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Differential Patterns of Delayed Emotion Circuit Maturation in Abused Girls with and without Internalizing Psychopathology

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Abstract

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 multi-site sample of 246 females (ages 8-18 years) completed clinical assessment, maltreatment histories, and high-resolution T1 structural magnetic resonance imaging (MRI). Girls were stratified by abuse history and internalizing disorder diagnosis: typically-developing (no abuse/no diagnosis), resilient (abuse/no diagnosis), and susceptible (abuse/current diagnosis). 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 estimates (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 lateral prefrontal, parietal, insular cortices, and 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.

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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 hippocampus on emotion circuit maturity in resilient girls may represent neurodevelopmental markers of reduced psychiatric risk following abuse.

INTRODUCTION

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 (e.g. (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 females(4). However, the neurodevelopmental mechanisms conferring resilience and susceptibility to disorder 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 (versus 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 youth 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 youth exposed to maternal deprivation stress(6), residing in disadvantaged socioeconomic neighborhoods(7), and 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 (e.g. abuse) versus deprivation-related (e.g. neglect) adversity(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 increases risk for psychopathology in adulthood(12). Additionally, abused youth 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. amygdala, insula, 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 lateral (l)PFC, are recalibrated in response. In contrast to earlier-developing structures, lPFC 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 lPFC is a key predictor for which youth develop internalizing psychopathology after early-life adversity, though this is likely highly dependent on the timing at which the adversity occurred.

In the current study, we asked whether abused girls show advanced structural maturation in emotion-related circuits, compared to whole-brain and language-related circuitry. Language-related circuitry was used as a control circuit to evaluate emotion circuit specificity. We asked 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) versus neglect (deprivation). The focus on internalizing disorders broadly was due to high rates of comorbidity between anxiety, depression, and post-traumatic stress disorders, which if segregated, would have considerably limited samples sizes and statistical power for psychopathology-related comparisons. Finally, we asked whether particular brain regions contributed to overall circuit maturation differently in internalizing resilient versus susceptible girls. 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 estimate (BrainAGE; predicted age minus chronological age), an index of relative circuit maturation. The BrainAGE has been shown to represent a biologically-meaningful index that is reliable(17,18), heritable(18), and associated with developmental neurophenotypes underlying illness(19,20). This index is specific to an individual's brain at the time the data was collected and should not be interpreted as reflecting a developmental trajectory that 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. amygdala, insula) would contribute to more positive (advanced) BrainAGE. Finally, we hypothesized

that late-developing regions underlying attentional processes and executive control (e.g. lPFC) would best differentiate circuit maturation in resilient versus susceptible abused girls.

METHODS

Participant Recruitment and Assessment

Two hundred and forty-six adolescent females (chronological age range of 8-18 years) were pooled from research studies at three sites: Madison, Wisconsin; Little Rock, Arkansas; Seattle, Washington. 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 given in Table 1 and Supplemental Table 1. 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, can be found in Supplemental Material. Importantly, girls were segregated into three groups based on binary abuse exposure (unexposed vs. exposed) and internalizing diagnosis (presence vs. absence): *typically-developing* (unexposed, no diagnoses), *Resilient* (exposed, no diagnoses), and *Susceptible* (exposed, at least one diagnosis). It is important to note, we use the terms *resilient* and *susceptible* to refer to the *current* absence or presence of internalizing psychopathology after abuse respectively. Because many youth in this sample had yet to reach chronological age corresponding to the average age of onset for some internalizing disorders, in this context, *resiliency* does not imply that these youth may not be susceptible to disorder in the future.

Image Acquisition and Individual Preprocessing

A detailed account of image acquisition and individual preprocessing of magnetic resonance imaging (MRI) data can be found in Supplemental Material and in Supplemental Table 1. Briefly, mean voxel-wise cortical and subcortical gray matter volume was extracted from processed T1-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 Supplemental Table 2 and diagrammed in Supplemental Figure 1. Finally, each region-of-interest was scaled to total intracranial volume and harmonized across MR 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 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 Supplemental Material.

Model Evaluation—The super learner and comprising submodels were evaluated with a validation set of typically-developing girls absent during training. Importantly, 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 1000 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 correlation (r) and BrainAGEs were calculated for all abused girls. Here, a negative BrainAGE 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- 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 the BrainAGE (24), there was an age bias in the super learner; therefore, chronological age was included as a covariate. Importantly, this bias correction was only included when analyzing BrainAGE at the group-level, and therefore doesn't not change the interpretability of the BrainAGE 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 ($\alpha = 0.017$; $p < 0.05/3$). 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 versus continuous analyses, and covariates can be found in Supplemental Material.

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 versus Susceptible girls. In order to determine how influential abuse-related gray matter volume was to BrainAGE, a perturbation sensitivity approach was used (Supplemental Figure 3). Importantly, "perturbation" in this context did not refer to an anxiety phenotype, but instead referred to a change in model performance after that model had been altered in some way. The goals of perturbation sensitivity were two-fold: first, to determine if an altered distribution of BrainAGEs was significantly different than the unaltered distribution of BrainAGEs (significant feature influence), and second, to determine if 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 impact 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 - true median BrainAGE). More details regarding abuse-related gray matter volume sampling and statistical tests comparing BrainAGE distributions can be found in Supplemental Material.

RESULTS

Participant Demographics

Aggregated demographic, clinical, and maltreatment variables across study sites are found in Table 1 and are split by study site in Supplemental Table 1. The pooled cohort consisted of 246 adolescent females between the ages of 8 and 18 (mean age 14.15 ± 2.47). In total, 99 girls had no abuse exposure nor 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 girls, 38 (44.7%) had an anxiety disorder, 59 (69.4%) had a depressive disorder, and 56 (65.9%) had PTSD; 62 (72.9%) had at least 2 of these disorders.

Normative Model Performance and Bias

The super learner and its submodels performed significantly better than chance expectations (all p's << 0.001). Model performances on the validation set of typically-developing girls for each super learner and comprising submodels are reported in Supplemental Table 4. 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, over and under estimating BrainAGEs in younger and older girls respectively (Supplemental Figure 4; emotion circuitry: $t_{756} = -11.963$, $p << 0.001$)

Group-Level BrainAGE Relationships

Group Differences in BrainAGE—In the whole-brain and language circuitry analyses, no significant abuse- 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; $F_{1,150} = 15.680$, $t_{150} = -2.366$, $p = 0.014$), an average of 0.70 years younger than typically-developing girls of the same

chronological age. There was a significant effect of physical neglect severity for whole-brain BrainAGE, where physical neglect experiences were positively associated with BrainAGE across all girls (β = 0.064, $F_{1,150}$ = 7.933; t_{150} = 2.817, p = 0.006). Importantly, there were no significant nor trending scanner effects (Supplemental Figure 5).

Symptom and Puberty Relationships with BrainAGE—In the symptom analyses with emotion circuit BrainAGEs, there was a significant effect of PTSD hyperarousal symptoms (PTSD-RI subscore D). Here, across all abused girls, hyperarousal symptom severity was negatively associated with BrainAGE (Figure 2D; β = −0.091, t_{96} = −2.050, p = 0.043). This relationship was only identified when controlling for all previous group-level covariates, abuse severity, and the remaining PTSD-RI subscores (unadjusted β = −0.053, t_{98}= −1.327, p = 0.187). Finally, there were no significant relationships between BrainAGE and total PTSD (t_{98}= 1.142, p = 0.256), anxiety (t_{65}= 0.354, p = 0.724), and depression (t_{110}= 0.340, p = 0.734) symptoms, or pubertal milestones (t_{65}= 1.114, 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 can be found in Table 2, separated by spatially overlapping (all abused girls) or unique (Resilient vs. Susceptible) 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: adj. R^2 = 0.087, FDR-p < 0.001; lateral prefrontal thalamus: adj. R^2 = 0.053, FDR-p = 0.040), and left lateral pulvinar nucleus (caudal temporal thalamus: adj. R^2 = 0.049, FDR-p = 0.005) all contributed to a positive shift in BrainAGE. Additionally, gray matter volume in the right caudal anterior cingulate cortex (ACC; adj. R^2 = 0.076, FDR-p < 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 BrainAGE included the left ventral lateral thalamic nucleus (premotor thalamus: adj. R^2 = 0.092, FDR-p < 0.001), the left rostral inferior parietal lobule (BA40; adj. R^2 = 0.098, FDR-p < 0.001), right dorsal inferior parietal lobule (BA 39; adj. R^2 = 0.087, FDR-p < 0.001), and right dorsolateral prefrontal cortex (dlPFC, BA 8; adj. R^2 = 0.087, FDR-p = 0.006). Regions that contributed to a negative shift in BrainAGE included the right posterior parahippocampal gyrus (BA 27; adj. R^2 = 0.098, FDR-p < 0.034), right dorsal insular cortex (BA 13; adj. R^2 = 0.083, FDR-p = 0.050), right lateral orbitofrontal cortex (BA 12/47; adj. R^2 = 0.080, FDR-p = 0.034), and right lateral opercular prefrontal cortex (BA 44; adj. R^2 = 0.079, FDR-p < 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: adj. $R^2 = 0.093$, FDR-$p < 0.001$), medial pulvinar nucleus (rostral temporal thalamus: adj. $R^2 = 0.088$, FDR-$p < 0.001$), left dorsal insular cortex (adj. $R^2 = 0.081$, FDR-$p < 0.001$), and right opercular PFC (BA 44; adj. $R^2 = 0.051$, FDR-$p = 0.028$). Regions that contributed to a negative shift in BrainAGE included bilateral caudal hippocampus (left: adj. $R^2 = 0.088$, FDR-$p < 0.001$; right: adj. $R^2 = 0.087$, FDR-$p < 0.001$).

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 versus deprivation stress on patterns of circuit-specific and whole-brain neurodevelopment. Further, 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, 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 been previously associated with younger developmental stage (children < adolescents < adults)(26,27), and 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 kind of threat generalization, typically only observed in younger children, likely delays increases in synaptic pruning, 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 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 reported findings here, as the majority of these previous reports documented adversity more specific to deprivation (maternal separation(6), disadvantaged socioeconomic neighborhoods(7)) or a combination of threat and deprivation (abuse with physical, 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 IPL gray matter volume contributing to a positive (advanced) shift in emotion circuit maturation, supporting our original hypotheses. We have previously reported internalizing-susceptible youth show developmentally delayed gray matter volume reduction in dlPFC(31) and cortical expansion of dlPFC differentiated which youth showed remission versus persistence of PTSD symptoms at one-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 non-threat mediates the relationship between anxiety disorders and generalized fear(36). Additionally, repetitive transcranial magnetic stimulation of 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 find that bilateral hippocampus gray matter volume contributed to negative (delayed) shifts in emotion circuit maturation in Susceptible, but not Resilient, abused girls. We have previously reported age-related hippocampus gray matter abnormalities in traumatized youth with PTSD(39), one of the most commonly-reported neural correlates of early-life stress in youth 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 reduced pool of stem cells into adulthood(45). In alignment with our findings, decreased hippocampal volume appears more pronounced in maltreatment victims with PTSD and other internalizing disorders relative to 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. dlPFC) versus early (e.g. 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. Importantly, the factors determining which children will undergo resilient circuit reorganization and which will not is unknown and warrants future study.

The majority of differences in BrainAGE influential regions between Resilient and Susceptible girls were found in nodes of the cingulo-opercular network, including insular cortex, opercular PFC, and lateral orbitofrontal cortex (OFC). 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 OFC, cross-sectionally and longitudinally, has been reported in studies of abused youth(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 versus 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 is modest. The small sample size for non-abused 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, pubertal milestones), and these data were missing not-at-random, 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 the BrainAGE and its ability to test hypotheses regarding maturation. Finally, the current sample only contains female youth. While relevant given the higher prevalence of internalizing disorders in girls, future 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 youth simultaneously, supporting the functional implications of structural maturity differences. Longitudinal studies are required to confirm maturational differences associated with abuse, as well as whether pre-adversity gray matter volume accounts for developmental delays and whether clinical interventions can bring emotion circuit maturity back into a healthy range.

Despite these limitations, the current study has many strengths. First is our use of ensemble machine learning and feature influence analyses. To our knowledge, this is the first report interrogating 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- versus 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 the BrainAGE to interrogate important questions in development, and more specifically, related to early-life adversity and psychopathology in youth. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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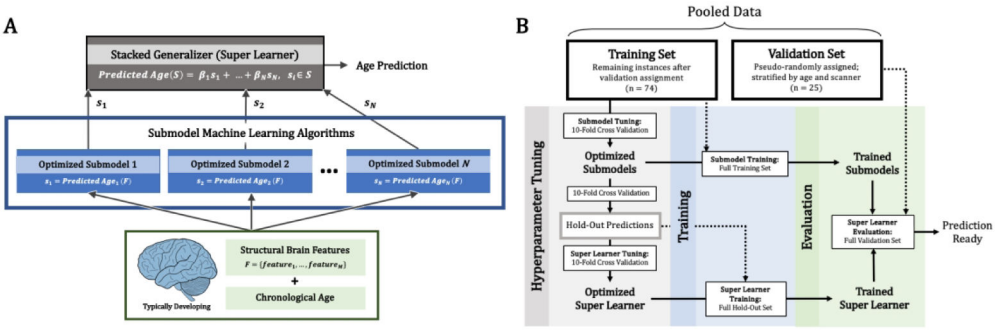

Figure 1.

The super learner algorithm and normative model building protocol. **(A)** The super learner was 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 BrainAGEs. **(B)** Schematic of the model building protocol for predicting chronological age and BrainAGE from gray matter volume features. Data were pooled and participants were pseudo-randomly assigned to the training or validation set (stratified by MR 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.

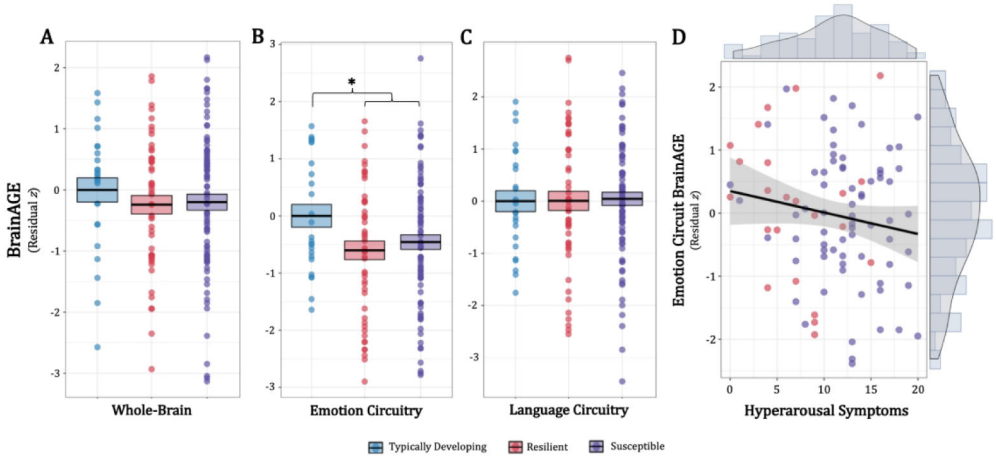

Figure 2.

Abuse- and internalizing diagnosis-related associations with BrainAGE for whole-brain, emotion circuit, and language circuit feature sets. BrainAGEs are represented as residualized *z*-scores relative to typically-developing girls, controlling for label (chronological age), MR scanner, IQ, and physical neglect. **(A)** For the whole-brain analysis, there were no significant differences in BrainAGE across groups. **(B)** For the emotion circuit analysis, an abuse main effect shows that Resilient and Susceptible girls show significantly reduced average BrainAGE relative to typically-developing girls. **(C)** For the language circuit analysis, there were no significant differences in BrainAGE across groups. **(D)** Symptom-level association with emotion circuit BrainAGEs across abused girls. Emotion circuitry BrainAGEs were negatively associated with hyperarousal symptoms (PTSD-RI subscore D). BrainAGE = brain age gap estimate; PTSD-RI = Post-Traumatic Stress Disorder Reaction Index.BrainAGE = brain age gap estimate; *$p < 0.017$ (after experiment-wide Bonferroni correction).

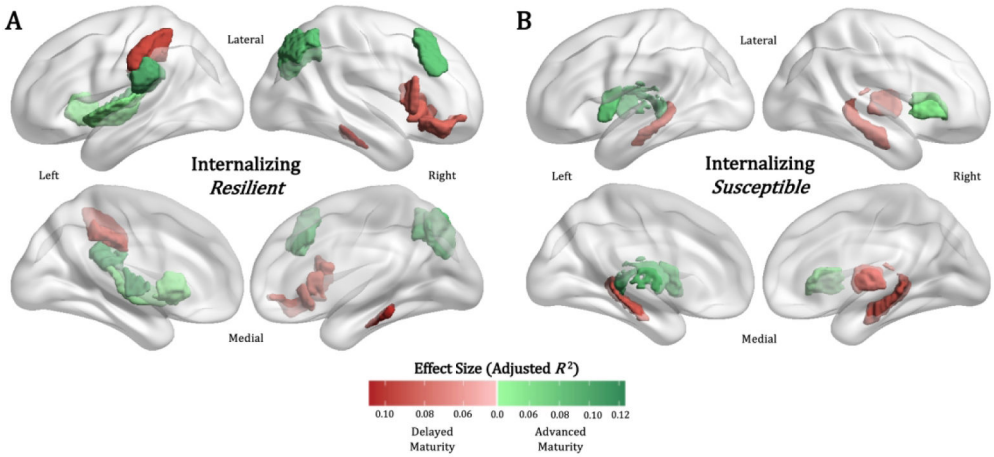

Figure 3.

Spatially unique feature influence results for **(A)** Resilient and **(B)** Susceptible girls from the perturbation sensitivity analysis. Region-of-interest color corresponds to the mean effect size (adj. R^2) of the 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. PS = noise perturbation sensitivity; BrainAGE = brain age gap estimate

Table 1.

Demographic, maltreatment, and clinical variables across the three study sites. Group comparison *F, t,* and *p* statistics are indicated with the effect direction/s for significant differences ($p < 0.05$) . Sus = Susceptible, Res = Resilient; CTQ = Childhood Trauma Questionnaire; PTSD = post-traumatic stress disorder; MFQ = Mood and Feelings Questionnaire; SCARED = Screen for Child Anxiety Related Emotional Disorders; PTSD-RI = PTSD Reaction Index; NS = non-significant * Indicates a variable that was not consistently available for all subjects (missing not-at-random). Statistics are provided for data that were available.

	Group						**Group Comparison**			
	Typically-Developing		**Resilient**		**Susceptible**		***F***	***t***	**Direction**	***p***
n	**99**		**50**		**85**		-			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**				
Age	13.78	2.64	14.15	2.25	14.55	2.32	2.59	NS	-	0.076
IQ	111.68	16.73	106.02	17.05	99.14	15.64	32.70	−3.31	Typically-Developing > Res	< 0.001
								−7.32	Res > Sus	< 0.001
Tanner Stage*	3.67	1.20	3.49	1.41	3.35	1.39	1.22	NS	-	0.296
CTQ Abuse	15.94	1.09	25.92	8.37	33.88	12.37	141.10	8.28	Typically-Developing < Res	< 0.001
								15.79	Res < Sus	< 0.001
CTQ Physical Neglect	6.76	3.08	8.76	3.57	9.69	4.44	13.82	2.74	Typically-Developing < Res	< 0.001
								5.00	Typically-Developing < Sus	< 0.001
MFQ*	-	-	4.60	4.39	17.01	10.53	171.20	12.97	Res < Sus	< 0.001
SCARED*	-	-	19.83	11.50	32. 84	16.54	36.43	67.80	Res < Sus	< 0.001
PTSD-RI*	-	-	20.58	15.42	43.53	17.62	89.72	3.07	Res < Sus	< 0.001
					Count	**Percentage**				
Anxiety Disorder	-		-		38	44.7%	-			
Depressive Disorder	-		-		59	69.4%	-			
PTSD	-		-		56	65.9%	-			

Table 2.

Perturbation sensitivity (feature influence) analysis in emotion circuitry; regions are separated by overlapping vs. unique effects between abuse groups. Within these separations, regions are sorted by descending adjusted R^2. R^2 and FDR-corrected p-values are for the abuse-perturbed BrainAGE vs. typically-developing-perturbed (chance) BrainAGE comparison. All probability values for the abuse-perturbed BrainAGE vs. true BrainAGE comparison were less than 0.001 and are absent to avoid redundancy.

Effect	Direction	Region	L/R	BA	Power *et al.* Network	Atlas Label	Adj. R^2	FDR p
Abuse Exposure	Greater BrainAGE	Medial Prefrontal Thalamus	L	-	Subcortical	Tha_8_1	0.087	< 0.001
		Caudal Anterior Cingulate Cortex	R	24	Cingulo-Opercular	CG_7_5	0.076	0.039
		Lateral Prefrontal Thalamus	R	-	Subcortical	Tha_8_8	0.053	0.040
		Caudal Temporal Thalamus	L	-	Subcortical	Tha_8_7	0.049	< 0.001
Unique to Resilient	Greater BrainAGE	Rostral Inferior Parietal Lobule	L	40	Fronto-Parietal	IPL_6_6	0.098	< 0.001
		Premotor Thalamus	L	-	Subcortical	Tha_8_2	0.092	< 0.001
		Dorsal Inferior Parietal Lobule	R	39	Fronto-Parietal	IPL_6_2	0.087	< 0.001
		Dorsolateral Prefrontal Cortex	R	8	Fronto-Parietal	MFG_7_5	0.087	0.006
		Primary Auditory Cortex	L	41	Auditory	STG_6_3	0.042	0.043
		Ventral Caudate Nucleus	L	-	Subcortical	BG_6_1	0.039	0.014
	Reduced BrainAGE	Posterior Parahippocampal Gyrus	R	27	Default-Mode	PhG_6_3	0.098	0.034
		Dorsal Inferior Parietal Lobule	L	39,40	Dorsal Attention	IPL_6_3	0.095	< 0.001
		Dorsal Agranular Insula	R	13	Cingulo-Opercular	INS_6_3	0.083	0.050
		Lateral Orbitofrontal Cortex	R	12/47	Cingulo-Opercular	OrG_6_6	0.080	0.034
		Lateral Opercular Prefrontal Cortex	R	44	Cingulo-Opercular	IFG_6_6	0.079	< 0.001
Unique to Susceptible	Greater BrainAGE	Occipital Thalamus	L	-	Subcortical	Tha_8_6	0.093	< 0.001
		Rostral Temporal Thalamus	L	-	Subcortical	Tha_8_4	0.088	< 0.001
		Dorsal Dysgranular Insula	L	13	Cingulo-Opercular	INS_6_6	0.081	< 0.001
		Opercular Prefrontal Cortex	R	44	Cingulo-Opercular	IFG_6_5	0.051	0.028
	Reduced BrainAGE	Caudal Hippocampus	L	-	Default-Mode	Hipp_2_2	0.088	< 0.001
		Caudal Hippocampus	R	-	Default-Mode	Hipp_2_2	0.087	< 0.001
		Rostral Temporal Thalamus	R	-	Subcortical	Tha_8_4	0.067	< 0.001