late Childhood	0.76%	-0.22	-0.39 to 0.26	.11	.66
	Middle Childhood	1.01%	0.18	-0.71 to 0.34	.34	.67
Betweenness Centrality of Prefrontal Cortex	Late Childhood	1.03%	-0.19	-0.35 to 0.05	.11	.66
	Middle Childhood	1.79%	0.15	-0.22 to 0.30	.39	.67
Betweenness Centrality of Amygdala	Early Childhood	0.90%	0.12	-0.26 to 0.28	.27	.66
	Late Childhood	0.18%	-0.04	-0.18 to 1.06	.74	.81
Warm Parenting						
Modularity	Middle Childhood	0.02%	-0.02	-0.08 to 3.15	.86	.87
	Early Childhood	0.01%	0.02	-Inf to -0.02	.87	.87
Global Efficiency	Early Childhood	1.63%	0.04	-0.02 to 0.08	.10	.21
	Middle Childhood	0.75%	0.02	-0.11 to 0.05	.29	.41
Small-World Propensity	Middle Childhood	2.89%	-0.12	-0.22 to 0.01	.03	.08
Prefrontal Cortex - Amygdala Connectivity	Late Childhood	0.29%	-0.08	-0.23 to 0.28	.27	.41
	Middle Childhood	0.63%	0.06	-0.47 to 0.20	.82	.87
Betweenness Centrality of Prefrontal Cortex	Middle Childhood	1.31%	-0.18	-0.31 to -0.03	.005	.03
	Early Childhood	4.70%	0.16	-0.04 to 0.29	.02	.08
Betweenness Centrality of Amygdala	Middle Childhood	4.11%	0.23	0.06 to 0.38	.003	.03
	Late Childhood	1.07%	-0.08	-0.22 to 0.25	.29	.41

Note. Only theoretical models (early childhood, middle childhood, late childhood, accumulation, or combination thereof) selected within each SLCMA model (see **eFigure1**) are presented. All analyses controlled for sex assigned at birth, race/ethnicity, pubertal

development, poverty ratio, parental education, and head motion. Graph theoretical analyses further controlled for average functional connectivity. R^2 change represents the incremental percentage of variance in the brain outcome explained by each theoretical model, while controlling for covariates. Coefficient represents standardized coefficients. P_{orig} denotes original *P*-values. P_{fdr} denotes *P*-values corrected for multiple comparisons using the false discovery rate (FDR), for the number of models selected within each dimension of parenting (11 for psychological aggression, 12 for physical aggression, 11 for warm parenting).

Supplemental Online Material

Michael C, Gard AM, Tillem S, et al. Developmental timing of associations among parenting, brain architecture, and mental health. *JAMA Pediatrics*.

eMethods

Participants

The Future of Families and Child Wellbeing Study (FFCWS) is a population-based birth cohort study of 4,898 children (52.4% boys) recruited from 20 large US cities (population over 200,000) from 1998 to 2000, with a 3:1 oversampling for non-marital births.[1] For the follow-up Study of Adolescent Neural Development (SAND) when magnetic resonance imaging (MRI) data were collected (ages 15-17 years), 506 families from Detroit (MI), Toledo (OH), and Chicago (IL) who participated in the FFCWS were contacted. Of the 506 families contacted, 237 families participated in SAND. The complete list of measures and data for this project is publicly available from the National Institutes of Mental Health data archive (https://nda.nih.gov/).

Of the 237 SAND families, 28 teens were not eligible to complete MRI scanning due to contraindications (e.g., braces, weight limit, etc.) or refusing to scan, and 12 teens did not have a sufficient number of usable scan sessions (e.g., due to excessive head motion) to generate "pseudo-rest" fMRI data (i.e., at least two usable sessions from the resting-state scan, the socioemotional face processing task-based scan, and the reward processing task-based scan). From the remaining 197 families, 22 teens did not meet coverage criteria (i.e., 22 participants had at least one node in their brain-wide connectivity matrix where either: >50% of voxels of the node had coverage issues, and/or <10 voxels in the node were usable after voxels with coverage issues were removed). Two more participants were excluded because of issues with signal artifact. Therefore, the final sample for the present investigation included 173 adolescents with valid pseudo-rest fMRI data. Participants included in the present study did not significantly differ from excluded participants on a range of relevant demographic variables, including age, sex

assigned at birth, pubertal development, annual household income, parental education, and race/ethnicity (see **Supplemental Table 1**).

Parenting Behaviors

We examined harsh and warm parenting behaviors through telephone and in-person assessments during early childhood (3 years), middle childhood (5 years), and late childhood (9 years). Similar to prior SAND studies,[2] to prevent artifacts associated with changing informants across waves, we limited our investigation to parenting provided by the biological mother, who represented the primary caregiver in 94% of the FFCWS families. Accordingly, parenting data were coded as missing if the primary caregiver was not the biological mother, or if the measures were not completed at each wave (see **Supplemental Tables 1-2** for details about missing data). Moreover, similar to prior SAND studies,[2] given our interest in the role of the developmental timing of exposure to different parenting behaviors, we only included items that were repeated across waves in our final harsh and warm parenting scores. The selected measures of harsh and warm parenting have been extensively used in previous FFCWS and SAND publications.[2–4]

We examined two dimensions of harsh parenting from the parent-reported Parent-Child Conflict Tactics Scale.[5] Mothers were asked to rate how many times over the past year they used each disciplinary tactic, from 0 (*never happened*) to 6 (*more than 20 times*). First, we calculated means for five items from the Psychological Aggression subscale ("shouted, yelled, or screamed at", "threatened to spank or hit but didn't actually do it", "swore or cursed at", "called child dumb or lazy or some other name like that", "said they would send them away or kick them out of the house"). Second, we calculated means for five items from the Physical Aggression

subscale (“shook child”, “hit child on the bottom with some hard object”, “spanked child on the bottom with bare hand”, “slapped child on hand, arm, or leg”, “pinched child”).

We operationalized warm parenting as sum scores from the Responsiveness subscale of the Home Observation for Measurement of the Environment.[6] This subscale included four items that indicate positive parenting behaviors that trained observers rated as present (1) or absent (0) during an in-home visit (“spoke twice or more to child during visit”, “verbally answered child’s questions or requests”, “voice conveyed positive feelings”, “caressed, kissed, or cuddled child once during visit”). As items for warmth were binary and observer ratings were not missing for any item, we calculated sums instead of means.

MR Data Acquisition

Participants were scanned with a research-dedicated GE Discovery MR750 3T scanner with an 8-channel head coil located at the University of Michigan Functional MRI Laboratory. Head movement was limited through the use of head paddings and detailed instructions provided to participants. High-resolution T1-weighted gradient echo (SPGR) images were collected (TR = 12ms, TE = 5ms, TI = 500ms, flip angle = 15^{o}, FOV = 26cm, slice thickness = 1.4mm, 256 x 192 matrix, 110 slices, voxel size = 1mm x 1mm x 1mm) and used for preprocessing. Functional neuroimaging data during the resting-state and the two tasks were obtained using T2*-weighted blood oxygenation level dependent (BOLD) images with a reverse spiral sequence (TR = 2000ms, TE = 30ms, flip angle = 90^{o}, FOV = 22cm, slice thickness = 3mm, 40 slices, voxel size = 3.44mm x 3.44mm x 3mm, ascending acquisition). Functional images encompassed the entire cerebrum and most of the cerebellum to maximize coverage of limbic regions of interest. Slices were prescribed parallel to the AC-PC plane (same locations as the structural scans) and were

acquired contiguously, which optimized the effectiveness of the movement postprocessing algorithms. Images were reconstructed offline using processing steps to remove distortions caused by magnetic field inhomogeneity and other sources of misalignment to the structural data, which yields excellent coverage of subcortical structures of interest.

MR Data Preprocessing

Anatomical images were skull-stripped (f = .25) using the Brain Extraction Tool (BET) in FSL version 6.0[7] and segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using FSL FAST. After removing large temporal spikes in the k-space functional data (>2 *SD*), field map correction was applied, and functional images were reconstructed using Matlab. Noise from cardiac and respiratory motion was removed using RETROICOR and slice-timing correction using SPM8 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk). Moreover, the first 10 volumes of functional data were removed to ensure the stability of signal intensity. Following these steps, the functional data were further preprocessed using the FSL fMRI Expert Analysis Tool (FEAT). Functional images were skull-stripped and spatially smoothed using FSL FMRIB's Automated Segmentation Tool,[8] and registered to subject-specific skull-stripped and segmented anatomical images. We performed motion correction using MCFLIRT and spatial smoothing using a Gaussian kernel of 6mm FWHM. Grand-mean intensity of the entire 4D dataset was normalized by a single multiplicative factor and FSL motion outliers were run to extract framewise displacement (FD) motion parameters.[9] ICA-AROMA was used to remove motion-related artifacts in the data, nuisance signal derived from white matter and CSF was regressed out, and data with signal below 0.01Hz were high-pass filtered. These processing steps have been described in detail in other studies.[3,10]

Motion Correction

A conservative, multi-step procedure was used to correct for motion artifacts combining multiple correction strategies.[11] First, the Artifact Detection Tools (ART) software package (http://www.nitrc.org/projects/artifact_detect/) was used to identify and remove motion artifacts from the fMRI time series (i.e., de-spiking), using a mean framewise displacement cut-off value of 0.5mm.[9] Scanner sessions where >20% of the session was identified as motion artifact were excluded from subsequent analyses. Participants who did not have at least two independent usable scanner sessions due to motion artifact after scrubbing were removed from the sample. Secondly, as described above, ICA-AROMA was applied at the subject-level to remove motion-related artifacts,[12,13] prior to the construction of subject-level connectivity matrices and networks.

Connectivity Analysis

The preprocessed resting-state data and residualized task-based fMRI data was entered into a region of interest (ROI) to ROI connectivity analysis using the CONN toolbox.[14] More specifically, data from all usable fMRI sessions were extracted from each ROI (i.e., node) for this analysis. Denoising procedures were then applied to the data, including: 1) orthogonalizing the time courses with respect to signal in the white matter and CSF, the six realignment parameters, the first- and second-order derivatives of each realignment parameter, and the de-spiking regressors; 2) band-pass filtering (0.008-0.09Hz); and 3) linear detrending. This multi-step denoising procedure reduced signal artifact originating from CSF and white matter, censored signal produced by excessive motion to greatly reduce the impact of motion artifact on the data, and mitigated signal artifact due to biological noise (e.g., breathing, heart rate, etc.).[14–16] Following denoising, the connectivity analysis was performed using the CONN toolbox ROI-to-

ROI first-level static connectivity analysis procedure.[14] This procedure generated pairwise correlations between each individual's time course for each pair of ROIs, ultimately producing a brain-wide connectivity matrix for each participant.

Functional Connectivity and Graph Theoretical Analyses

We initially constructed a bilateral mask for the amygdala (4 ROIs corresponding to left and right medial and lateral amygdala) and key regions of prefrontal cortex (PFC; 46 ROIs from Brodmann areas 9, 10, 11, 24, 32, and 47) that are densely interconnected with the amygdala and support important regulatory functions, consistent with previous SAND studies and non-human primate tracer studies.[17–19] We constructed bilateral masks because we had no a priori hypotheses about parenting behaviors being differentially associated with the architecture of the right versus left amygdala and PFC as a function of developmental timing of exposure. See **Supplemental Table 3** for a list of selected ROIs for the amygdala and PFC masks.

All graph theoretical analyses were conducted using the Brain Connectivity Toolbox (2019.03.03) in Matlab (version 2022a).[20] Consistent with other graph theoretical studies,[20,21] we set all negative connections within each brain-wide connectivity matrix to zero and then Fisher *r*-to-*z* transformed each connectivity matrix. We retained all connections without additional thresholding given controversies around gold-standard thresholding approaches and the cognitive relevance of weak connections.[21–23] We used these matrices to construct weighted, undirected brain-wide graphs. Specifically, the strength of each functional connection was retained rather than binarized because, relative to unweighted graphs, weighted graphs have closer resemblance to biological systems and generate more robust metrics of brain architecture.[21,23,24]

At the brain-wide level, we characterized measures of network segregation (modularity), network integration (global efficiency), and small-worldness (small-world propensity). First, modularity probes the extent to which the brain organizes into distinct networks, involving stronger within- and weaker between-network connectivity.[25] Modularity measures segregation by comparing the observed within-network connectivity against that estimated from a network partition that maximizes modularity.[26] Second, global efficiency quantifies how efficiently information flows across the brain, computed as the average inverse shortest path length across all brain nodes.[27] Finally, small-world propensity is a recently developed metric optimized for weighted graphs that compares the relative segregation and integration observed against respective lattice and random networks.[28,29] Higher values on these metrics reflect greater network segregation, network integration, and small-worldness, respectively.

At the regional level, we calculated the betweenness centrality of each ROI within the constructed bilateral masks of the amygdala and PFC, and averaged across all ROIs within each mask to estimate the overall betweenness centrality of the amygdala and PFC. Betweenness centrality quantifies the fraction of all shortest paths among each pair of nodes that cross through the node of interest.[30] Brain regions with higher betweenness centrality can exert a stronger influence on global information flow across the whole-brain system. In other words, higher betweenness centrality values are thought to characterize regions that strongly regulate information flow across the brain.

Covariates

In our main analyses, we focus on covariate-adjusted models given the importance of statistically controlling for neuroimaging-related covariates (e.g., head motion, mean functional

connectivity) in graph theoretic studies of brain architecture.[9,31] Specifically, we controlled for multiple potential confounding variables similar to past connectivity and graph theoretic investigations characterizing the neurobiological embedding of environmental experiences during childhood.[10,32,33]

First, we controlled for sex assigned at birth (male versus female) to account for sex differences in functional brain architecture.[34,35] Second, we controlled for ethnoracial identity, as reported by youth during the neuroimaging wave (15 years) by selecting options from predefined categories using three dummy-coded variables (White, Hispanic/Latino, and Other against Black/Non-Hispanic as the reference category). We controlled for ethnoracial identity as a social construct to statistically account for systematic differences in exposure to structural and personal racism, discrimination, and unequal experiences of poverty, stress, and opportunity among people of color in the United States that were not directly measured in the present study.[10,32,36,37] Although ethnoracial identity was reported at age 15, we controlled for this variable as a proxy for lifetime exposure to inequality.

Third, similar to other neuroimaging studies in the present sample,[3,10,19] we controlled for pubertal development during the neuroimaging wave (15 years) using continuous child-reported mean scores on the Pubertal Development Scale (or parent-reported mean scores when child-reports were not available; $n = 13$). Controlling for pubertal development allowed us to account for the associations of pubertal physiology and tempo with functional brain architecture,[38,39] thus increasing the likelihood that individual differences in neural architecture map onto contextual variation in earlier experiences of parenting. Fourth, we controlled for poverty ratio during the neuroimaging wave (15 years), computed as a ratio of parent-reported household income to the official poverty thresholds established by the US Census Bureau. We controlled for this variable

as a proxy for lifetime experiences of disadvantage to account for socioeconomic constraints on parental behavior and long-reaching associations with functional brain architecture.[32,33,40–43] Fifth, we controlled for parental education during the neuroimaging wave (15 years), with scores ranging from 0 (*Lower than High School*) to 4 (*College or Graduate School*), since parental educational attainment has been extensively associated with parenting practices and could be a confounding factor.[44] Sixth, we controlled for mean FD to further account for head motion during fMRI scanning, and thus motion artifact in our estimates of functional brain connectivity and architecture.

Graph theoretical analyses also controlled for average functional connectivity across the thresholded brain-wide graph to ensure that our findings reflect variation in brain architecture rather than overall connectivity strength.[21,31] Finally, analyses with mental health during early adulthood further statistically controlled for baseline symptoms of anxiety (scores from the Screen for Anxiety Related Disorders[45]) and depression (scores from the Mood and Feelings Questionnaire[46]) during the neuroimaging wave (15 years). Accordingly, our analyses with mental health investigated whether parenting-related variation in functional brain architecture longitudinally relates to internalizing symptomatology above and beyond current mental health.

Null Network Models

While the structured life-course modeling approach (SLCMA) and our approach to accounting for multiple comparisons protect against identifying and interpreting false positives (i.e., type I error), we sought to cross-reference whether the identified associations among harsh and warm parenting behaviors, functional brain architecture, and anxiety and depression differ from those we would expect by chance. To this end, we repeated our graph theoretical analyses

after generating graph metrics from two null network models that randomized different graph properties with different levels of stringency.[33,47] The first null model randomly rewired each connection approximately 20 iterative times while preserving each region's degree (i.e., number of connections) distribution. The second null model randomly rewired each connection five times and sorted connection weights at each 30th step while preserving each region's degree and strength (i.e., strength of connections) distribution, providing a more conservative model for null testing more suitable for weighted graphs. For each participant, we generated 20 null graphs for each model and averaged across them to derive one value for each graph metric of interest (modularity, global efficiency, small-world propensity, betweenness centrality of the amygdala, betweenness centrality of PFC) and each participant. We next repeated (a) SLCMA with the graph metrics derived from the two null network models, extracting the same number of parenting variables (i.e., early childhood, middle childhood, late childhood, accumulation) as in the main analyses and (b) indirect effect analyses with mental health.

If associations among parenting behaviors, functional brain architecture derived from randomly permuted graphs, and mental health are statistically significant, this observation would suggest that our findings may be due to chance. Conversely, if associations among parenting behaviors, functional brain architecture derived from randomly permuted graphs, and mental health are not statistically significant, this observation would demonstrate that our findings are specific to the observed brain architectures and are above what would be expected by chance.

Warm Parenting Modeled as Binary rather than Continuous Variable

Most participants in our sample had high scores on our measure of warm parenting across childhood, especially at earlier waves. During early childhood, 6 youth had a score below 3, 32

youth had a score of 3, and 82 youth had a score of 4. During middle childhood, 14 youth had a score below 3, 38 youth had a score of 3, and 56 youth had a score of 4. During late childhood, 48 youth had a score below 3, 59 youth had a score of 3, and 29 youth had a score of 4. Despite this skewed distribution, our primary analyses modeled this variable as continuous because a considerable proportion of youth had lower scores of warm parenting during late childhood.

However, given that warm parenting scores were negatively skewed in early and middle childhood, we conducted sensitivity analyses in which we binarized our warm parenting variable into 0 ("lower" exposure to warm parenting) if scores were ≤3, or 1 ("higher" exposure to warm parenting) if scores were 4. We controlled for the same covariates as our primary analyses (i.e., sex, race/ethnicity, pubertal development, poverty ratio, parental education, head motion, mean functional connectivity in graph theoretic analyses, and anxiety or depression at age 15 in mental health analyses).

These sensitivity analyses revealed similar associations as our primary analyses. In our SLCMA analyses relating warm parenting to brain architecture, we found that participants with higher exposure to warm parenting during *middle childhood* had marginally greater betweenness centrality of the amygdala ($\beta = 0.37$, $P_{fdr} = .096$, 95% CI [-0.01, 0.68]) and significantly lower betweenness centrality of PFC ($\beta = -0.44$, $P_{fdr} = .027$, 95% CI [-0.71, 0.004]). No other associations between warm parenting and brain architecture reached statistical significance (all P_{fdr}'s > .351). Second, in our indirect effect analyses, we found that participants with higher exposure to warm parenting during *middle childhood* had significantly reduced anxiety (95% CI [-0.19, -0.01]) in early adulthood during the COVID-19 pandemic via greater amygdala centrality during adolescence, though the indirect effect to depressive symptoms did not reach statistical significance (95% CI [-0.15, 0.01]). Moreover, similar to our main analyses, no

indirect effects were found for warm parenting during middle childhood to mental health during early adulthood via betweenness centrality of PFC for either anxiety (95% CI [-0.13, 0.02]) or depression (95% CI [-0.07, 0.08]). These findings suggest that our reported associations among warm parenting, regional cortico-limbic architecture, and internalizing symptoms are not an artifact of the skewed distribution of our warm parenting measure. Findings were in the same direction and of similar effect size, though significance levels were slightly lower, likely due to the loss of statistical power associated with dichotomizing continuous variables.

eResults

eTable1. Participant Demographics

	Included Sample (*n* = 173)	Excluded Sample (*n* = 64)	Statistical Comparison
Age	*M* = 15.88y | *SD* = 0.53y	*M* = 15.83y | *SD* = 0.57y	$t(105.60) = 0.62$, $p = 1.000$
Puberty[1]	*M* = 3.27 | *SD* = 0.58	*M* = 3.14 | *SD* = 0.62	$t(105.63) = 1.42$, $p = .950$
Sex[2]	Female = 95 | Male = 78	Female = 29 | Male = 35	$\chi^2(1) = 1.73$, $p = 1.000$
Ethnoracial Identity[3]	Black = 138 | Hispanic = 9 | Other/Multiple = 9 | White = 17	Black = 43 | Hispanic = 4 | Other/Multiple = 2 | White = 15	$\chi^2(2) = 7.43$, $p = .146$
Annual Family Income[4]	*M* = $49,878.49 | *SD* = $56,797.26	*M* = $48,210.00 | *SD* = $47,623.57	$t(133.55) = 0.23$, $p = 1.000$
Parent Education[5]	*M* = 2.60 | *SD* = 0.97	*M* = 2.63 | *SD* = 1.00	$t(107.56) = -0.22$, $p = 1.000$

Note. p-values adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (*n* = 6)

[1] Puberty represents continuous scores on the Pubertal Development Scale

[2] Sex represents sex assigned at birth

[3] Information about the Other/Multiple category is not publicly available, so other groups are reported as a single category. Chi-square test comparing the ethnoracial identity of included versus excluded participants collapsed across Hispanic and Other/Multiple identities into a single category to enable reliable inferential analyses (i.e., cell sizes > 5)

[4] *n* of included participants = 172 for annual family income

[5] *n* of included participants = 171 for parental education

eTable2. Descriptive statistics of parenting, neuroimaging, and mental health data in the included sample

Measure	*n*	Mean	*SD*
Parenting Behaviors			
Psychological Aggression (Early Childhood)	135	1.97	0.96
Psychological Aggression (Middle Childhood)	149	1.80	1.08
Psychological Aggression (Late Childhood)	153	1.63	1.04
Physical Aggression (Early Childhood)	134	1.59	1.10
Physical Aggression (Middle Childhood)	149	1.31	0.99
Physical Aggression (Late Childhood)	153	1.00	0.97
Warm Parenting (Early Childhood)	120	3.58	0.76
Warm Parenting (Middle Childhood)	108	3.32	0.87
Warm Parenting (Late Childhood)	136	2.60	1.10
Functional Brain Architecture			
Modularity	173	0.24	0.03
Global Efficiency	173	0.16	0.01
Small-World Propensity	173	0.56	0.04
Prefrontal Cortex-Amygdala Connectivity	173	0.00	0.02
Betweenness Centrality of Prefrontal Cortex	173	620.00	106.62
Betweenness Centrality of Amygdala	173	367.23	152.43
Mental Health			
Anxiety (Adolescence)	166	16.89	11.13
Depression (Adolescence)	167	15.20	9.86
Anxiety (Early Adulthood)	118	9.92	10.78
Depression (Early Adulthood)	116	11.10	8.95

eTable3. Coordinates for constructed bilateral masks representing regulatory regions of prefrontal cortex from the Gordon cortical atlas and the amygdala from the Tian subcortical atlas

Brain Region	MNI x-coordinate	MNI y-coordinate	MNI z-coordinate	Network Affiliation
Prefrontal Cortex Mask				
Cluster 22	-8	10	38	Cingulo-Opercular
Cluster 25	-4	38	36	Default Mode
Cluster 27	-6	24	36	Cingulo-Opercular
Cluster 28	-8	24	28	Cingulo-Opercular
Cluster 29	-8	36	20	Salience
Cluster 44	-20	28	56	Default Mode
Cluster 78	-40	54	-12	Fronto-Parietal
Cluster 79	-46	40	-12	Ventral Attention
Cluster 80	-32	20	-18	Ventral Attention
Cluster 85	-46	34	-4	Ventral Attention
Cluster 86	-46	26	2	Ventral Attention
Cluster 114	-26	50	4	Default Mode
Cluster 116	-6	64	-2	Default Mode
Cluster 117	-6	36	-12	Default Mode
Cluster 145	-14	54	34	Default Mode
Cluster 146	-20	56	28	Default Mode
Cluster 148	-20	58	0	Fronto-Parietal
Cluster 149	-30	56	4	Fronto-Parietal
Cluster 150	-6	48	26	Default Mode
Cluster 151	-14	62	14	Default Mode
Cluster 152	-6	44	12	Default Mode
Cluster 154	-26	26	40	Default Mode
Cluster 157	-40	24	42	Default Mode
Cluster 183	8	32	24	Salience
Cluster 184	6	42	-2	Default Mode
Cluster 185	6	16	36	Cingulo-Opercular
Cluster 187	8	16	44	Cingulo-Opercular
Cluster 188	4	26	26	Cingulo-Opercular

Brain Region	MNI x-coordinate	MNI y-coordinate	MNI z-coordinate	Network Affiliation
Cluster 240	42	48	0	Fronto-Parietal
Cluster 241	48	38	-8	Ventral Attention
Cluster 242	46	28	-10	Ventral Attention
Cluster 247	32	26	-8	Salience
Cluster 248	34	20	6	Cingulo-Opercular
Cluster 277	28	52	2	Fronto-Parietal
Cluster 278	6	68	-8	Default Mode
Cluster 279	6	48	-14	Default Mode
Cluster 315	22	28	46	Default Mode
Cluster 316	22	38	34	Default Mode
Cluster 319	24	54	2	Fronto-Parietal
Cluster 320	32	52	16	Fronto-Parietal
Cluster 321	16	62	16	Default Mode
Cluster 322	8	56	6	Default Mode
Cluster 323	6	58	26	Default Mode
Cluster 324	14	40	48	Default Mode
Cluster 325	6	44	46	Default Mode
Cluster 327	40	22	50	Fronto-Parietal
Amygdala Mask				
Cluster 21	28	-2	-14	Subcortical
Cluster 22	22	2	-18	Subcortical
Cluster 48	-26	-2	-24	Subcortical
Cluster 49	-20	-12	-12	Subcortical

eTable4. Zero-order correlations among brain-wide, circuit-level, and regional brain metrics

Variable	1	2	3	4	5
1. Modularity					
2. Global Efficiency	.02				
3. Small-World Propensity	.47**	.69**			
4. Prefrontal Cortex - Amygdala Connectivity	-.05	.09	.06		
5. Betweenness Centrality - Amygdala	.03	.01	-.02	.10	
6. Betweenness Centrality - Prefrontal Cortex	.15	-.38**	-.29**	.10	-.13

Note. ** indicates $P < .01$.

eTable5. Zero-order correlations among predictor variables (parenting behaviors) and covariates

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Psych Agg (3y)																
2. Psych Agg (5y)	.50**															
3. Psych Agg (9y)	.35**	.58**														
4. Phys Agg (3y)	.61**	.47**	.25**													
5. Phys Agg (5y)	.31**	.62**	.48**	.56**												
6. Phys Agg (9y)	.16	.38**	.61**	.36**	.56**											
7. Warmth (3y)	-.16	-.06	-.05	-.18*	-.02	-.17										
8. Warmth (5y)	-.23*	-.13	-.09	-.22*	-.25**	-.08	.06									
9. Warmth (9y)	.02	-.01	-.06	-.15	-.10	-.10	.07	.06								
10. Sex	.09	.06	.14	.08	.13	.16	-.07	.02	-.02							
11. Race (Black)	.19*	.16	.11	.24**	.27**	.15	-.10	-.18	-.07	-.04						
12. Race (White)	-.22*	-.15	-.18*	-.17	-.21*	-.18*	.09	.08	-.02	-.06	-.66**					
13. Race (Hispanic)	-.11	-.04	.04	-.11	-.13	.03	-.05	.15	.14	.10	-.47**	-.08				
14. Race (Other/Multi)	.05	-.04	.01	-.09	-.07	-.04	.10	.10	.03	.05	-.47**	-.08	-.05			
15. Puberty	-.14	-.09	-.09	-.11	-.15	-.21**	.00	.06	.07	-.63**	-.03	.06	.02	-.05		
16. Income	-.28**	-.17*	-.17*	-.20*	-.16	-.16	.15	.22*	.00	-.08	-.35**	.33**	.10	.09	.08	
17. Education	-.17	-.19*	-.12	-.03	-.01	-.08	.04	.03	-.06	-.03	-.11	.16*	-.07	.06	.04	.35**

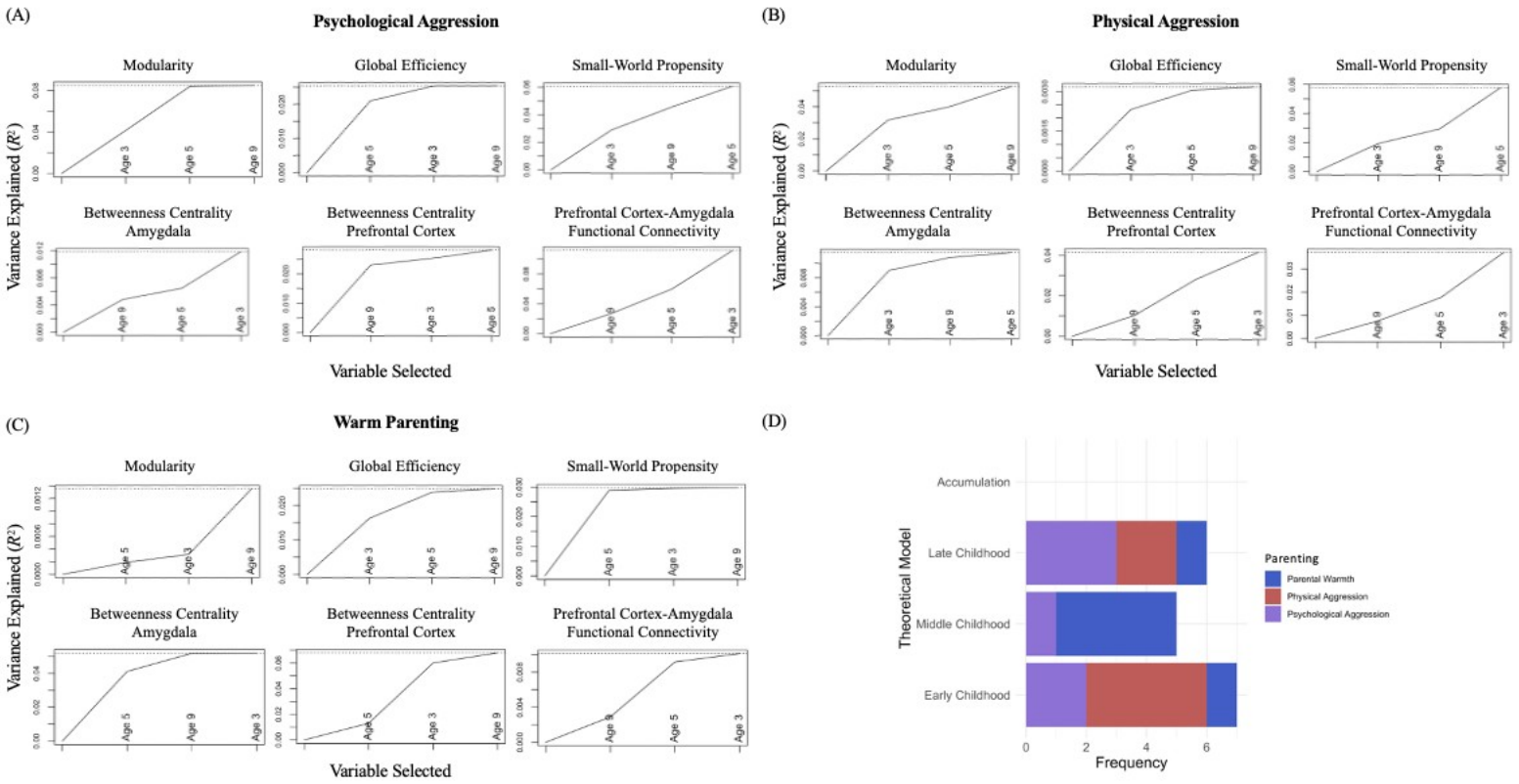
Note. Psych Agg represents psychological aggression. Phys Agg represents physical aggression. Warmth represents warm parenting. * indicates $P < .05$, ** indicates $P < .01$.

eTable6. Structured life-course modeling approach (SLCMA) results relating the accumulation of, versus the developmental timing of exposure to, harsh and warm parenting during childhood to functional brain architecture during adolescence from baseline models without covariates.

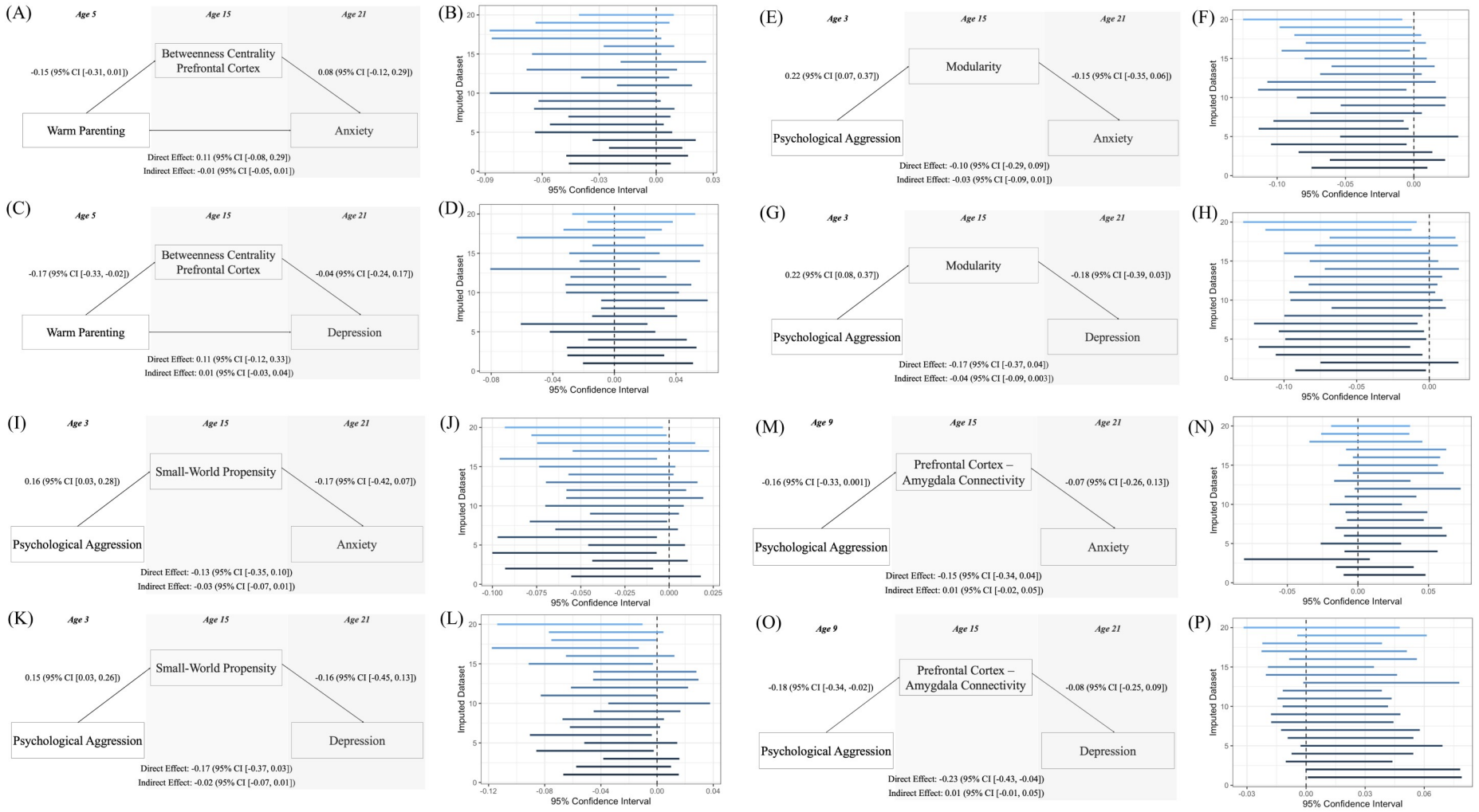
SLCMA Model	Selected Variables	R^2 Change	Coefficient	95% CI	P_{orig}	P_{fdr}
Psychological Aggression						
Modularity	Early Childhood	1.50%	0.29	0.11 to 0.46	<.001	.005
	Middle Childhood	5.58%	-0.24	-0.41 to -0.05	.004	.02
Global Efficiency	Late Childhood	1.19%	-0.15	-0.33 to 0.45	.40	.62
	Middle Childhood	0.29%	0.07	-0.91 to 0.23	.74	.81
Small-World Propensity	Early Childhood	0.20%	0.18	-0.01 to 0.33	.03	.06
	Late Childhood	3.94%	-0.17	-0.33 to 0.02	.04	.07
Prefrontal Cortex - Amygdala Connectivity	Late Childhood	1.96%	-0.37	-0.54 to -0.13	<.001	.005
	Middle Childhood	3.81%	0.30	-0.05 to 0.47	.02	.04
Betweenness Centrality of Prefrontal Cortex	Middle Childhood	0.33%	-0.11	-0.22 to 1.18	.68	.81
Betweenness Centrality of Amygdala	Late Childhood	0.14%	-0.08	-0.24 to 1.12	.68	.81
	Middle Childhood	0.14%	0.06	-1.89 to 0.20	.81	.81
Physical Aggression						
Modularity	Early Childhood	1.14%	0.30	0.07 to 0.47	.007	.08
	Middle Childhood	4.09%	-0.26	-0.44 to 0.03	.03	.12
Global Efficiency	Early Childhood	0.29%	-0.08	-0.24 to 0.26	.32	.39
	Late Childhood	0.37%	0.05	-0.49 to 0.21	.62	.62

SLCMA Model	Selected Variables	R^2 Change	Coefficient	95% CI	P_{orig}	P_{fdr}
Small-World Propensity	Early Childhood	0.73%	0.17	-0.32 to 0.35	.15	.28
	Middle Childhood	0.66%	-0.12	-0.28 to 0.66	.39	.43
Prefrontal Cortex - Amygdala Connectivity	Late Childhood	0.37%	-0.19	-0.36 to 0.36	.13	.28
	Middle Childhood	0.91%	0.16	-0.71 to 0.32	.24	.33
Betweenness Centrality of Prefrontal Cortex	Late Childhood	2.16%	-0.23	-0.40 to -0.03	.02	.10
	Middle Childhood	1.46%	0.13	-0.16 to 0.31	.21	.32
Betweenness Centrality of Amygdala	Early Childhood	1.18%	0.11	-0.15 to 0.26	.11	.28
Warm Parenting						
Modularity	Late Childhood	0.23%	0.05	-0.52 to 0.19	.44	.53
	Middle Childhood	0.04%	-0.02	-0.08 to 3.80	.96	.96
Global Efficiency	Early Childhood	3.26%	-0.21	-0.36 to -0.03	.01	.03
	Late Childhood	1.26%	0.09	-0.35 to 0.24	.36	.50
Small-World Propensity	Early Childhood	2.20%	-0.17	-0.32 to 0.10	.35	.50
Prefrontal Cortex - Amygdala Connectivity	Late Childhood	0.31%	-0.08	-0.23 to 0.26	.36	.50
	Middle Childhood	0.43%	0.05	-0.47 to 0.19	.84	.92
Betweenness Centrality of Prefrontal Cortex	Early Childhood	2.26%	0.25	0.09 to 0.40	<.001	.006
	Middle Childhood	6.09%	-0.18	-0.33 to -0.02	.009	.03
Betweenness Centrality of Amygdala	Middle Childhood	3.73%	0.23	0.07 to 0.39	.006	.03
	Late Childhood	1.78%	-0.10	-0.25 to 0.16	.14	.31

Note. Only theoretical models (early childhood, middle childhood, late childhood, accumulation, or combination thereof) selected within each SLCMA model are presented. R^2 change represents the incremental percentage of variance in the brain outcome explained by each theoretical model. Coefficient represents standardized coefficients. P_{orig} denotes original *P*-values. P_{fdr} denotes *P*-values corrected for multiple comparisons using the false discovery rate (FDR), for the number of models selected within each dimension of parenting (11 for psychological aggression, 11 for physical aggression, 11 for warm parenting).

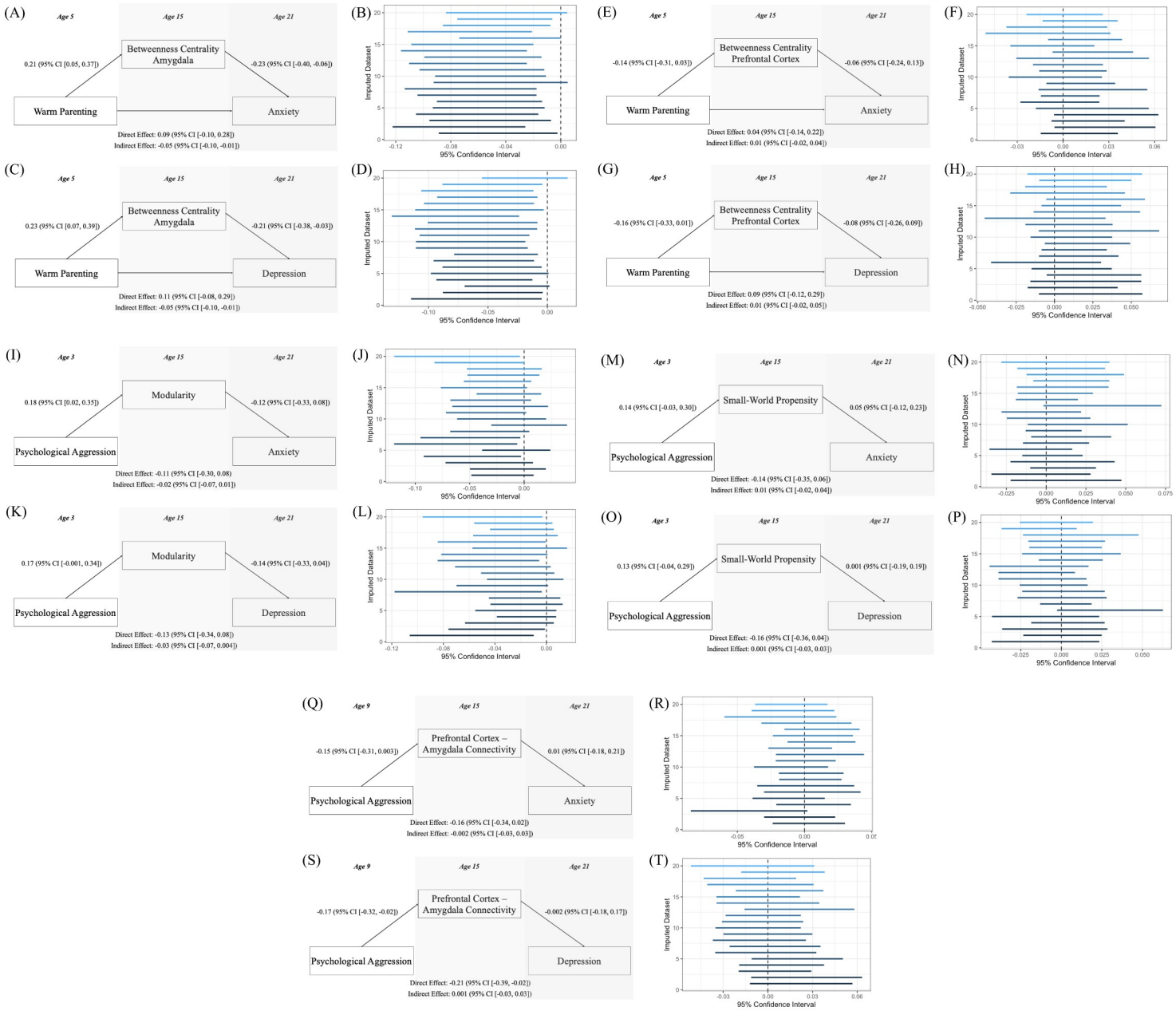


eFigure1. Developmental periods selected from the structured life-course modeling analyses. (A-C) Elbow plots illustrating the percentage of variance in each measure of functional brain architecture explained by each theoretical model (early childhood, middle childhood, late childhood, accumulation) for (A) psychological aggression, (B) physical aggression, and (C) warm parenting. Models controlled for sex assigned at birth, race/ethnicity, pubertal development, poverty ratio, parental education, and head motion. Graph theoretical analyses further controlled for average functional connectivity. The number of hypotheses tested in the second stage of the analysis for each model was based on the location of the elbow plot for each metric of brain architecture. (D) Summary plot depicting the number of times each theoretical model (early childhood, middle childhood, late childhood, or accumulation) was selected as the dominant explanatory variable in the first stage of model selection.

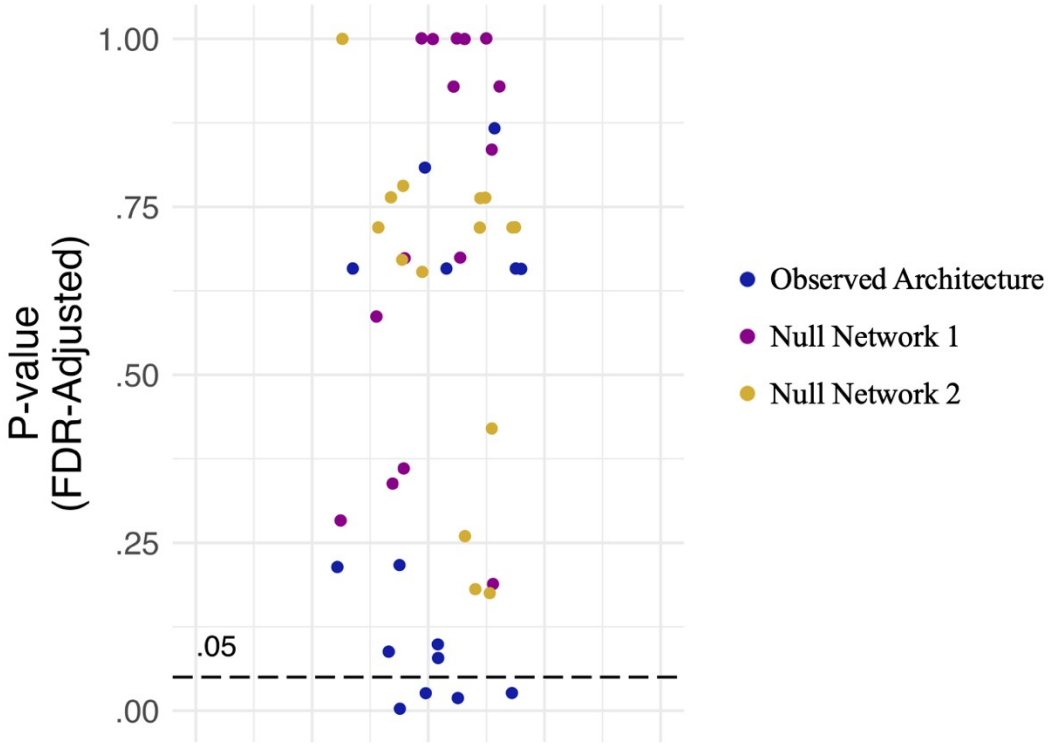


eFigure2. Longitudinal associations among harsh/warm parenting, functional brain architecture, and mental health during the COVID-19 pandemic. Indirect effects were examined only for metrics of brain architecture that were significantly associated with parenting during childhood. Statistically significant indirect effects (i.e., betweenness centrality of the amygdala) are depicted in

the Main Text, and non-significant indirect effects (i.e., betweenness centrality of prefrontal cortex, modularity, small-world propensity, and prefrontal cortex-amygdala functional connectivity) are depicted in the Supplement. Paths among parenting, brain architecture, and internalizing symptoms represent standardized regression coefficients and 95% confidence intervals derived from standard errors pooled across imputed datasets using Rubin's rules. Indirect effects were assessed from estimates and bias-corrected 95% confidence intervals with 10,000 bootstraps averaged across imputed datasets. All analyses controlled for sex assigned at birth, race/ethnicity, pubertal development, poverty ratio, parental education, head motion, and anxiety or depression during adolescence. Graph theoretical analyses further controlled for average functional connectivity.


(A)
Age 5
Age 15
Age 21
Betweenness Centrality Amygdala
0.21 (95% CI [0.05, 0.37])
-0.23 (95% CI [-0.40, -0.06])
Warm Parenting
Anxiety
Direct Effect: 0.09 (95% CI [-0.10, 0.28])
Indirect Effect: -0.05 (95% CI [-0.10, -0.01])
(B)
Imputed Dataset
95% Confidence Interval
(C)
Age 5
Age 15
Age 21
Betweenness Centrality Amygdala
0.23 (95% CI [0.07, 0.39])
-0.21 (95% CI [-0.38, -0.03])
Warm Parenting
Depression
Direct Effect: 0.11 (95% CI [-0.08, 0.29])
Indirect Effect: -0.05 (95% CI [-0.10, -0.01])
(D)
Imputed Dataset
95% Confidence Interval
(E)
Age 5
Age 15
Age 21
Betweenness Centrality Prefrontal Cortex
-0.14 (95% CI [-0.31, 0.03])
-0.06 (95% CI [-0.24, 0.13])
Warm Parenting
Anxiety
Direct Effect: 0.04 (95% CI [-0.14, 0.22])
Indirect Effect: 0.01 (95% CI [-0.02, 0.04])
(F)
Imputed Dataset
95% Confidence Interval
(G)
Age 5
Age 15
Age 21
Betweenness Centrality Prefrontal Cortex
-0.16 (95% CI [-0.33, 0.01])
-0.08 (95% CI [-0.26, 0.09])
Warm Parenting
Depression
Direct Effect: 0.09 (95% CI [-0.12, 0.29])
Indirect Effect: 0.01 (95% CI [-0.02, 0.05])
(H)
Imputed Dataset
95% Confidence Interval
(I)
Age 3
Age 15
Age 21
Modularity
0.18 (95% CI [0.02, 0.35])
-0.12 (95% CI [-0.33, 0.08])
Psychological Aggression
Anxiety
Direct Effect: -0.11 (95% CI [-0.30, 0.08)
Indirect Effect: -0.02 (95% CI [-0.07, 0.01])
(J)
Imputed Dataset
95% Confidence Interval
(K)
Age 3
Age 15
Age 21
Modularity
0.17 (95% CI [-0.001, 0.34])
-0.14 (95% CI [-0.33, 0.04])
Psychological Aggression
Depression
Direct Effect: -0.13 (95% CI [-0.34, 0.08])
Indirect Effect: -0.03 (95% CI [-0.07, 0.004])
(L)
Imputed Dataset
95% Confidence Interval
(M)
Age 3
Age 15
Age 21
Small-World Propensity
0.14 (95% CI [-0.03, 0.30])
0.05 (95% CI [-0.12, 0.23])
Psychological Aggression
Anxiety
Direct Effect: -0.14 (95% CI [-0.35, 0.06])
Indirect Effect: 0.01 (95% CI [-0.02, 0.04])
(N)
Imputed Dataset
95% Confidence Interval
(O)
Age 3
Age 15
Age 21
Small-World Propensity
0.13 (95% CI [-0.04, 0.29])
0.001 (95% CI [-0.19, 0.19])
Psychological Aggression
Depression
Direct Effect: -0.16 (95% CI [-0.36, 0.04])
Indirect Effect: 0.001 (95% CI [-0.03, 0.03])
(P)
Imputed Dataset
95% Confidence Interval
(Q)
Age 9
Age 15
Age 21
Prefrontal Cortex – Amygdala Connectivity
-0.15 (95% CI [-0.31, 0.003])
0.01 (95% CI [-0.18, 0.21])
Psychological Aggression
Anxiety
Direct Effect: -0.16 (95% CI [-0.34, 0.02])
Indirect Effect: -0.002 (95% CI [-0.03, 0.03])
(R)
Imputed Dataset
95% Confidence Interval
(S)
Age 9
Age 15
Age 21
Prefrontal Cortex – Amygdala Connectivity
-0.17 (95% CI [-0.32, -0.02])
-0.002 (95% CI [-0.18, 0.17])
Psychological Aggression
Depression
Direct Effect: -0.21 (95% CI [-0.39, -0.02])
Indirect Effect: 0.001 (95% CI [-0.03, 0.03])
(T)
Imputed Dataset
95% Confidence Interval

eFigure3. Longitudinal associations among harsh/warm parenting, functional brain architecture, and mental health during the COVID-19 pandemic in baseline models without covariates. Indirect effects were examined only for metrics of brain architecture that were significantly associated with parenting during childhood in the primary covariate-adjusted models. Paths among parenting, brain architecture, and internalizing symptoms represent standardized regression coefficients and 95% confidence intervals derived from standard errors pooled across imputed datasets using Rubin's rules. Indirect effects were assessed from estimates and bias-corrected 95% confidence intervals with 10,000 bootstraps averaged across imputed datasets.



eFigure4. Significance of associations between harsh/warm parenting and brain architecture estimated from observed versus null networks. Only graph theoretical metrics generated from the observed functional brain architecture are significantly associated with parenting behaviors during childhood following correction for multiple comparisons using the false discovery rate (FDR) within each dimension of parenting (i.e., psychological aggression, physical aggression, parental responsiveness). These findings indicate that identified associations between parenting and brain architecture are above what would be expected by chance. The first null network model randomized brain architecture while preserving the degree distribution. The second, more conservative null network model randomized brain architecture while preserving both the degree and strength distribution. The lowest *P*-value was selected from each

model regardless of which developmental periods (or accumulation) were most strongly related to functional brain architecture in the original structured life-course modeling analysis.

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