Differential Patterns of Delayed Emotion Circuit Maturation in Abused Girls With and Without Internalizing Psychopathology

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Objective: Childhood abuse represents one of the most potent risk factors for developing psychopathology, especially in females. Evidence suggests that exposure to early-life adversity may be related to advanced maturation of emotion processing neural circuits. However, it remains unknown whether abuse is related to early circuit maturation and whether maturation patterns depend on the presence of psychopathology.

Methods: A multisite sample of 234 girls (ages 8–18 years) completed clinical assessment, maltreatment histories, and high-resolution T_1-weighted structural MRI. Girls were stratified by abuse history and internalizing disorder diagnosis into typically developing (no abuse/no diagnosis), resilient (abuse/no diagnosis), and susceptible (abuse/current diagnosis) groups. Machine learning models of normative brain development were aggregated in a stacked generalization framework trained to predict chronological age using gray matter volume in whole-brain, emotion, and language circuit parcellations. Brain age gap estimations (BrainAGEs; predicted age minus true chronological age) were calculated as indices of relative circuit maturation.

Results: Childhood abuse was related to reduced BrainAGE (delayed maturation) specific to emotion circuits. Delayed emotion circuit BrainAGE was further related to increased hyperarousal symptoms. Childhood physical neglect was associated with increased whole-brain BrainAGE (advanced maturation). Neural contributors to emotion circuit BrainAGE differed in girls with and without an internalizing diagnosis, especially in the lateral prefrontal, parietal, and insular cortices and the hippocampus.

Conclusions: Abuse exposure in girls is associated with a delayed structural maturation pattern specific to emotion circuitry, a potentially adaptive mechanism enhancing threat generalization. Physical neglect, on the other hand, is associated with a broader brain-wide pattern of advanced structural maturation. The differential influence of fronto-parietal cortices and the hippocampus on emotion circuit maturity in resilient girls may represent neurodevelopmental markers of reduced psychiatric risk following abuse.

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Exposure to potentially traumatic events during childhood is pervasive, with two-thirds of children experiencing violence (physical abuse, sexual abuse, or witnessing community or domestic violence) by age 16 (1). Early-life exposure to violence can markedly alter neurobiological, psychological, and social development (2). These changes increase the risk for developing both first-onset and comorbid internalizing psychopathology (3), which has especially high overlap in symptom expression in adolescent girls (4). However, the neurodevelopmental mechanisms conferring resilience and susceptibility to psychiatric disorders following abuse remain unclear. Recent models suggest that early-life adversity may alter maturation patterns in emotion-processing circuits, but it remains unknown how neurodevelopmental maturity may influence the relationship between threat-related (compared with deprivation-related) stress and risk for internalizing psychopathology. Identification of neural maturational markers of resilience and susceptibility could have important implications for clinical monitoring and treatment for youths who are victims of abuse.

Evolutionary trade-offs between an individual's survival and development (e.g., investment in growth) and reproductive success (e.g., investment in sexual maturity) likely underlie individual differences in child development after early-life adversity. Life history theory and the differential susceptibility

model suggest that these trade-offs are likely constrained by the susceptibility of various developmental milestones to early experiences. The stress acceleration hypothesis extends these frameworks by integrating early-life adversity and child neurodevelopment (5). According to the hypothesis, early-life adversity may promote early development of emotion circuits, particularly those underlying threat-safety processing, to meet potentially dangerous environmental demands. Indeed, stress-related changes in the recruitment of emotion circuits often show patterns suggesting advanced development. For example, early development of amygdala-medial prefrontal cortex (mPFC) functional connectivity has been observed in youths exposed to maternal deprivation stress (6) and those residing in disadvantaged socioeconomic neighborhoods (7), and it has been found to be longitudinally associated with the severity of early-life adversity generally (8). However, a more thorough review of the related literature indicates mixed results overall, equally suggesting both delayed maturation and no maturational differences (9). Importantly, the stress acceleration model of adversity and the development of emotion-related circuits may be dependent on the characteristics of adversity experienced; this has been suggested by recent work incorporating the dimensional model of adversity and psychopathology (10), where advanced biological aging measured via telomere shortening, epigenetic age, and pubertal development were specific to threat-related adversity (e.g., abuse) compared with deprivation-related adversity (e.g., neglect) (11).

The relationship between emotion circuit maturation after abuse and resilience or susceptibility to subsequent psychopathology is also unclear. Current evidence suggests that fast developmental strategies during childhood increase risk for psychopathology in adulthood (12). Additionally, abused youths are at increased risk for internalizing psychopathology earlier, with greater severity, and with more comorbidities (13, 14). The latent vulnerability model (15) suggests that resilience and susceptibility to psychopathology after early-life adversity depends on the degree of neurodevelopmental flexibility in systems underlying salience detection, threat appraisal, and emotion regulation in adapting to future adversity. Earlier-developing circuits underlying salience detection and threat appraisal (e.g., the amygdala, insula, and mPFC) are likely recalibrated toward increased recruitment to threat-related stimuli, spurring development toward a more mature threat processing phenotype. We suspected that vulnerability to psychopathology may then fundamentally depend on how later-developing circuits, especially in the lateral PFC, are recalibrated in response. In contrast to earlier-developing structures, the lateral PFC does not reach developmental plateau until early adulthood, remaining highly plastic throughout adolescence by maintaining increased levels of synaptogenesis and experience-dependent pruning, myelination, and apoptosis (16). Therefore, such systems likely show greater variability in their developmental trajectories after early-life adversity, leading to greater variability in executive control processes underlying resilience or susceptibility to psychopathology. We posit that adaptive flexibility in the maturation of the lateral PFC is a key predictor for the development of internalizing psychopathology after early-life adversity, although this is likely highly dependent on the timing of the adversity.

In this study, we examined whether abused girls show advanced structural maturation in emotion-related circuits compared with whole-brain and language-related circuitry. Language-related circuitry was used as a control circuit to evaluate emotion circuit specificity. We examined whether the degree of structural maturity depended on the absence (resilience) or presence (susceptibility) of internalizing disorders and whether these effects were specific to abuse (threat) compared with neglect (deprivation). The focus on internalizing disorders broadly was a result of high rates of comorbidity between anxiety, depression, and posttraumatic stress disorder (PTSD), which if segregated would have considerably limited sample sizes and statistical power for psychopathology-related comparisons. Finally, we examined whether particular brain regions contributed to overall circuit maturation differently in abused girls who are resilient to internalizing disorders compared with those who are susceptible to internalizing disorders. By using machine learning in a stacked generalization framework, we implemented a normative development model trained to predict chronological age from regional gray matter volume estimates in typically developing girls. We then used the normative model to calculate a brain age gap estimation (BrainAGE; predicted age minus chronological age), an index of relative circuit maturation. BrainAGE has been shown to represent a biologically meaningful index that is reliable (17, 18), heritable (18), and associated with developmental neuro-phenotypes underlying illness (19, 20). This index is specific to an individual's brain at the time the data were collected and should not be interpreted as reflecting a developmental trajectory that the brain will follow into the future. We hypothesized that abused girls, both resilient and susceptible to internalizing disorders, would show greater emotion circuit BrainAGE (indicating advanced maturation) relative to typically developing girls. We also hypothesized that abuse-related gray matter volume in early-developing regions underlying salience detection and threat appraisal (e.g., the amygdala and insula) would contribute to more positive (advanced) BrainAGE. Finally, we hypothesized that late-developing regions underlying attentional processes and executive control (e.g., the lateral PFC) would best differentiate circuit maturation in resilient compared with susceptible abused girls.

METHODS

Participant Recruitment and Assessment

A total of 246 adolescent girls (chronological age range, 8–18 years) were pooled from research studies at three sites: Madison, Wisc.; Little Rock, Ark.; and Seattle. We investigated violence exposure-related differences specific to abuse (physical, sexual, and emotional). Details regarding sample sizes, MRI parameters, and demographic information for each site are presented in Table 1 and Table S1 in the online

TABLE 1. Demographic, maltreatment, and clinical characteristics of participants[a]

| | Group | | | | | | Comparison[c] | | | | |
| | Typically Developing (N=99) | | Resilient (N=50) | | Susceptible (N=85)[b] | | | | | | |
Characteristic	Mean	SD	Mean	SD	Mean	SD	F	t	df	Direction	p
Age (years)	13.78	2.64	14.15	2.25	14.55	2.32	2.59	n.s.	1, 150	—	0.076
IQ	111.68	16.73	106.02	17.05	99.14	15.64	32.70	−3.31	1, 150	Typically developing > resilient	<0.001
								−7.32	1, 150	Resilient > susceptible	<0.001
Tanner stage[d]	3.67	1.20	3.49	1.41	3.35	1.39	1.22	n.s.	1, 65	—	0.296
CTQ abuse	15.94	1.09	25.92	8.37	33.88	12.37	141.10	8.28	1, 150	Typically developing < resilient	<0.001
								15.79	1, 150	Resilient < susceptible	<0.001
CTQ physical neglect	6.76	3.08	8.76	3.57	9.69	4.44	13.82	2.74	1, 150	Typically developing < resilient	<0.001
								5.00	1, 150	Typically developing < susceptible	<0.001
MFQ[d]	—	—	4.60	4.39	17.01	10.53	171.20	12.97	1, 110	Resilient < susceptible	<0.001
SCARED[d]	—	—	19.83	11.50	32.84	16.54	36.43	67.80	1, 64	Resilient < susceptible	<0.001
PTSD-RI[d]	—	—	20.58	15.42	43.53	17.62	89.72	3.07	1, 97	Resilient < susceptible	<0.001

[a] CTQ=Childhood Trauma Questionnaire; MFQ=Mood and Feelings Questionnaire; n.s.=nonsignificant; PTSD=posttraumatic stress disorder; PTSD-RI=UCLA Child and Adolescent PTSD Reaction Index for DSM-5; SCARED=Screen for Child Anxiety Related Emotional Disorders.

[b] Internalizing disorders in the susceptible group were as follows: anxiety disorder, N=38 (44.7%); depressive disorder, N=59 (69.4%); and posttraumatic stress disorder, N=56 (65.9%).

[c] Group comparison statistics are indicated with the effect directions for significant differences (p<0.05).

[d] Variables that were not consistently available for all participants (missing not at random).

supplement. Written informed consent and/or verbal assent were obtained from all participants, and study procedures were approved by institutional review boards. A detailed account of clinical assessments, including diagnostic battery, anxiety, depression, and PTSD symptom severity, and maltreatment history is provided in the online supplement. The girls were classified into three groups based on binary abuse exposure (unexposed compared with exposed) and internalizing diagnosis (presence compared with absence): typically developing (unexposed, no diagnoses), resilient (exposed, no diagnoses), and susceptible (exposed, at least one diagnosis). It is important to note that we use the terms resilient and susceptible to refer to the current absence or presence of internalizing psychopathology after abuse, respectively. Because many youths in this sample had yet to reach the chronological age corresponding to the average age at onset for some internalizing disorders, in this context, resiliency does not imply that these youths may not be susceptible to disorders in the future.

Image Acquisition and Individual Preprocessing

A detailed account of image acquisition and individual preprocessing of MRI data is provided in the Materials section and Table S1 in the online supplement. Briefly, mean voxel-wise cortical and subcortical gray matter volume was extracted from processed T_1-weighted MRI scans using the Brainnetome Atlas (21). Neurosynth (22) was used to identify regions of interest belonging to emotion-related and language-related circuits, which are listed in Table S2 and diagrammed in Figure S1 in the online supplement. Finally, each region of interest was scaled to total intracranial volume and harmonized across scanners.

Normative Models of Gray Matter Volume Development

Model building and training. Ensemble machine learning using a stacked generalization (23) approach was used to build normative models of gray matter volume development with respect to whole-brain, emotion, and language circuit features. More specifically, a "super learner," optimizing the aggregation of multiple learning algorithms and minimizing cross-validation risk, was implemented for each neural feature set. Stacked generalization is a form of ensemble machine learning whereby individual "lower-level" learning algorithms are aggregated to increase predictive power by utilizing the strengths of each base model (referred to as submodels). A super learner, therefore, is a final prediction aggregation model with the objective of finding the optimal combination of submodel predictions. A more detailed overview of the super learning algorithm (Figure 1A) and the model-building protocol (Figure 1B) are provided in the online supplement.

Model evaluation. The super learner and comprising submodels were evaluated with a validation set of typically developing girls absent during training. Girls in the validation set were pseudorandomly assigned so as to remain representative of the training set (stratified by age and scanner). Mean absolute error was used to evaluate model performance. To ensure above-chance performance, a null distribution was created with 1,000 bootstrap samples of the label vector (chronological age), and age was predicted with each bootstrap. Median differences between the true performance and null performance distributions were calculated. All models underwent a final evaluation step comparing predicted and chronological ages using Pearson's correlation (r), and BrainAGEs were

FIGURE 1. Super-learner algorithm and normative model-building protocol[a]
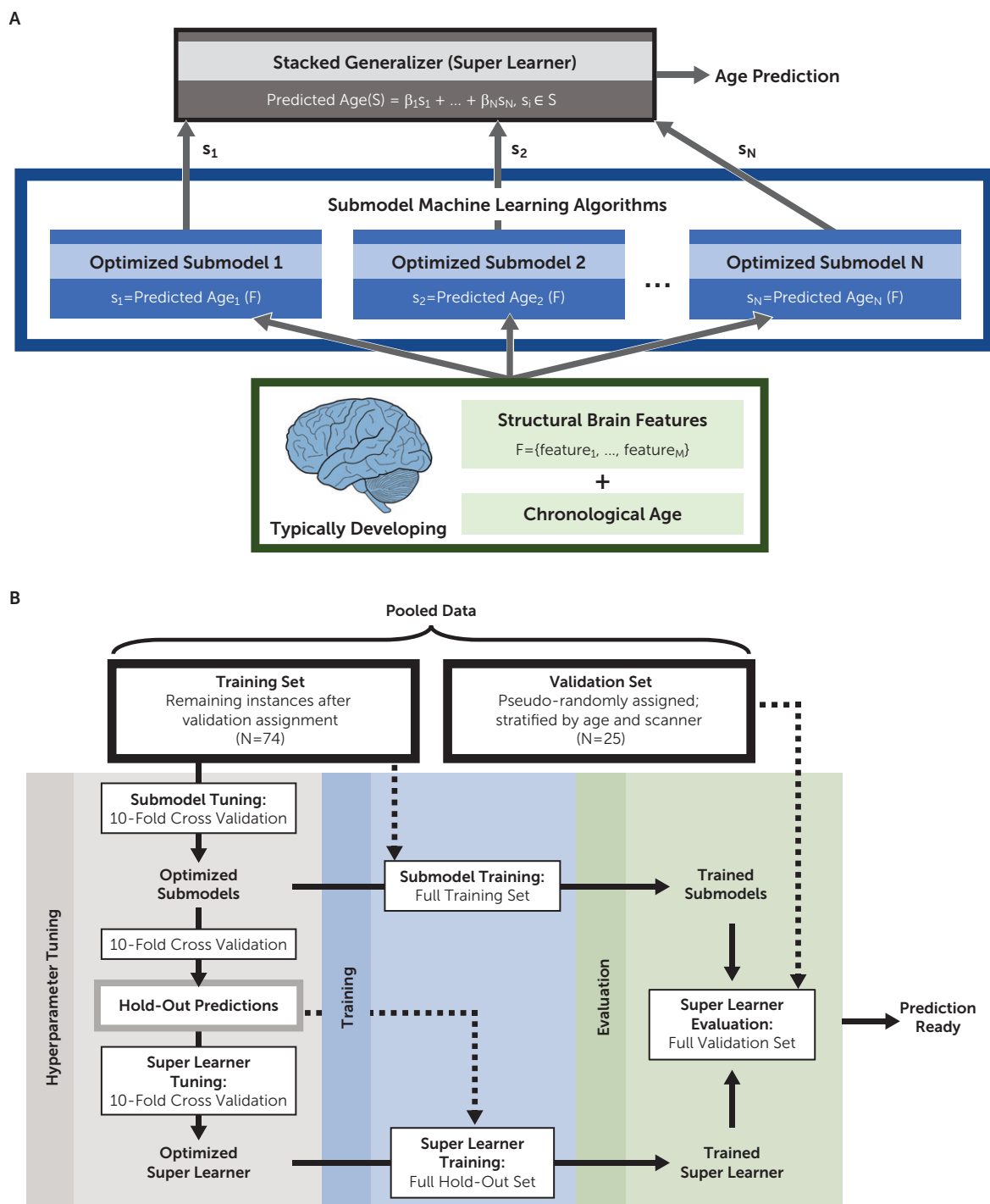
[a] Panel A shows the super-learner algorithm as implemented with an L2-penalized linear combination of predictions from *N* unique machine learning algorithms (submodels, including general linear ridge, multilayer perceptron, random forest, support vector machine, and gradient-boosting machine regression). Submodel held-out predictions in each round of cross-validation were used to tune the super-learner parameters. The full training set was used to train each submodel and the super-learner coefficients ($\beta_1 \ldots \beta_N$). Submodel predictions, $S=(S_1 \ldots S_N)$, were input to the super learner to make final age predictions and calculate brain age gap estimations (BrainAGEs). Panel B shows a schematic of the model-building protocol for predicting chronological age and BrainAGE from gray matter volume features. Data were pooled, and participants were pseudorandomly assigned to the training or validation set (stratified by scanner and age). First, hyperparameters for each submodel algorithm were tuned using 10-fold cross-validation. The optimized submodels make predictions using 10-fold cross-validation, and the hold-out set is used to tune the super-learner hyperparameters. Finally, the optimized submodels are trained on the full training, and the optimized super learner is trained on the full hold-out set. The trained super learner is then evaluated using the set-aside validation set.

calculated for all abused girls. Here, a negative BrainAGE in abused girls relative to typically developing girls indicates the extent of delayed maturation, and a positive BrainAGE indicates the extent of advanced maturation.

BrainAGE Group-Level Analyses

Linear mixed-effects models in R (lme4 package) were used to determine abuse-related and diagnosis-related differences in BrainAGE from whole-brain, emotion, and language circuit features. BrainAGEs for abused girls were standardized to the typically developing set, and for each neural feature set, an abuse-by-diagnosis interaction and main effects were included. As is common with BrainAGE (24), there was an age bias in the super learner; therefore, chronological age was included as a covariate. This bias correction was only included when analyzing BrainAGE at the group level and therefore does not change the interpretability of the Brain-AGE as a maturational index. Additionally, IQ (gray matter volume is strongly associated with IQ in older children and adolescents [25]), scanner, and physical neglect experiences were included as covariates to safeguard against scanner effects and test specificity to abuse. Finally, an additional Bonferroni correction was applied across the three sets of circuit features (alpha=0.017, 0.05/3). Post hoc analyses were conducted if significant relationships were identified, investigating the relationship between BrainAGE differences and internalizing symptom severity (PTSD, depression, and anxiety symptoms) and pubertal stage. Additional details regarding all models tested, binarized compared with continuous analyses, and covariates are provided in the online supplement.

Feature Influence Analysis

Calculating regional influence on BrainAGE. We hypothesized that regional gray matter volume phenotypes related to abuse may differentially influence BrainAGE estimates in resilient girls compared with susceptible girls. In order to determine how influential abuse-related gray matter volume was to BrainAGE, a perturbation sensitivity approach was used (see Figure S3 in the online supplement). Perturbation in this context does not refer to an anxiety phenotype but rather to a change in model performance after that model had been altered in some way. The goals of perturbation sensitivity were twofold: first, to determine whether an altered distribution of BrainAGEs was significantly different from the unaltered distribution of BrainAGEs (significant feature influence), and second, to determine whether perturbation with an abuse-related phenotype caused a shift in BrainAGE distribution relative to the distribution observed with typically developing perturbation (beyond chance expectations). In pursuit of these goals, perturbation across more than two of the groups at once was ruled out as a possible approach. The rationale for this analysis is as follows: perturbing a typically developing gray matter volume phenotype with an abuse-related gray matter volume phenotype should strongly affect the normative model's age prediction (and related BrainAGE) if that region's abuse phenotype is informative to

either significantly increased or decreased BrainAGE. Similarly, if an abuse-related phenotype is not informative for the model's age prediction, there will be no significant change in the distribution of BrainAGEs. Feature influence was calculated as the median change in BrainAGE distribution after perturbation (perturbed median BrainAGE minus true median BrainAGE). Further details regarding abuse-related gray matter volume sampling and statistical tests comparing BrainAGE distributions are provided in the online supplement.

RESULTS

Participant Demographic Characteristics

Aggregated demographic, clinical, and maltreatment variables across study sites are summarized in Table 1 and are split by study site in Table S1 in the online supplement. The pooled cohort comprised 234 adolescent girls between 8 and 18 years old (mean age, 14.15 years [SD=2.47]). In total, 99 girls had no abuse exposure or diagnosed internalizing psychopathology (typically developing), 50 girls had abuse exposure and no diagnosis (resilient), and 85 girls had abuse exposure and at least one diagnosis (susceptible). Within the susceptible group, 38 girls (44.7%) had an anxiety disorder, 59 (69.4%) had a depressive disorder, and 56 (65.9%) had PTSD; 62 girls (72.9%) had at least two of these disorders.

Normative Model Performance and Bias

The super learner and its submodels performed significantly better than chance expectations (all p values <<0.001). Model performances on the validation set of typically developing girls for each super learner and comprising submodels are reported in Table S4 in the online supplement. Models generalized well to the validation set (means for whole-brain: mean absolute error=2.463 years, r=0.507, p=0.048; means for emotion: mean absolute error=1.851 years, r=0.594, p=0.003; means for language: mean absolute error=2.326 years, r=0.566, p=0.009). For each feature set, the super learner performed better than all comprising submodels (whole-brain: mean absolute error=1.666 years, r=0.677, p<0.001; emotion: mean absolute error=1.602 years, r=0.663, p<0.001; language: mean absolute error=1.569 years, r=0.655, p<0.001). There was an age bias in each super learner, overestimating and underestimating BrainAGEs in younger and older girls, respectively (see Figure S4 in the online supplement; emotion circuitry: t=−11.963, df=756, p<<0.001)

Group-Level BrainAGE Relationships

Group differences in BrainAGE. In the whole-brain and language circuitry analyses, no significant abuse-related or diagnosis-related differences were identified (Figure 2A, 2C). In the emotion circuitry analysis, an abuse effect was identified, where girls exposed to abuse showed significantly reduced BrainAGE (Figure 2B) (F=15.680, df=1, 150, p<0.001; t=−2.366, df=150, p=0.014), an average of 0.70 years younger than typically developing girls of the same chronological age. There was a significant effect of physical

FIGURE 2. Abuse-related and internalizing diagnosis-related associations with brain age gap estimates (BrainAGEs) for whole-brain, emotion circuit, and language circuit feature sets[a]
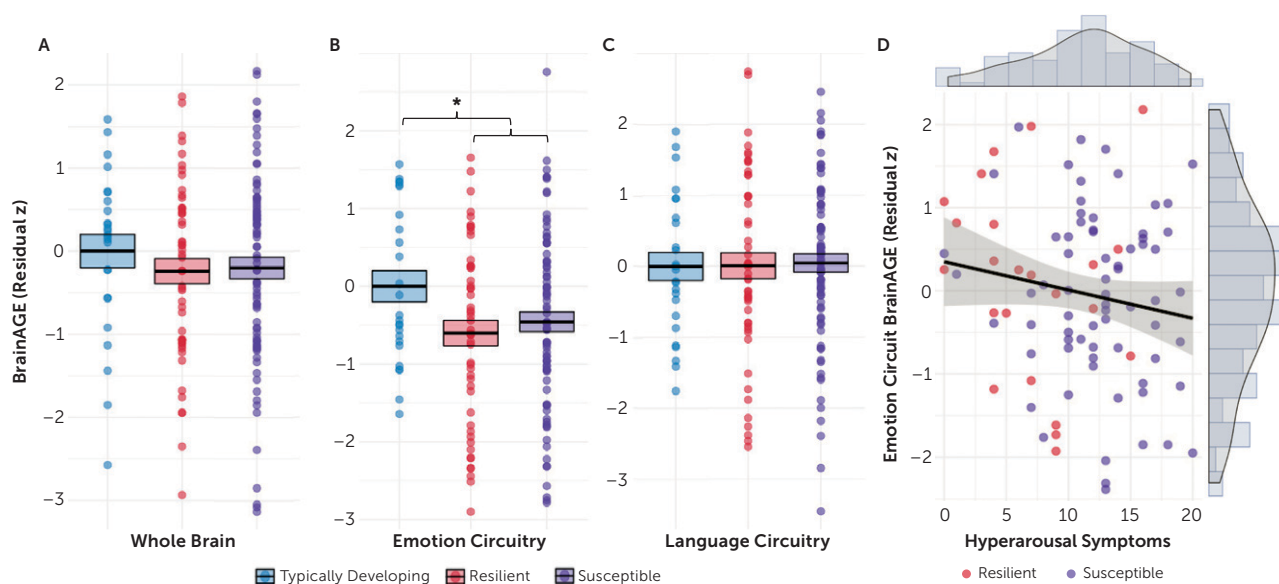
[a] BrainAGEs for abused girls are represented as residualized z-scores relative to typically developing girls, controlling for label (chronological age), scanner, IQ, and physical neglect. For the whole-brain analysis, there were no significant differences in BrainAGE across groups (panel A). For the emotion circuit analysis, an abuse main effect reveals that resilient and susceptible girls showed significantly reduced average BrainAGEs relative to typically developing girls (panel B). For the language circuit analysis, there were no significant differences in BrainAGE across groups (panel C). Symptom-level association with emotion circuit BrainAGEs across abused girls are shown in panel D. Emotion circuitry BrainAGEs were negatively associated with hyperarousal symptoms (UCLA Child and Adolescent PTSD Reaction Index for DSM-5 subscale D score).

* $p < 0.017$ after experiment-wide Bonferroni correction.

neglect severity for whole-brain BrainAGE, where physical neglect experiences were positively associated with BrainAGE across all girls ($\beta = 0.064$; F=7.933, df=1, 150, p=0.006; t=2.817, df=150, p=0.006). There were no significant or nearly significant scanner effects (see Figure S5 in the online supplement).

Symptom and puberty relationships with BrainAGE. In the symptom analyses with emotion circuit BrainAGEs, there was a significant effect of PTSD hyperarousal symptoms (UCLA Child and Adolescent PTSD Reaction Index for DSM-5 [PTSD-RI] subscale D score). Here, across all abused girls, hyperarousal symptom severity was negatively associated with BrainAGE (Figure 3) ($\beta = -0.091$; t=−2.050, df=96, p=0.043). This relationship was identified only when controlling for all previous group-level covariates, abuse severity, and the remaining PTSD-RI subscale scores (unadjusted $\beta = -0.053$; t=−1.327, df=98, p=0.187). Finally, there were no significant relationships between BrainAGE and total PTSD (t=1.142, df=98, p=0.256), anxiety (t=0.354, df=65, p=0.724), and depression (t=0.340, df=110, p=0.734) symptoms or pubertal milestones (t=1.114, df=65, p=0.270).

Regional Influence on Abuse-Related BrainAGE Distribution

Regions influencing BrainAGE: all abused girls. A summary of results from the feature influence analysis is presented in

Table 2, separated by spatially overlapping (all abused girls) or unique (resilient compared with susceptible girls) contributors to BrainAGE. Resilient and susceptible girls showed few overlapping influential regions. Generally, thalamic gray matter volume from abused girls contributed to a positive (advanced) shift in BrainAGE: gray matter volume in the left and right mediodorsal thalamus (medial prefrontal thalamus: adjusted $R^2 = 0.087$, false discovery rate-corrected p [p_{FDR}] p<0.001; lateral prefrontal thalamus: adjusted $R^2 = 0.053$, $p_{FDR} = 0.040$) and the left lateral pulvinar nucleus (caudal temporal thalamus: adjusted $R^2 = 0.049$, $p_{FDR} = 0.005$) contributed to a positive shift in BrainAGE. Additionally, gray matter volume in the right caudal anterior cingulate cortex (adjusted $R^2 = 0.076$, $p_{FDR} < 0.039$) contributed to a positive shift in BrainAGE for both resilient and susceptible girls. No regions contributed to a negative (delayed) shift in BrainAGE.

Regions influencing BrainAGE: resilient girls. Resilient girls showed regional gray matter volume phenotypes that uniquely influenced BrainAGE relative to susceptible girls (Table 2, Figure 3A). Regions contributing to a positive shift in BrainAGE included the left ventral lateral thalamic nucleus (premotor thalamus: adjusted $R^2 = 0.092$, $p_{FDR} < 0.001$), the left rostral inferior parietal lobule (Brodmann's area [BA] 40; adjusted $R^2 = 0.098$, $p_{FDR} < 0.001$), the right dorsal inferior parietal lobule (BA 39; adjusted $R^2 = 0.087$, $p_{FDR} < 0.001$), and the right dorsolateral prefrontal cortex (dlPFC; BA 8;

FIGURE 3. Spatially unique feature influence results for resilient and susceptible girls from the perturbation sensitivity analysis[a]
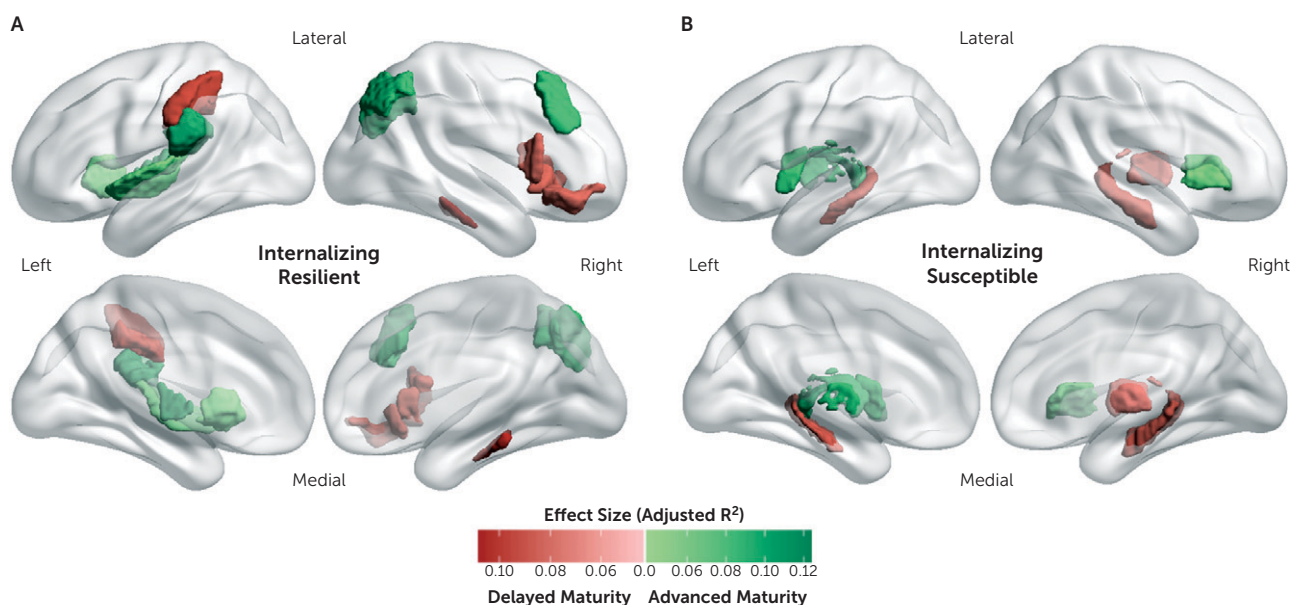
[a] The region-of-interest color corresponds to the mean effect size (adjusted R^2) of the brain age gap estimation (BrainAGE) distribution shift when the region is perturbed with an abuse-related gray matter volume phenotype. Darker green indicates greater positive shift, and darker red indicates greater negative shift.

adjusted $R^2=0.087$, $p_{FDR}=0.006$). Regions that contributed to a negative shift in BrainAGE included the right posterior parahippocampal gyrus (BA 27; adjusted $R^2=0.098$, $p_{FDR}<0.034$), the right dorsal insular cortex (BA 13; adjusted $R^2=0.083$, $p_{FDR}=0.050$), the right lateral orbitofrontal cortex (BA 12/47; adjusted $R^2=0.080$, $p_{FDR}=0.034$), and the right lateral opercular prefrontal cortex (BA 44; adjusted $R^2=0.079$, $p_{FDR}<0.001$).

Regions influencing BrainAGE: susceptible girls. Susceptible girls showed regional gray matter volume phenotypes that uniquely influenced BrainAGE relative to resilient girls (Table 2, Figure 3B). Regions that contributed to a positive shift in BrainAGE included the left lateral geniculate nucleus (occipital thalamus: adjusted $R^2=0.093$, $p_{FDR}<0.001$), the medial pulvinar nucleus (rostral temporal thalamus: adjusted $R^2=0.088$, $p_{FDR}<0.001$), the left dorsal insular cortex (adjusted $R^2=0.081$, $p_{FDR}<0.001$), and the right opercular PFC (BA 44; adjusted $R^2=0.051$, $p_{FDR}=0.028$). Regions that contributed to a negative shift in BrainAGE included the left and right caudal hippocampus (left: adjusted $R^2=0.088$, $p_{FDR}<0.001$; right: adjusted $R^2=0.087$, $p_{FDR}<0.001$).

DISCUSSION

Abused girls, regardless of diagnostic status, showed delayed maturity in emotion circuitry (counter to our original hypothesis), which was further associated with increased hyperarousal symptoms. Advanced whole-brain BrainAGE was associated with increased physical neglect severity, suggesting

differential effects of threat and deprivation stress on patterns of circuit-specific and whole-brain neurodevelopment. Additionally, we found unique regional contributors to emotion circuitry maturation in resilient and susceptible girls, most prominently in frontoparietal, hippocampal, and insular gray matter. Altogether, our findings provide new insights into brain maturational patterns related to threat- and deprivation-related adversity and internalizing psychopathology and point to potential systems-level mechanisms differentiating resilient and susceptible developmental trajectories.

Abuse exposure was associated with delayed emotion circuit maturity relative to typically developing girls, which was further related to increased hyperarousal symptoms (but only when controlling for group-level covariates and other PTSD-related symptoms). Although speculative, this suggests that delayed structural maturity in emotion circuits may underlie sensitive salience and threat detection systems in the brain, potentially leading to reduced threat-safety discrimination and states of generalized hypervigilance. Although enhanced threat bias in neurobiological reactivity is likely adaptive in abusive environments, this may lead to reliably misinterpreting safety cues as dangerous. Indeed, reduced threat-safety discrimination has previously been associated with younger developmental stage (children < adolescents < adults) (26, 27), as well as with increased recruitment of threat processing circuits with maltreatment exposure and increased risk for psychopathology (28, 29). For this reason, girls exposed to abuse may habitually recruit threat-related circuitry even in canonically safe contexts: this type of threat generalization, typically observed only in younger children, likely delays increases in synaptic pruning,

TABLE 2. Perturbation sensitivity (feature influence) analysis in emotion circuitry in female adolescents ages 8–18 years[a]

Effect and Direction	Region	Hemisphere	Brodmann's Area	Power et al. (52) Network Parcellations	Atlas Label	Adjusted R^2	False Discovery Rate p
Abuse exposure							
Greater BrainAGE	Medial prefrontal thalamus	Left	—	Subcortical	Tha_8_1	0.087	<0.001
	Caudal anterior cingulate cortex	Right	24	Cingulo-opercular	CG_7_5	0.076	0.039
	Lateral prefrontal thalamus	Right	—	Subcortical	Tha_8_8	0.053	0.040
	Caudal temporal thalamus	Left	—	Subcortical	Tha_8_7	0.049	<0.001
Unique to resilient							
Greater BrainAGE	Rostral inferior parietal lobule	Left	40	Fronto-parietal	IPL_6_6	0.098	<0.001
	Premotor thalamus	Left	—	Subcortical	Tha_8_2	0.092	<0.001
	Dorsal inferior parietal lobule	Right	39	Fronto-parietal	IPL_6_2	0.087	<0.001
	Dorsolateral prefrontal cortex	Right	8	Fronto-parietal	MFG_7_5	0.087	0.006
	Primary auditory cortex	Left	41	Auditory	STG_6_3	0.042	0.043
	Ventral caudate nucleus	Left	—	Subcortical	BG_6_1	0.039	0.014
Reduced BrainAGE	Posterior parahippocampal gyrus	Right	27	Default mode	PhG_6_3	0.098	0.034
	Dorsal inferior parietal lobule	Left	39, 40	Dorsal attention	IPL_6_3	0.095	<0.001
	Dorsal agranular insula	Right	13	Cingulo-opercular	INS_6_3	0.083	0.050
	Lateral orbitofrontal cortex	Right	12, 47	Cingulo-opercular	OrG_6_6	0.080	0.034
	Lateral opercular prefrontal cortex	Right	44	Cingulo-opercular	IFG_6_6	0.079	<0.001
Unique to susceptible							
Greater BrainAGE	Occipital thalamus	Left	—	Subcortical	Tha_8_6	0.093	<0.001
	Rostral temporal thalamus	Left	—	Subcortical	Tha_8_4	0.088	<0.001
	Dorsal dysgranular insula	Left	13	Cingulo-opercular	INS_6_6	0.081	<0.001
	Opercular prefrontal cortex	Right	44	Cingulo-opercular	IFG_6_5	0.051	0.028
Reduced BrainAGE	Caudal hippocampus	Left	—	Default mode	Hipp_2_2	0.088	<0.001
	Caudal hippocampus	Right	—	Default mode	Hipp_2_2	0.087	<0.001
	Rostral temporal thalamus	Right	—	Subcortical	Tha_8_4	0.067	<0.001

[a] Regions are separated by overlapping compared with unique effects between abuse groups. Within these separations, regions are sorted by descending adjusted R^2. The R^2 and false discovery rate-corrected p values are for the abuse-perturbed brain age gap estimation (BrainAGE) comparison relative to the typically developing perturbed (chance) BrainAGE comparison. All probability values for the abuse-perturbed BrainAGE comparison relative to the true BrainAGE comparison were less than 0.001 and are not included to avoid redundancy.

circuit myelination, and other related processes that result in age-appropriate reductions in gray matter volume.

Physical neglect experiences, on the other hand, were positively associated with whole-brain maturity across typically developing and abused girls. Here, increased physical neglect corresponded to advanced whole-brain maturation. In contrast to the delayed emotion circuit maturation associated with abuse, this suggests that neglect and deprivation-related adversity may have global rather than circuit-specific effects on brain maturation. Indeed, the absence of expected age-typical cognitive and social inputs to the brain, as is often the case with physical neglect, likely affects the association cortex broadly, representing a global acceleration of neuronal and synapse elimination mechanisms typical of low-complexity environments (10, 30). These mechanisms would translate to decreased gray matter volume in a deprivation context for equivalent chronological age, an advanced maturation phenotype. This may also explain the seeming discrepancy between previously reported findings of advanced emotion circuit development with adversity and the findings reported here, because the majority of these previous studies documented adversity more specific to deprivation (maternal separation [6], disadvantaged socioeconomic neighborhoods

[7]) or a combination of threat and deprivation (abuse with physical or emotional neglect [8]). Thus, we suspect that the current formulation of the stress acceleration hypothesis, as it pertains to brain maturation, may more accurately account for broader whole-brain patterns specific to deprivation-related adversity. Additionally, because co-occurrence of deprivation- and threat-related adversity is common, global advanced maturation patterns specific to deprivation may mask threat-specific delayed maturation patterns only observed in emotion circuits when not examined separately, causing them to go unnoticed in earlier studies.

We observed unique gray matter volume phenotypes from abused girls contributing to significant shifts in BrainAGE distribution. Resilient, but not susceptible, abused girls showed dlPFC and lateral inferior parietal lobule gray matter volumes contributing to a positive (advanced) shift in emotion circuit maturation, supporting our original hypotheses. We previously reported that internalizing-susceptible youths show developmentally delayed gray matter volume reduction in the dlPFC (31), and cortical expansion of the dlPFC differentiated which youths showed remission or persistence of PTSD symptoms at 1-year follow-up (32). Although abnormal dlPFC structure has not been reliably associated with childhood

abuse exposure (9), changes in dlPFC structure and function have been broadly associated with reduced internalizing symptoms (33, 34) and recovery from trauma (35). For example, an inability to recruit the dlPFC during differentiation of threat from nonthreat mediates the relationship between anxiety disorders and generalized fear (36). Additionally, repetitive transcranial magnetic stimulation of the dlPFC, altering functional connectivity with the amygdala (37) and nucleus accumbens (38), has been shown to reduce both anxiety and depression symptoms. Therefore, fronto-parietal structures contributing to advanced emotion circuit maturation in resilient girls may translate to a compensatory trajectory promoting more mature attentional and executive control processes, approaching adult patterns of function and decreasing psychiatric risk.

We also found that bilateral hippocampus gray matter volume contributed to negative (delayed) shifts in emotion circuit maturation in susceptible, but not resilient, abused girls. We previously reported age-related hippocampus gray matter abnormalities in traumatized youths with PTSD (39), one of the most commonly reported neural correlates of early-life stress in youths and adults. Here, both childhood maltreatment and trauma exposure generally are associated with decreased hippocampal volume (40–42), likely driven by a combination of decreased neurogenesis/neural progenitor cells (43), atrophy of dendrites and reduced postsynaptic dendritic spines (44), and a reduced pool of stem cells into adulthood (45). In alignment with our findings, decreased hippocampal volume appears to be more pronounced in maltreatment victims with PTSD and other internalizing disorders compared with those without (42). Together, these results suggest that neurodevelopment underlying resilience to internalizing after abuse is critically dependent on regional patterns of maturation, where regions with a late (e.g., the dlPFC) compared with an early (e.g., the hippocampus) developmental plateau may have extended windows of change susceptibility in which to reorganize, a key factor in the development of pathology-inducing circuit phenotypes. The factors determining which children will undergo resilient circuit reorganization and which will not are unknown and warrant investigation.

The majority of differences in BrainAGE influential regions between resilient and susceptible girls were found in nodes of the cingulo-opercular network, including the insular cortex, opercular PFC, and lateral orbitofrontal cortex. Gray matter volume from susceptible and resilient girls contributed to more positive (advanced) and more negative (delayed) shifts in emotion circuit maturation, respectively. The cingulo-opercular network is a key substrate of threat-processing circuitry and is recruited by salient or unexpected stimuli to reorient attention circuitry toward relevant cues and inform subsequent responses (46, 47). Abnormal development of the orbitofrontal cortex, cross-sectionally and longitudinally, has been reported in studies of abused youths (31, 39). As the brain's "engine of alertness," abnormalities likely underlie symptoms of hyperarousal and hypervigilance commonly observed after abuse (48, 49). In fact, meta-analyses across all DSM-IV axis I disorders suggest that gray matter volume in the insular cortex is the best differentiator of individuals with diagnosable psychopathology broadly and those without (50, 51). We suspect that differences in the maturation of the cingulo-opercular network underlie important differences between resilient and susceptible girls after abuse, presumably through biasing attentional processes toward threat detection and the promotion of emotional reactivity.

Our study is not without limitations. First, as is the case for many pediatric neuroimaging studies, the sample size of typically developing and abused girls was modest. The small sample size for nonabused girls with internalizing diagnoses precluded us from an omnibus analysis interrogating maturation patterns specific to internalizing psychopathology. Second, given that many measures collected had substantial missing data (depression, anxiety symptoms, and pubertal milestones), and these were not missing-at-random data, associated null findings should be interpreted with caution. For example, in a full sample, we would expect that earlier pubertal milestones for the same chronological age would be associated with more positive BrainAGE and, accordingly, that abuse exposure would be associated with delayed pubertal milestones. This would represent an important step in evaluating the biological validity of BrainAGE and its ability to test hypotheses regarding maturation. Finally, our sample included only female youths. While relevant given the higher prevalence of internalizing disorders in girls, studies including boys could begin to disentangle which reported effects are sex specific. Future research would be strengthened by using both structural and functional MRI data for abused youths simultaneously, supporting the functional implications of structural maturity differences. Longitudinal studies are required to confirm maturational differences associated with abuse, as well as whether preadversity gray matter volume accounts for developmental delays and whether clinical interventions can bring emotion circuit maturity back into a healthy range.

Despite these limitations, our study has many strengths. First is our use of ensemble machine learning and feature influence analyses. To our knowledge, this is the first study to interrogate multivariate circuit-specific BrainAGEs, where constraining the neural feature set to specific domains of function allows a more precise indexing of maturation. This allows for the detection of altered circuit maturation, which may normally go undetected in whole-brain analyses. These methods also allowed us to explore how abuse-related gray matter volume phenotypes contributed to changes in BrainAGE, an important step in understanding the neurodevelopmental relationships learned by the normative model. Second, our study focused on disentangling the effects of threat-related adversity compared with deprivation-related adversity on circuit maturation, which are all too often aggregated into a single "adversity" cohort. Finally, this is one of only a handful of studies using BrainAGE to interrogate important questions in development, and more specifically, related to early-life adversity and psychopathology in youths. Normative

neurodevelopment models and the BrainAGE maturity index have the potential to allow researchers to test treatment strategies targeting specific circuits and help clinicians monitor the neurodevelopmental trajectories of their patients, with the aim of helping guide them back into healthy ranges.

REFERENCES

1. Finkelhor D, Turner HA, Shattuck A, et al: Prevalence of childhood exposure to violence, crime, and abuse: results from the National Survey of Children's Exposure to Violence. JAMA Pediatr 2015; 169:746–754

2. Herrenkohl TI, Sousa C, Tajima EA, et al: Intersection of child abuse and children's exposure to domestic violence. Trauma Violence Abuse 2008; 9:84–99

3. McLaughlin KA, Koenen KC, Hill ED, et al: Trauma exposure and posttraumatic stress disorder in a national sample of adolescents. J Am Acad Child Adolesc Psychiatry 2013; 52:815–830.e14

4. Merikangas KR, Nakamura EF, Kessler RC: Epidemiology of mental disorders in children and adolescents. Dialogues Clin Neurosci 2009; 11:7–20

5. Callaghan BL, Tottenham N: The stress acceleration hypothesis: effects of early-life adversity on emotion circuits and behavior. Curr Opin Behav Sci 2016; 7:76–81

6. Gee DG, Gabard-Durnam LJ, Flannery J, et al: Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. Proc Natl Acad Sci USA 2013; 110:15638–15643

7. Ramphal B, DeSerisy M, Pagliaccio D, et al: Associations between amygdala-prefrontal functional connectivity and age depend on neighborhood socioeconomic status. Cereb Cortex Commun 2020; 1(1)tgaa033. doi: 10.1093/texcom/tgaa033

8. Miller JG, Ho TC, Humphreys KL, et al: Early life stress, frontoamygdala connectivity, and biological aging in adolescence: a longitudinal investigation. Cereb Cortex 2020; 30:4269–4280

9. McLaughlin KA, Weissman D, Bitrán D: Childhood adversity and neural development: a systematic review. Annu Rev Dev Psychol 2019; 1: 277–312

10. McLaughlin KA, Sheridan MA, Lambert HK: Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neurosci Biobehav Rev 2014; 47:578–591

11. Colich NL, Rosen ML, Williams ES, et al: Biological aging in childhood and adolescence following experiences of threat and deprivation: a systematic review and meta-analysis. Psychol Bull 2020; 146:721–764

12. Hurst JE, Kavanagh PS: Life history strategies and psychopathology: the faster the life strategies, the more symptoms of psychopathology. Evol Hum Behav 2017; 38:1–8

13. Hovens JGFM, Wiersma JE, Giltay EJ, et al: Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. Acta Psychiatr Scand 2010; 122:66–74

14. Hovens JGFM, Giltay EJ, Wiersma JE, et al: Impact of childhood life events and trauma on the course of depressive and anxiety disorders. Acta Psychiatr Scand 2012; 126:198–207

15. McCrory EJ, Gerin MI, Viding E: Annual research review: childhood maltreatment, latent vulnerability and the shift to preventative psychiatry—the contribution of functional brain imaging. J Child Psychol Psychiatry 2017; 58:338–357

16. Gogtay N, Thompson PM: Mapping gray matter development: implications for typical development and vulnerability to psychopathology. Brain Cogn 2010; 72:6–15

17. Franke K, Gaser C: Ten years of BrainAGE as a neuroimaging biomarker of brain aging: what insights have we gained? Front Neurol 2019; 10:789

18. Cole JH, Poudel RPK, Tsagkrasoulis D, et al: Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. Neuroimage 2017; 163:115–124

19. Truelove-Hill M, Erus G, Bashyam V, et al: A multidimensional neural maturation index reveals reproducible developmental patterns in children and adolescents. J Neurosci 2020; 40:1265–1275

20. Gur RE, Moore TM, Rosen AFG, et al: Burden of environmental adversity associated with psychopathology, maturation, and brain behavior parameters in youths. JAMA Psychiatry 2019; 76:966–975

21. Fan L, Li H, Zhuo J, et al: The human Brainnetome Atlas: a new brain atlas based on connectional architecture. Cereb Cortex 2016; 26:3508–3526

22. Yarkoni T, Poldrack RA, Nichols TE, et al: Large-scale automated synthesis of human functional neuroimaging data. Nat Methods 2011; 8:665–670

23. Naimi AI, Balzer LB: Stacked generalization: an introduction to super learning. Eur J Epidemiol 2018; 33:459–464

24. Beheshti I, Nugent S, Potvin O, et al: Bias-adjustment in neuroimaging-based brain age frameworks: a robust scheme. Neuroimage Clin 2019; 24:102063

25. Wilke M, Sohn J-H, Byars AW, et al: Bright spots: correlations of gray matter volume with IQ in a normal pediatric population. Neuroimage 2003; 20:202–215

26. Schiele MA, Reinhard J, Reif A, et al: Developmental aspects of fear: comparing the acquisition and generalization of conditioned fear in children and adults. Dev Psychobiol 2016; 58:471–481

27. Waters AM, Theresiana C, Neumann DL, et al: Developmental differences in aversive conditioning, extinction, and reinstatement: a study with children, adolescents, and adults. J Exp Child Psychol 2017; 159:263–278

28. McLaughlin KA, Sheridan MA, Gold AL, et al: Maltreatment exposure, brain structure, and fear conditioning in children and adolescents. Neuropsychopharmacology 2016; 41:1956–1964

29. Lange I, Goossens L, Bakker J, et al: Neurobehavioural mechanisms of threat generalization moderate the link between childhood maltreatment and psychopathology in emerging adulthood. J Psychiatry Neurosci 2019; 44:185–194

30. McLaughlin KA, Sheridan MA, Nelson CA: Neglect as a violation of species-expectant experience: neurodevelopmental consequences. Biol Psychiatry 2017; 82:462–471

31. Heyn SA, Keding TJ, Ross MC, et al: Abnormal prefrontal development in pediatric posttraumatic stress disorder: a longitudinal structural and functional magnetic resonance imaging study. Biol Psychiatry Cogn Neurosci Neuroimaging 2019; 4:171–179

32. Heyn SA, Herringa RJ: Longitudinal cortical markers of persistence and remission of pediatric PTSD. Neuroimage Clin 2019; 24:102028

33. Golkar A, Lonsdorf TB, Olsson A, et al: Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. PLoS One 2012; 7:e48107

34. Warren SL, Crocker LD, Spielberg JM, et al: Cortical organization of inhibition-related functions and modulation by psychopathology. Front Hum Neurosci 2013; 7:271

35. Lyoo IK, Kim JE, Yoon SJ, et al: The neurobiological role of the dorsolateral prefrontal cortex in recovery from trauma: longitudinal brain imaging study among survivors of the South Korean subway disaster. Arch Gen Psychiatry 2011; 68:701–713

36. Balderston NL, Hsiung A, Ernst M, et al: Effect of threat on right dlPFC activity during behavioral pattern separation. J Neurosci Off J Soc Neurosci 2017; 37:9160–9171

37. Eshel N, Keller CJ, Wu W, et al: Global connectivity and local excitability changes underlie antidepressant effects of repetitive transcranial magnetic stimulation. Neuropsychopharmacology 2020; 45:1018–1025

38. Du L, Liu H, Du W, et al: Stimulated left DLPFC-nucleus accumbens functional connectivity predicts the anti-depression and anti-anxiety effects of rTMS for depression. Transl Psychiatry 2018; 7:3

39. Keding TJ, Herringa RJ: Abnormal structure of fear circuitry in pediatric post-traumatic stress disorder. Neuropsychopharmacology 2015; 40:537–545

40. Woon FL, Sood S, Hedges DW: Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34:1181–1188

41. Woon FL, Hedges DW: Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. Hippocampus 2008; 18:729–736

42. Calem M, Bromis K, McGuire P, et al: Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. Neuroimage Clin 2017; 14:471–479

43. Kino T: Stress, glucocorticoid hormones, and hippocampal neural progenitor cells: implications to mood disorders. Front Physiol 2015; 6:230

44. Hall BS, Moda RN, Liston C: Glucocorticoid mechanisms of functional connectivity changes in stress-related neuropsychiatric disorders. Neurobiol Stress 2015; 1:174–183

45. Youssef M, Atsak P, Cardenas J, et al: Early life stress delays hippocampal development and diminishes the adult stem cell pool in mice. Sci Rep 2019; 9:4120

46. Corbetta M, Shulman GL: Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002; 3:201–215

47. Corbetta M, Patel G, Shulman GL: The reorienting system of the human brain: from environment to theory of mind. Neuron 2008; 58:306–324

48. Coste CP, Kleinschmidt A: Cingulo-opercular network activity maintains alertness. Neuroimage 2016; 128:264–272

49. Sadaghiani S, D'Esposito M: Functional characterization of the cingulo-opercular network in the maintenance of tonic alertness. Cereb Cortex 2015; 25:2763–2773

50. McTeague LM, Goodkind MS, Etkin A: Transdiagnostic impairment of cognitive control in mental illness. J Psychiatr Res 2016; 83:37–46

51. McTeague LM, Huemer J, Carreon DM, et al: Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. Am J Psychiatry 2017; 174:676–685

52. Power JD, Cohen AL, Nelson SM, et al: Functional network organization of the human brain. Neuron 2011; 72:665–678

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Examination Questions: Keding et al.

1. **The Stress Acceleration Hypothesis states that youth in adverse environments show:**
   a. Precocious pubertal onset.
   b. Precocious neurodevelopment in emotion-related circuits.
   c. Precocious reproductive success.
   d. Precocious neurodevelopment in the visual system.

2. **Feature importance results suggest that gray matter volume development in which systems best differentiate abused girls with and without internalizing psychopathology?**
   a. Inferior parietal and visual cortices.
   b. Fronto-parietal cortices and hippocampus.
   c. Ventromedial prefrontal cortex and amygdala.
   d. Cingulo-opercular cortices.

3. **Emotion circuitry maturation (BrainAGE) was delayed in which of the following groups?**
   a. Non-abused typically developing girls
   b. Abused, resilient girls with no internalizing diagnosis
   c. Abused, susceptible girls with an internalizing diagnosis
   d. Abused girls, regardless of resilience or susceptibility (b and c)