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Enhanced Prefrontal-Amygdala Connectivity Following Childhood Adversity as a Protective Mechanism Against Internalizing in Adolescence

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ABSTRACT

BACKGROUND: Much research has focused on the deleterious neurobiological effects of childhood adversity that may underlie internalizing disorders. Although most youth show emotional adaptation following adversity, the corresponding neural mechanisms remain poorly understood.

METHODS: In this longitudinal community study, we examined the associations among childhood family adversity, adolescent internalizing symptoms, and their interaction on regional brain activation and amygdala/hippocampus functional connectivity during emotion processing in 132 adolescents.

RESULTS: Consistent with prior work, childhood adversity predicted heightened amygdala reactivity to negative, but not positive, images in adolescence. However, amygdala reactivity was not related to internalizing symptoms. Furthermore, childhood adversity predicted increased prefrontal-amygdala connectivity to negative, but not positive, images, yet only in lower internalizing adolescents. Childhood adversity also predicted increased prefrontal-hippocampus connectivity to negative images but was not moderated by internalizing. These findings were unrelated to adolescent adversity or externalizing symptoms, suggesting specificity to childhood adversity and adolescent internalizing.

CONCLUSIONS: Together, these findings suggest that adaptation to childhood adversity is associated with augmentation of prefrontal-subcortical circuits specifically for negative emotional stimuli. Conversely, insufficient enhancement of prefrontal-amygdala connectivity, with increasing amygdala reactivity, may represent a neural signature of vulnerability for internalizing by late adolescence. These findings implicate early childhood as a critical period in determining the brain's adaptation to adversity and suggest that even normative adverse experiences can have a significant impact on neurodevelopment and functioning. These results offer potential neural mechanisms of adaptation and vulnerability that could be used in the prediction of risk for psychopathology following childhood adversity.

Keywords: Adolescence, Anxiety, Childhood adversity, Depression, Neuroimaging, Stress adaptation

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Childhood adversity, such as parental mental illness and household dysfunction, is common, affecting nearly two thirds of youth by age 18 (1). Much research has focused on childhood adversity as a risk factor for developing mood and anxiety disorders (2). However, many youth show emotional adaptation even in the face of severe childhood adversity and do not develop mental illness (3,4). The neurobiological mechanisms conferring adaptation to childhood adversity remain poorly understood. Such knowledge is vital for predicting individual outcomes following childhood adversity, determining which youth should receive early intervention, and developing biologically informed treatments for symptomatic youth.

Many neuroimaging studies have documented neural abnormalities during emotion processing in relation to childhood adversity. However, it is less clear which of these abnormalities may be adaptive versus abnormalities that directly contribute to psychopathology. For example, amygdala hyperactivation has been reported across many types of childhood adversity (e.g., poverty, caregiver deprivation, interpersonal violence, maltreatment, stressful life events) (5–16), appears to be specific to negative emotional stimuli (6,9,12,14) [however, see Suzuki *et al.* (13)], and is generally independent of symptom levels (5–13). Together, these studies suggest that amygdala hyperactivation to negative stimuli may be an adaptive response to early life adversity, perhaps allowing enhanced threat detection. In contrast, prefrontal findings during emotion processing have been more variable and include mixed findings (increased and decreased activation) in the medial prefrontal cortex (mPFC) (5,17), dorsolateral PFC (dlPFC) (5,7,9,18), and ventrolateral PFC (5–7,17) in relation to interpersonal violence/maltreatment, caregiver deprivation, and poverty. Abnormal prefrontal activation following

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early-life adversity may also be specific to negative stimuli (6,9). Furthermore, adversity-related increases in dorsal/lateral prefrontal activation may serve a compensatory role in emotion regulation (7,9,18).

Relative to brain activation studies, even less is known about emotion-related functional connectivity patterns that may confer adaptation versus vulnerability following childhood adversity. Gee *et al.* (6) found that more "mature" mPFC-amygdala connectivity to negative stimuli following caregiver deprivation may be partially adaptive, in that it was associated with some reduction in anxiety symptoms. Relatedly, work from our group has shown that trauma-exposed youth with posttraumatic stress disorder (PTSD) show reduced mPFC-amygdala connectivity to negative stimuli, which was inversely related to PTSD severity (19). An intriguing possibility is that although amygdala hyperactivity to emotional stimuli may be a typical response to childhood adversity, augmentation of coupling between the amygdala and prefrontal regulatory regions may be a crucial determinant of adaptive emotion regulatory responses. Consistent with this notion, prefrontal-amygdala connectivity is associated with emotion regulation success and lower anxiety in healthy adults (20,21).

A major limitation of prior emotion-related imaging studies of childhood adversity is that they have not incorporated measures of childhood adversity and emotional adaptation in the same individual brain model. This risks conflating adaptive and maladaptive sequelae of adversity, given that they may have opposing effects in the same circuits. In addition, prior studies have focused on severe adversity (e.g., maltreatment, caregiver deprivation), leaving it unclear whether similar neural sequelae occur with more normative types of adversity. Prior work in the present community sample of adolescents revealed decreased intrinsic mPFC-amygdala connectivity in relation to normative levels of family adversity and experiences of maltreatment, which mediated some risk for adolescent internalizing symptoms (22,23). However, it is unclear how normative experiences of childhood adversity may affect prefrontal-amygdala function and connectivity during emotion processing and which patterns may serve an adaptive role. Finally, to our knowledge, no studies have examined the effects of childhood adversity on hippocampal functional connectivity during emotion processing. The hippocampus plays an important role in the contextual gating of fear and anxiety (24), and we previously reported reduced intrinsic mPFC-hippocampus functional connectivity in relation to maltreatment experiences (23).

To address these knowledge gaps, we explored the neural substrates of adversity adaptation during emotion processing in a prospective, longitudinal community sample of adolescents. To index childhood adversity, we focused on family adversity levels during childhood (infancy to age 11), given our prior work showing that childhood, but not adolescent, adversity predicts weaker intrinsic prefrontal-amygdala and prefrontal-hippocampus connectivity (22,23). We defined emotional adaptation as the relative absence of internalizing (anxiety and depressive) symptoms (25) in adolescence (spanning ages 15–18 years). At age 18, adolescents underwent functional magnetic resonance imaging (MRI) while performing an emotion processing task in which they rated negative, positive, and neutral images (26). Group-level analyses examined the effects of childhood adversity, adolescent internalizing, and their interaction on activation and functional connectivity in prefrontal-amygdala and prefrontal-hippocampal pathways. We hypothesized that childhood adversity would be associated with increased amygdala reactivity to negative, but not positive, emotional content. However, emotional adaptation would be associated with adversity-related augmentation of prefrontal-amygdala and prefrontal-hippocampus connectivity to negative emotional content. Attenuated recruitment of these pathways following childhood adversity would be associated with greater internalizing symptoms in adolescence (i.e., childhood adversity by internalizing interaction). Within these analyses, we explored the specificity of neural findings to adolescent adversity, externalizing symptoms, and potential sex differences.

METHODS AND MATERIALS

Participants

Recruitment for the Wisconsin Study of Families and Work (originally Wisconsin Maternity Leave and Health Project) (27) began in 1990, and the study was designed to gather information on parental leave and health outcomes from a community sample in and around two cities in southern Wisconsin. While attending routine prenatal visits in clinics and hospitals, 570 women and their partners were initially recruited. Mothers had to be >18 years old, in their second trimester of pregnancy, and living with the baby's biological father. Selection for the present study was based on proximity to the laboratory and MRI exclusionary criteria. Of participants, 138 completed MRI. Six of these participants were missing data on either childhood adversity or adolescent internalizing, resulting in a final sample of 132 adolescents (69 female; mean age, 18.63 years). See Table 1 for participant and family characteristics. Our prior intrinsic functional connectivity studies (22,23) represent a subsample of the present set of adolescents. Informed consent (and parental permission in childhood) was obtained for all assessments. University of Wisconsin-Madison institutional review boards approved all procedures.

Behavioral Measures

Childhood adversity was based on a composite of maternal reports of normative types of family adversity, including maternal depression, negative parenting, parental conflict/family anger, maternal role overload, and financial stress (27). We focused on family adversity because it encompasses a broad array of common family stressors, was available prospectively, and would be less likely to introduce bias when included with adolescent internalizing in the same brain model. The adversity composite was created at each time point using principle components analysis and averaged across seven assessments spanning the child's infancy to age 11. Adolescent internalizing symptoms were assessed four times annually, from ages 15 to 18 years, with the adolescent version of the MacArthur Health and Behavior Questionnaire (25). At each time point, principal components analysis was used to create a composite score across reporters—mother, teacher (age 15 only), and adolescent. Composite scores were then averaged across time points. Internalizing comprised MacArthur Health and Behavior Questionnaire subscales measuring symptoms of generalized anxiety, social anxiety, and depression. Figure 1 is a schematic of behavioral measures and their use in the

Table 1. Participant and Family Characteristics

Characteristic	Value
No. Participants	132
Age, Years	18.63 ± 0.26 (18.15–19.48)
Female Sex	69 (52%)
Race/Ethnicity	
Caucasian	119 (90%)
Native American/Alaskan	7 (5%)
African American	5 (4%)
Asian	1 (1%)
Family Income at Child's Age 4.5 Years	$68,296 ± $40,676 ($20,000–$300,000)
Years of Parental Education at Child's Age 3.5 Years	
Mother	15.2 ± 2.0 (10–20)
Father	14.9 ± 2.2 (10–20)
Lifetime Internalizing Diagnoses	
Any diagnosis	38 (29%)
Major depressive disorder	19 (14%)
Social anxiety disorder	16 (12%)
Specific phobia	8 (6%)
Generalized anxiety disorder	3 (2%)
Panic disorder	2 (2%)
Depressive disorder NOS	1 (1%)
PTSD	1 (1%)
Lifetime Externalizing Diagnoses	
Attention-deficit/hyperactivity disorder	8 (6%)
Oppositional defiant disorder	4 (3%)

Values are presented as number (%) or mean ± SD (range).
NOS, not otherwise specified; PTSD, posttraumatic stress disorder.

functional MRI model. See Supplemental Methods for description of additional measures for adolescent adversity, externalizing, and clinical diagnoses.

Functional MRI Experimental Task

During functional MRI, participants completed an emotion processing task in an event-related design as previously described (19,26). In this task version, participants viewed 180 images from the International Affective Picture System (IAPS) (28), evenly split among negative, neutral, and positive images. The task also included presentation of neutral male faces after image offset in two thirds of trials, with the intent of examining the effect of emotional content on subsequent face processing. Each image was presented for 4 seconds, and each face was presented for 500 ms. The current analyses focused only on IAPS responses (negative-neutral, positive-neutral), although all stimuli were modeled at the individual level. Participants were instructed to rate picture valence via button press and were not explicitly instructed to regulate their emotional responses. The task consisted of five runs approximately 8 minutes each. Additional task details are in Supplemental Methods.

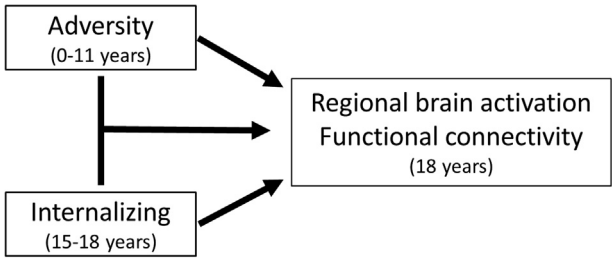

Figure 1. Summary of behavioral measures and use in analysis for functional magnetic resonance imaging. The statistical model for functional magnetic resonance imaging analysis included effects of childhood adversity (infancy to age 11 years), adolescent internalizing symptoms (ages 15–18 years), and their interaction on regional brain activation and functional connectivity of the amygdala and hippocampus during emotion processing. This model allows for testing of the effects of childhood adversity on neural patterns as moderated by internalizing status in adolescence.

Image Acquisition and Processing

Structural and functional images were collected on a 3T MRI scanner (Discovery MR750; GE Healthcare, Milwaukee, WI) with an eight-channel radiofrequency head coil array. T1-weighted structural images (1 mm^3 voxels) were acquired axially with an isotropic magnetization prepared rapid acquisition gradient-echo sequence (echo time = 3.18 ms, repetition time = 8.13 ms, inversion time = 450 ms, flip angle = 12°). Functional scans were acquired using a gradient echo planar sequence (64 × 64 in-plane resolution, 240 mm field of view, echo time = 25 ms, repetition time = 2 seconds, flip angle = 60°, 30 × 5 mm interleaved sagittal slices, 265 volumes per run).

Anatomic images were segmented and transformed to Montreal Neurological Institute space using linear (12 parameter affine) and nonlinear (DARTEL) (29) warps with SPM8 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom). For functional data, the first four volumes of each time series were removed because of T1-equilibrium effects. Functional data were concatenated across runs, slice time corrected, realigned to the last volume of each run, and coregistered with the anatomic image using Analysis of Functional NeuroImages (AFNI) (30). Images were resampled to $2 \times 2 \times 2$ mm^3 voxels and smoothed with an 8-mm Gaussian (full width at half maximum) kernel.

Individual Level Analysis

Functional data of each participant were entered into a general linear model (GLM) in AFNI (3dDeconvolve), including regressors for each stimulus condition (positive, negative, or neutral IAPS; face presentation) convolved with a sine basis function. Each trial was modeled in two epochs to examine brain activation during reactivity (2–6 seconds after image onset) and recovery (6–14 seconds after image onset) periods (26). Six motion parameters were included as nuisance regressors. Motion parameters were unrelated to childhood adversity or adolescent internalizing (all $p \geq .2$). Additionally, time points were censored if the motion of a point 87 mm from the center of rotation was >2 mm/degrees. At the run level, a run was excluded if >25% of time points were censored. This resulted in the exclusion of one run from four subjects. Finally, linear and quadratic trends were modeled to control for correlated drift. For the present study, contrasts of interest included negative-neutral and positive-neutral IAPS. Results from the first-level GLM were then transformed to Montreal Neurological Institute space with the anatomical warp parameters using SPM8.

Group Level Analysis

Individual level regression coefficients were submitted to random-effects, group-level analyses in AFNI (3dttest++). A single group test was used for negative-neutral and positive-neutral contrasts with covariates including childhood adversity, adolescent internalizing, and their interaction. All covariates were mean centered, with the interaction term generated from the mean-centered variables. A priori regions of interest included the PFC and bilateral amygdala/hippocampus using masks generated in AFNI. Multiple comparison correction was applied at the cluster level following Monte Carlo simulations in AFNI (3dClustSim). Multiple comparison correction was performed separately for the amygdala/hippocampus complex to avoid type II error given the small volume of this region (31). Additional results outside of a priori regions surviving whole-brain correction are reported in the Supplement. Using a voxelwise $p = .01$, the cluster-forming threshold for corrected $\alpha \leq .05$ was 295 voxels for PFC, 39 voxels for amygdala/hippocampus, and 471 voxels for whole brain.

Functional Connectivity Analyses

A psychophysiologic interaction analysis was conducted within AFNI to examine task-dependent connectivity with the amygdala and hippocampus using the full hemodynamic response time course. As in our previous studies (22,23), binary masks of the left and right amygdala and hippocampus were defined by placing 4-mm-radius spheres at locations of the amygdala and midhippocampus according to the Talairach Daemon (32). A GLM was carried out for each participant as described earlier, with additional regressors for each seed region time series, and the interaction of task and time series. Individual-level psychophysiologic interaction coefficients were then entered into a random-effects, group-level analysis as for the activation analysis, with multiple comparison correction as described earlier.

Secondary Analyses

Secondary analyses were conducted in IBM SPSS statistics for Windows version 21 (IBM Corp., Armonk, NY) on extracted cluster averages obtained in the voxelwise analyses. Cluster averages were examined for outliers, and any outliers were winsorized to the next nearest non-outlier value. Next, a GLM of the primary model was repeated in SPSS, which confirmed the primary imaging results (see the Supplement). Subsequent analyses examined potential sex differences and specificity of effects to adolescent adversity and externalizing symptoms.

RESULTS

Childhood Adversity and Adolescent Internalizing Characteristics

Childhood adversity was very consistent across time points (intraclass correlation = 0.88, $F_{116,348} = 8.63$, $p < .001$). For a descriptive summary of adversity experiences, see Supplemental Results. Adolescent internalizing symptoms were also very consistent across time points (intraclass correlation = 0.90, $F_{113,339} = 10.46$, $p < .001$). Nearly one third ($n = 38$) of youth had a lifetime diagnosis of any internalizing disorder (Table 1). Lifetime internalizing diagnoses increased with adolescent internalizing levels, ranging from 11% to 46% for internalizing Z scores <-0.5 and >0.5, respectively.

Childhood Adversity, Adolescent Internalizing, and Regional Brain Activation During Emotion Processing

Analysis of a priori regions for the negative-neutral image contrast revealed that right amygdala reactivity was positively correlated with childhood adversity (k = 141 voxels, peak $t = 3.07$, x y z = 20, −4, −24) (Figure 2) but showed no relationship with adolescent internalizing or an adversity by internalizing interaction. No significant effects were found in the negative-neutral contrast for PFC or hippocampal activation. In the positive-neutral contrast, no significant effects were observed with amygdala or PFC activation. However, right hippocampus reactivity was negatively correlated with internalizing (k = 36 voxels, peak $t = -3.95$, x y z = 36, −20, −18). No significant findings were observed for either contrast in the recovery period when split by face and no face trials.

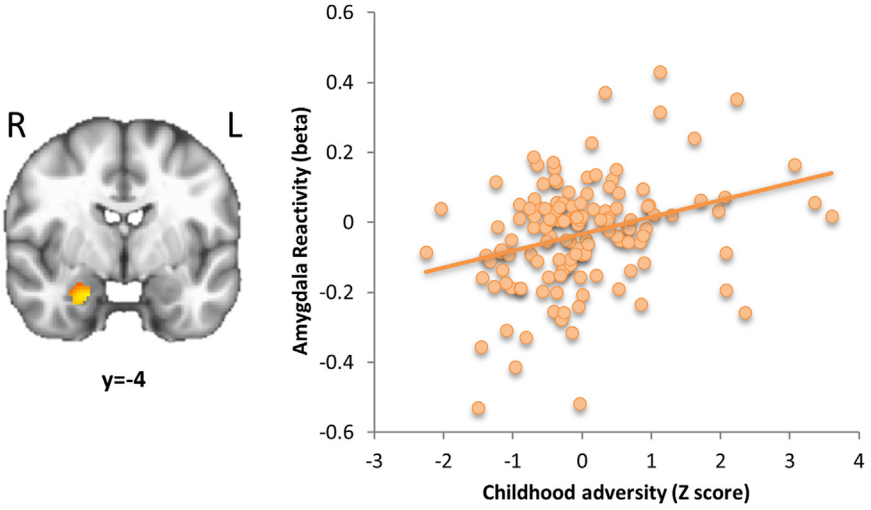

Figure 2. Childhood adversity predicts greater amygdala reactivity to negative vs. neutral images in adolescence. Reactivity was defined as activation 2–6 seconds after image onset. A scatterplot of amygdala reactivity vs. childhood adversity (*Z*-scored) is displayed on the right. $N = 132$; k = 141 voxels, $p < .05$ corrected for the amygdala/hippocampus search region. L, left; R, right.

See Supplemental Table S1 for results outside of a priori regions.

Childhood Adversity, Adolescent Internalizing, and Functional Connectivity of the Amygdala and Hippocampus During Emotion Processing

Complete results for a priori search regions are presented in Table 2. See Supplemental Table S2 for results outside of a priori regions.

Amygdala Functional Connectivity

Analysis of the negative-neutral contrast revealed that childhood adversity positively predicted functional connectivity of the right amygdala to bilateral mPFC (Brodmann areas 9, 10) (Figure 3A). Furthermore, an adversity by internalizing interaction was present in an overlapping cluster in the dorsomedial PFC (dmPFC). Childhood adversity effects on amygdala-dmPFC functional connectivity were moderated by internalizing levels, such that adversity-related increases in connectivity were attenuated in adolescents with higher internalizing (Figure 3B). To further explore this interaction, a conditional effects plot examined the effect of childhood adversity on amygdala-dmPFC connectivity across the full range of internalizing symptoms. Childhood adversity predicted significantly greater amygdala-dmPFC connectivity only in adolescents with internalizing *Z* scores <0.25, whereas no significant association between adversity and connectivity was observed at higher internalizing levels (Figure 3B). Finally, no relationships were observed among childhood adversity, adolescent internalizing, or their interaction with prefrontal-amygdala connectivity in the positive-neutral contrast.

Hippocampus Functional Connectivity

Analyses of the negative-neutral contrast revealed that childhood adversity positively predicted functional connectivity of the left and right hippocampus to bilateral dm/dlPFC (Brodmann areas 8, 9, 32) (Figure 4), but no adversity by internalizing interaction. No relationships were observed among childhood adversity, adolescent internalizing, or their interaction with prefrontal-hippocampus connectivity in the positive-neutral contrast.

Potential Sex Differences in the Effects of Childhood Adversity and Adolescent Internalizing on Brain Activation and Functional Connectivity

Given our prior work demonstrating a greater impact of childhood adversity on intrinsic prefrontal-amygdala connectivity in female adolescents compared with male adolescents (22,23), we explored possible sex differences in our primary findings. Within this sample, there was a main effect of sex for adolescent internalizing symptoms as expected (*Z*-scored averages of 0.19 and −0.21 for girls and boys, respectively [$F_{1,128} = 6.38$, $p = .01$]). Using extracted clusters from the negative-neutral contrast, we conducted a GLM including sex, interactions of sex with childhood adversity and adolescent internalizing, and their three-way interaction. We found no significant main effects of sex or interactions of sex explaining the above-mentioned findings.

Developmental Timing of Adversity Effects on Brain Activation and Functional Connectivity

Next, we asked whether the neural effects of adversity were specific to exposure in childhood versus adolescence. Using extracted clusters from the negative-neutral contrast, we repeated our original GLM (childhood adversity, adolescent internalizing, and their interaction) with the inclusion of recent adolescent adversity (past 6 months negative events) and the interaction of adolescent adversity with internalizing. In each case, the original effects of childhood adversity and childhood adversity by internalizing interactions remained, with no significant effects of adolescent adversity or adolescent adversity by internalizing. Furthermore, substituting adolescent adversity for childhood adversity entirely revealed no significant effects of adolescent adversity or adolescent adversity by internalizing interactions, suggesting specificity of neural effects to adversity in childhood.

Table 2. Summary of Results From the Psychophysiologic Interaction Analysis in A Priori Regions Using a Seed-Based Approach With the Amygdala or Hippocampus

Contrast	Seed	Effect	Cluster	BA	k	*t*	x	y	z
Negative-Neutral	L amyg	I	R amyg	—	39	−3.40	26	−6	−26
	R amyg	A	B mPFC	9, 10	699	3.29	−2	58	2
	R amyg	A × I	B dmPFC	9, 10	333	−2.92	0	52	18
	L hippo	A	B dm/dlPFC	8, 9	480	2.82	2	42	50
	R hippo	A	L dm/dlPFC	8, 9, 32	1054	2.66	0	38	58
	R hippo	A	R dm/dlPFC	8, 9	939	3.76	20	46	42
Positive-Neutral	No significant effects								

Clusters shown survived correction ($\alpha \leq .05$) within a priori search regions of the prefrontal cortex or amygdala-hippocampus complex. Peak coordinates (x, y, z) are based on the Montreal Neurological Institute atlas in left posterior inferior orientation. The statistical model included childhood adversity (A), adolescent internalizing (I), and their interaction term (A × I).

amyg, amygdala; B, bilateral; BA, Brodmann area; dm/dlPFC, dorsomedial/dorsolateral prefrontal cortex; hipp, hippocampus; L, left; mPFC, medial prefrontal cortex; R, right.

Symptom Specificity of Brain Activation and Connectivity Findings: Internalizing Versus Externalizing

Finally, we asked whether adolescent externalizing versus internalizing showed any relationship to our primary brain findings. Externalizing and internalizing symptoms were modestly correlated ($r = .40$, $p < .001$). Using clusters from the negative-neutral contrast, we repeated our original GLM with inclusion of adolescent externalizing and the interaction of childhood adversity with externalizing. In each case, the original effects of childhood adversity and childhood adversity by internalizing interactions remained, with no significant effects of externalizing or childhood adversity by externalizing.

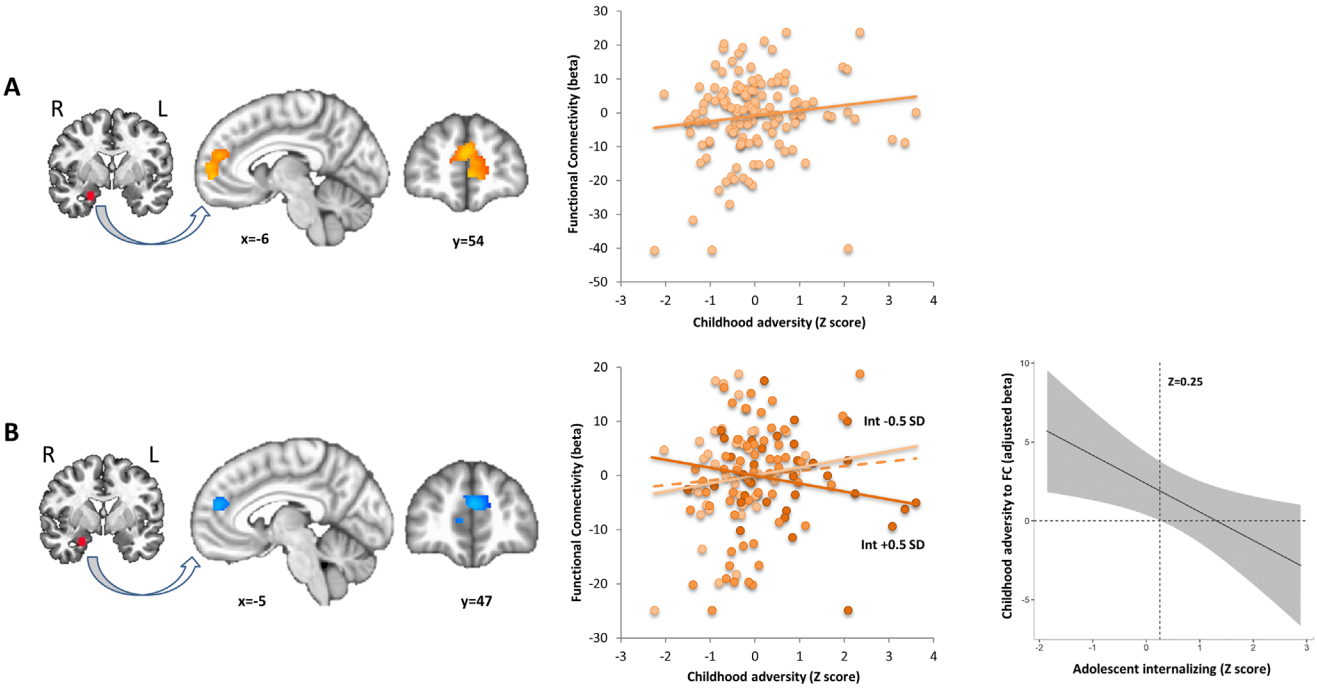

Figure 3. Childhood adversity predicts greater amygdala–medial prefrontal cortex (mPFC) functional connectivity (FC) in adolescence, but it is moderated by internalizing (Int) symptoms. Functional connectivity estimates were derived from the negative vs. neutral image contrast, using a seed-based approach. The seed region and connectivity results are shown on the left, with scatterplots of childhood adversity (*Z*-scored) vs. functional connectivity cluster averages in the middle panel. **(A)** Main effect of childhood adversity on amygdala-mPFC connectivity ($k = 699$ voxels, $p < .05$ corrected). **(B)** Childhood adversity by adolescent internalizing interaction in an overlapping cluster revealed that childhood adversity predicts greater amygdala–dorsomedial PFC connectivity in lower, but not higher, internalizing adolescents ($k = 333$ voxels, $p < .05$ corrected). The middle panel shows a scatterplot depicting the interaction, with trend lines shown for childhood adversity vs. functional connectivity at adolescent internalizing *Z* scores <-0.5 or >0.5 (i.e., ± 0.5 SD). The points and lines are color coded for internalizing levels. The dashed line represents the average effect across all participants. The right panel shows a conditional effects plot demonstrating the effect of childhood adversity on amygdala-mPFC connectivity across the full range of internalizing levels. Childhood adversity predicted significantly greater amygdala-mPFC connectivity only in adolescents with internalizing *Z* scores <0.25 (vertical dashed line). $N = 132$. L, left; R, right.

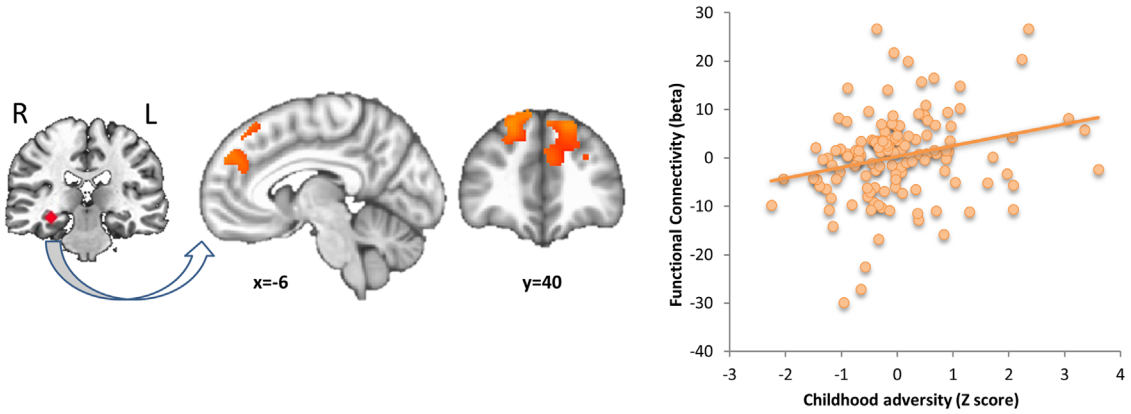

Figure 4. Childhood adversity predicts greater hippocampus–dorsomedial/dorsolateral prefrontal cortex (dm/dlPFC) functional connectivity in adolescence. Functional connectivity estimates were derived from the negative vs. neutral image contrast, using a seed-based approach. The seed region and connectivity results are shown on the left, with a scatterplot of childhood adversity (*Z*-scored) vs. functional connectivity cluster averages on the right. Shown in the scatterplot are results for hippocampus–left dm/dlPFC connectivity. A similar pattern was observed for hippocampus–right dm/dlPFC connectivity. $N = 132$; $k = 1054$ voxels (left dm/dlPFC) and 941 voxels (right dm/dlPFC), $p < .05$ corrected for PFC and whole-brain search regions. L, left; R, right.

Furthermore, substituting externalizing for internalizing entirely revealed no significant effects of externalizing or childhood adversity by externalizing interactions, suggesting specificity of reported effects to adolescent internalizing.

DISCUSSION

Our study offers novel insights on how normative experiences of childhood adversity may alter the brain's emotion circuitry by adolescence and how adaptive neural patterns may become compromised in vulnerable adolescents. Consistent with prior studies of more severe adversity, childhood adversity was associated with greater amygdala reactivity in adolescence. At the same time, childhood adversity predicted greater functional connectivity between the amygdala and hippocampus to dorsal prefrontal regions important in the regulation of fear and anxiety. However, adversity-related augmentation of prefrontal-amygdala connectivity was attenuated in adolescents with higher internalizing, despite increasing amygdala reactivity. These findings were specific to adversity during childhood, to symptoms of internalizing in adolescence, and to negative emotional content. Together, these findings suggest that even normative experiences of childhood adversity bias the amygdala toward reactivity to negative content, yet also adaptively augment prefrontal regulatory pathways, which are compromised in more vulnerable youth. These results implicate childhood as a critical developmental period in the brain's response to adversity, potentially tipping emotion regulatory circuits toward adaptation or vulnerability by late adolescence.

The present findings revealed that childhood adversity is associated with augmentation of prefrontal-amygdala coupling in adolescents with lower internalizing, suggesting a potential neural mechanism of adaptation to adversity. However, adolescents with higher internalizing also tended to have higher levels of childhood adversity. Furthermore, on one hand, maternal depressive symptoms in childhood, part of our adversity composite, could partially reflect heritable vulnerability factors transmitted to the child. On the other hand, maternal depression is, in and of itself, a significant form of childhood/family adversity (33). Thus, attenuated augmentation of prefrontal-amygdala coupling in adolescents with higher internalizing could reflect a combination of greater childhood adversity and heritable vulnerability, reflecting the complex interplay between genetic predisposition and early-life environment (3,34).

Amygdala reactivity was not itself associated with internalizing symptoms, consistent with prior studies of childhood adversity (5–13), suggesting that it may be a more general response to childhood adversity allowing improved detection of potential threat. Although amygdala hyperactivation is commonly reported in studies of internalizing disorders (35,36), our findings suggest that augmentation of dorsal prefrontal–amygdala coupling may be a crucial determinant in emotional adaptation following childhood adversity, by counteracting increased amygdala reactivity. The dorsal prefrontal–amygdala pathway is notable for its role in effortful emotion regulation (37), and connectivity between dorsal/lateral PFC and the amygdala has been associated with emotion regulation success and lower anxiety levels in healthy adults (20,21). Consistent with this regulatory hypothesis, work from our group using the current task in youth with PTSD revealed decreased amygdala-dmPFC coupling, which further related to illness severity (19). Furthermore, recent studies have demonstrated that, controlling for symptom severity, childhood maltreatment is associated with increased dorsolateral prefrontal activation in emotion tasks requiring cognitive control (9,18), which may counteract re-experiencing symptoms (18) and amygdala hyperactivity (9).

Within this framework, one possible interpretation is that vulnerable youth show impaired augmentation of dorsal prefrontal–amygdala coupling following adversity, which then leads to deficient emotion regulation and internalizing symptoms. Alternatively, the development of internalizing symptoms in adolescence may cause a "degradation" of prefrontal-amygdala coupling, in effect negating adversity augmentation of this pathway. In either case, reduced dorsal prefrontal–amygdala coupling to negative stimuli appears to

be a key neural marker of vulnerability for internalizing symptoms following childhood adversity. Future longitudinal neuroimaging studies in adolescence (before and after development of internalizing) are warranted to fully explore the developmental course of these effects.

Similar to the amygdala, we found that childhood adversity predicted enhanced coupling between the hippocampus and dm/dlPFC to negative emotional content. The hippocampus is notable for its role in providing contextual information to the PFC in gating fear and emotional responses (24). Rodent studies suggest that the hippocampus is capable of both promoting and extinguishing conditioned fear responses based on context (38). The present findings suggest that adaptive neural responses to childhood adversity involve increased coupling between the hippocampus and dm/dlPFC, which may allow for more flexible engagement of regulatory circuits based on environmental context. Consistent with this notion, enhanced mPFC-hippocampus coupling in adults exposed to trauma appears to mitigate the development of PTSD symptoms (39). Furthermore, lower gray matter volume in both hippocampus and dmPFC has been shown to mediate the relationship between childhood adversity and adult anxiety symptoms (40). Thus, impaired adversity-related augmentation of this circuit could contribute to impaired contextual modulation of fear and anxiety in adolescence, as has been observed in anxiety disorders and PTSD (24).

Although this study has numerous strengths, including the large sample size, longitudinal design, and examination of normative types of adversity, it also has some limitations. First, differences in brain function could represent a predisposing trait to experience childhood adversity. Second, temporal overlap in brain and internalizing measures precludes direct inference on brain differences contributing to internalizing, or vice versa, and this will require future studies employing longitudinal neuroimaging. Third, we do not have an independent measure of emotion regulation, such as corrugator activity (21), to directly demonstrate the benefit of augmented prefrontal-amygdala connectivity. Relatedly, psychophysiologic interaction analyses cannot determine directionality (i.e., top-down vs. bottom-up changes in connectivity). Future studies employing causal modeling approaches are warranted to explore these effects. Fourth, although our findings suggest that childhood adversity is particularly important in the neural differences reported here, we cannot exclude the possibility that different types of adversity captured by our childhood and adolescent measures account for apparent specificity to childhood. Additionally, it is possible that other forms of adversity outside the home, such as exposure to violence or bullying, may influence the brain's adaptive capacity. Finally, our definition of emotional adaptation was restricted to the relative absence of adolescent internalizing/externalizing symptoms and does not necessarily generalize to other indicators, such as well-being, which would merit exploration in future studies.

In conclusion, the current data suggest neural signatures of adaptation to childhood adversity involving augmentation of prefrontal-amygdala and prefrontal-hippocampus pathways important in the regulation of fear and anxiety. Furthermore, adversity-related augmentation of prefrontal-amygdala connectivity was attenuated in adolescents with higher internalizing, suggesting that either vulnerable youth fail to benefit from this adaptation or it becomes degraded with the development of internalizing. Finally, our results suggest that childhood, but not late adolescence, is a particularly important developmental period in determining neural adaptation to adversity. These findings have great relevance for understanding the development of adversity-related psychopathology, such as depression, anxiety disorders, and PTSD, most of which emerge by late adolescence (41). These findings offer neural markers of vulnerability that could be used in the prediction of risk for psychopathology following childhood adversity, in the institution of timely interventions in at-risk youth, and as treatment targets in adolescents with internalizing disorders and PTSD.

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REFERENCES

1. Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield C, Perry BD, *et al*. (2006): The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci 256: 174–186.
2. Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC (2010): Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. Arch Gen Psychiatry 67:113–123.
3. Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, de Kloet ER (2013): The three-hit concept of vulnerability and resilience: Toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrinology 38:1858–1873.

4. DuMont KA, Widom CS, Czaja SJ (2007): Predictors of resilience in abused and neglected children grown-up: The role of individual and neighborhood characteristics. Child Abuse Negl 31:255–274.
5. Garrett AS, Carrion V, Kletter H, Karchemskiy A, Weems CF, Reiss A (2012): Brain activation to facial expressions in youth with PTSD symptoms. Depress Anxiety 29:449–459.
6. Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, *et al*. (2013): Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. Proc Natl Acad Sci U S A 110:15638–15643.
7. Kim P, Evans GW, Angstadt M, Ho SS, Sripada CS, Swain JE, *et al*. (2013): Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. Proc Natl Acad Sci U S A 110: 18442–18447.
8. McCrory EJ, De Brito SA, Sebastian CL, Mechelli A, Bird G, Kelly PA, Viding E (2011): Heightened neural reactivity to threat in child victims of family violence. Curr Biol 21:R947–948.
9. McLaughlin KA, Peverill M, Gold AL, Alves S, Sheridan MA (2015): Child maltreatment and neural systems underlying emotion regulation. J Am Acad Child Adolesc Psychiatry. 54:753–762.
10. Swartz JR, Williamson DE, Hariri AR (2015): Developmental change in amygdala reactivity during adolescence: effects of family history of depression and stressful life events. Am J Psychiatry 172:276–283.
11. Dannlowski U, Stuhrmann A, Beutelmann V, Zwanzger P, Lenzen T, Grotegerd D, *et al*. (2012): Limbic scars: Long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. Biol Psychiatry 71:286–293.
12. Dannlowski U, Kugel H, Huber F, Stuhrmann A, Redlich R, Grotegerd D, *et al*. (2013): Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. Hum Brain Mapp 34:2899–2909.
13. Suzuki H, Luby JL, Botteron KN, Dietrich R, McAvoy MP, Barch DM (2014): Early life stress and trauma and enhanced limbic activation to emotionally valenced faces in depressed and healthy children. J Am Acad Child Adolesc Psychiatry 53; 800–813.e10.
14. Maheu FS, Dozier M, Guyer AE, Mandell D, Peloso E, Poeth K, *et al*. (2010): A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. Cogn Affect Behav Neurosci 10:34–49.
15. Malter Cohen M, Jing D, Yang RR, Tottenham N, Lee FS, Casey BJ (2013): Early-life stress has persistent effects on amygdala function and development in mice and humans. Proc Natl Acad Sci U S A 110:18274–18278.
16. Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, Casey BJ (2011): Elevated amygdala response to faces following early deprivation. Dev Sci 14:190–204.
17. Crozier JC, Wang L, Huettel SA, De Bellis MD (2014): Neural correlates of cognitive and affective processing in maltreated youth with posttraumatic stress symptoms: does gender matter? Dev Psychopathol 26:491–513.
18. Fonzo GA, Huemer J, Etkin A (2016): History of childhood maltreatment augments dorsolateral prefrontal processing of emotional valence in PTSD. J Psychiatr Res 74:45–54.
19. Wolf RC, Herringa RJ (2016): Prefrontal-amygdala dysregulation to threat in pediatric posttraumatic stress disorder. Neuropsychopharmacology 41:822–831.
20. Kim MJ, Gee DG, Loucks RA, Davis FC, Whalen PJ (2011): Anxiety dissociates dorsal and ventral medial prefrontal cortex functional connectivity with the amygdala at rest. Cereb Cortex 21:1667–1673.
21. Lee H, Heller AS, van Reekum CM, Nelson B, Davidson RJ (2012): Amygdala-prefrontal coupling underlies individual differences in emotion regulation. Neuroimage 62:1575–1581.
22. Burghy CA, Stodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler JA, *et al*. (2012): Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. Nat Neurosci 15:1736–1741.
23. Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, Essex MJ (2013): Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. Proc Natl Acad Sci U S A 110:19119–19124.
24. Maren S, Phan KL, Liberzon I (2013): The contextual brain: Implications for fear conditioning, extinction and psychopathology. Nat Rev Neurosci 14:417–428.
25. Essex MJ, Boyce WT, Goldstein LH, Armstrong JM, Kraemer HC, Kupfer DJ (2002): The confluence of mental, physical, social, and academic difficulties in middle childhood. II: Developing the MacArthur Health and Behavior Questionnaire. J Am Acad Child Adolesc Psychiatry 41:588–603.
26. Schuyler BS, Kral TRA, Jacquart J, Burghy CA, Weng HY, Perlman DM, *et al*. (2014): Temporal dynamics of emotional responding: Amygdala recovery predicts emotional traits. Soc Cogn Affect Neurosci 9:176–181.
27. Essex MJ, Klein MH, Cho E, Kalin NH (2002): Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behavior. Biol Psychiatry 52:776–784.
28. Lang PJ, Bradley MM, Cuthbert BN (2008): International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Technical Report A-8. Gainesville, FL: University of Florida.
29. Ashburner J (2007): A fast diffeomorphic image registration algorithm. Neuroimage 38:95–113.
30. Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173.
31. Britton JC, Grillon C, Lissek S, Norcross MA, Szuhany KL, Chen G, *et al*. (2013): Response to learned threat: An FMRI study in adolescent and adult anxiety. Am J Psychiatry 170:1195–1204.
32. Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, *et al*. (2000): Automated Talairach Atlas labels for functional brain mapping. Hum Brain Mapp 10:120–131.
33. Essex MJ, Kraemer HC, Armstrong JM, Boyce WT, Goldsmith HH, Klein MH, *et al*. (2006): Exploring risk factors for the emergence of children's mental health problems. Arch Gen Psychiatry 63:1246–1256.
34. Rutter M (2012): Resilience as a dynamic concept. Dev Psychopathol 24:335–344.
35. Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH (2012): Functional neuroimaging of major depressive disorder: A meta-analysis and new integration of base line activation and neural response data. Am J Psychiatry 169:693–703.
36. Etkin A, Wager TD (2007): Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 164: 1476–1488.
37. Ochsner KN, Silvers JA, Buhle JT (2012): Functional imaging studies of emotion regulation: A synthetic review and evolving model of the cognitive control of emotion. Ann N Y Acad Sci 1251:E1–24.
38. Milad MR, Quirk GJ (2012): Fear extinction as a model for translational neuroscience: Ten years of progress. Annu Rev Psychol 63: 129–151.
39. Admon R, Lubin G, Stern O, Rosenberg K, Sela L, Ben-Ami H, Hendler T (2009): Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. Proc Natl Acad Sci U S A 106:14120–14125.
40. Gorka AX, Hanson JL, Radtke SR, Hariri AR (2014): Reduced hippocampal and medial prefrontal gray matter mediate the association between reported childhood maltreatment and trait anxiety in adulthood and predict sensitivity to future life stress. Biol Mood Anxiety Disord 4:12.
41. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:593–602.