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Adverse Childhood Experiences and Amygdalar Reduction: High-Resolution Segmentation Reveals Associations with Subnuclei and Psychiatric Outcomes

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Abstract

The aim of the present study was two-fold: 1) to utilize improved amygdala segmentation and exploratory factor analysis to characterize the latent volumetric structure among amygdala nuclei, and 2) to assess the effect of adverse childhood experiences (ACEs) on amygdalar morphometry and current psychiatric symptoms. To investigate these aims, structural (T1) MRI and self-report data were obtained from 119 emerging adults. Regression analysis showed that higher ACE scores were related to reduced volume of the right, but not the left, amygdalar segments. Further, exploratory factor analysis yielded a two-factor structure, basolateral and central-medial nuclei of the right amygdala. Path analyses revealed that higher ACE scores were significantly related to a reduced volume of the right basolateral and central-medial segments. Furthermore, reduction in the right basolateral amygdala was associated with increased anxiety, depressive symptoms, and alcohol use. This association supports an indirect effect between early adversity and psychiatric problems via reduced right basolateral amygdalar volume. The high-resolution segmentation results reveal a latent structure among amygdalar nuclei that is consistent with prior work conducted in non-human mammals. These findings extend previous reports linking early adversity, right amygdala volume, and psychopathology.

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Disclosure

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Keywords

Adverse Childhood Experiences; Child Maltreatment; Amygdala; Basolateral Nucleus; Central-Medial Nucleus; Anxiety; Depression; Alcohol

Introduction

Extant empirical evidence suggests that adverse childhood experiences (ACEs) impact neurobiological development, mediating the risk for affective and substance use problems (Anda et al., 2006; Shonkoff et al., 2012). According to the developmental psychopathology perspective, ACEs (e.g., childhood maltreatment) can negatively influence the development of the growing child across biological and socioemotional systems (Cicchetti, 2016; McEwen & Gianaros, 2010; Teicher & Samson, 2013). Exposure to ACEs involves chronic stress, often in the absence of a supportive and nurturing caregiver, which in turn can lead to the disruptions in brain development that are associated with prospective psychopathology (Cicchetti, 2016). As such, continued developmental neuroscience research is needed to better understand and treat psychopathology stemming, in part, from these ACEs.

Substantial focus has been placed on the effect of ACEs on morphometry of the amygdala and attendant psychopathology. Specifically, numerous investigations indicate that exposure to ACEs can negatively impact the structure and functioning of the amygdala, a subcortical structure that functions as a neural hub for fear and emotional processing as well as socioemotional development (De Bellis & Zisk, 2014; Hackman, Farah, & Meaney, 2010). These volumetric changes are hypothesized to mediate the effect of early life experiences on the development of emotional psychopathology and reward system-related addictive behaviors, such as alcohol use problems (Sinha, 2008). A recent meta-analysis of common psychiatric disorders found consistent gray matter loss in a number of brain regions, including the amygdala (Goodkind et al., 2015). This body of research suggests that amygdalar deficits (Hasler, Drevets, Manji, & Charney, 2004; Milham et al., 2005) may serve as a transdiagnostic risk mechanism for affective symptomatology. Concurrently, multiple theoretical models of psychopathology purport that that stress-driven neural (mal)adaptations, such as amygdalar structure change, may be associated with behavioral outcomes such as diminished regulation and reward processing (Haas & Canli, 2008; Harrison & Critchley, 2007). These changes can subsequently give rise to a cascade of neurobiological risks that underlie the emergence of affective psychopathology (e.g., anxiety and depression; Gatt et al., 2009; Hanson et al., 2015) and heavy drinking as a coping mechanism for negative affect (Koob & Kreek, 2007).

Although diverse lines of inquiry have linked early adversity to the amygdala, there is ambiguity about the specific effect of ACEs on amygdalar volume (Calem, Bromis, McGuire, Morgan, & Kempton, 2017). Some studies suggest that ACEs are linked with increased amygdala volume (Mehta et al., 2009), while others show ACEs to be linked with reduced amygdala volume (Gatt et al., 2009; Hanson et al., 2015; Morey et al., 2012). This inconsistency may be, in part, because the amygdala is a structurally and functionally heterogeneous collection of nuclei lying in the anterior medial portion of each temporal lobe

(Rooszendaal, McEwen, & Chattarji, 2009). For example, the amygdala's lateral and basal nuclei process the value of rewarding stimuli, chiefly via its connections with orbitofrontal regions (Baxter & Murray, 2002). In addition, the central nucleus is regarded as a mediator of behavioral and emotional output to threatening stimuli via its connectivity with the hypothalamus, basal forebrain, and brainstem (Kalin, Shelton, & Davidson, 2004; Phillips & LeDoux, 1992).

Some of the inconsistency in findings may also be attributable to laterality associations with volume and function (Sergeie, Chochol, & Armony, 2008; Williams et al., 2006). For example, subjects with PTSD showed differential amygdalar responses across hemispheric laterality to an induced fear task: as compared to control subjects, the right amygdala showed suppression in the early stages of a fear task, while the left amygdala showed increased activation in the later stages of the task (Williams et al., 2006). Additionally, a meta-analysis found hemispheric differences in activation to emotional stimuli in block design studies (Sergeie, Chochol, & Armony, 2008). However, another meta-analysis has suggested that lateralized differences in amygdalar volume and function are inconclusive and need more thorough empirical investigation (Fusar-Poli et al., 2009). Thus, the importance of laterality remains unclear at this time, and further empirical investigation is needed.

The present study seeks to address these inconsistencies in several ways. Given the amygdala's complex structure and function, we hypothesized that differences in reports about the effect of ACEs on the amygdala may partially stem from limitations of prior methods in morphometric estimation (Saygin et al., 2017) and the lack of attention to amygdalar laterality, as well its subnuclei, which are reported to have specialized behavioral manifestations (Baas, Aleman, & Kahn, 2004). By using a novel Bayesian-based algorithm (in Freesurfer version 6.0), the present study analyzed individual volumetric data of the left and right amygdala nuclei to more accurately delineate the neural architecture affected by ACEs. Specifically, this study applied exploratory factor analysis to volumetric measurements to derive distinct latent factors of nuclei of both the left and right sections of the amygdala. Second, given the known covariance concerns in modeling linkages between brain regions and reported behaviors (Horwitz, Tagamets, & McIntosh, 1999), structural equation modeling (SEM) was employed to model the relationship of amygdala morphology with ACEs and several indices of psychological well-being. SEM can be particularly advantageous in neuroscience research by delineating superordinate structures through interregional covariances among more focal brain regions. Specifically, SEM allowed the current study to delineate nuclear volume, while accounting for their inherent covariance, by incorporating several sub regions into oblique factors (Lahey et al., 2012). These methodological innovations may clarify the apparently inconsistent findings regarding the effect of ACE on amygdalar volume. Third, the current study used a widely used adverse childhood experiences measure, while controlling for other types of adversity often confounded with ACEs, such as poverty. This adjustment strategy allows an evaluation of the link between ACEs and volumetric changes in the amygdala independently of SES. Lastly, behavioral and psychological measures were used to extend the ACE-amygdala findings, thereby enabling cross-validation between the identified structural morphology affected by ACEs and attendant risk for affective and alcohol use outcomes. The current

study focused on affective and alcohol-related problems because ACE has been consistently linked to emotional symptomatology, including anxiety and depression (Gatt et al., 2009; Mersky, Topitzes, & Reynolds, 2013), as well as to reward circuits linked to drinking problems (Koob & Kreek, 2007).

Three main hypotheses were generated in the current study. With regard to the link between ACEs and amygdalar volume, the literature is inconsistent. Yet, the preponderance of studies suggests that a reduction in amygdalar volume is to be expected. Thus, we hypothesized that ACEs would be associated with reduced amygdalar volume. Second, based on previous research, reduction in amygdalar volume was expected to be associated with increased levels of psychopathological symptomatology (Gatt et al., 2009; Pardini, Raine, Erickson, & Loeber, 2014; Weniger, Lange, Sachsse, & Irle, 2009). Lastly, we hypothesized that there would be significant indirect effects from severity of ACES to alcohol use, depressive symptoms, and anxiety symptoms, via reduced amygdalar volume.

Methods

Participants

A sample of 119 right-handed African Americans (mean age at last time point was 24.62 years, $SD = .67$; 62 women) from rural Georgia was randomly selected from a larger longitudinal parent study of a randomized prevention trial on rural African-American families ($N = 408$) (described below). Data collection for the present study was conducted at the same time as the last time point of the parent study. Of the 119 participants scanned, 3 were excluded for excessive movement during MRI, resulting in unreliable data. Specifically, volumes that exhibited more than 0.3 mm movement in any direction were excluded from the analyses and the participant was excluded if more than 25% of volumes exhibited excessive movement. Therefore, the current final analyses included 116 participants (60 females). Subjects provided written informed consent after receiving a complete description of the study.

Parent study.

The current study utilizes data obtained from 119 participants from a parent study of 408 youth, who were randomly selected to take part in a neuroimaging sub-study. Participants in the longitudinal parent study and their primary caregivers provided data at four assessments beginning at 11 years of age (see Brody et al., 2017 for more details). The original sample of the parent study can be characterized as low income; 46.3% of the youth's families lived below federal poverty standards, despite primary caregivers' working an average of 39.4 hours per week. The MRI scanning session occurred at wave 4 (mean age 24.62 years old).

Measures

Adverse Childhood Experiences (ACE).—Participants' scores on the ACE measure were assessed through 10 items (Felitti et al., 1998) at T4 of the parent study. An example item includes: *“Did a parent or other adult in the household often or very often swear at you, insult you, put you down, or humiliate you; or act in a way that made you afraid that you might be physically hurt.”* Responses included “yes”(coded as 1) and “no”(coded as 0). A

sum score was calculated to create the ACE index. See Supplemental Materials Table S2 for descriptive statistics of all items included in the ACE index.

Affective problems.—Participants' anxiety and depression symptom severity over the past two weeks was assessed using the General Anxiety Disorder –7 and Patient Health Questionnaire-9 (Spitzer, Kroenke, Williams, & Group, 1999; Spitzer, Williams, Kroenke, Hornyak, & McMurray, 2000) at the same time as the neuroimaging assessment. Anxiety severity, as measured by seven items with responses ranging from “0” (not at all) to “2” (more than half the days), exhibited good internal consistency ($\alpha = .80$). Depression severity was measured by nine items with responses ranging from “0” (not at all) to “3” (nearly every day) and also exhibited good internal consistency ($\alpha = .88$).

Alcohol use problems.—Participants' alcohol use problems were assessed using ten items on the Alcohol Use Disorder Identification Test (AUDIT; Babor, Higgins-Biddle, Saunders, Monteiro, & Organization, 2001) at the same time as the neuroimaging assessment. The AUDIT was developed by the World Health Organization for screening for hazardous alcohol use; the internal consistency of this scale was good ($\alpha = .81$).

Covariates.—Sex was coded as 0 = male and 1 = female. In order to make a distinction between SES risk and experiences of adverse and traumatic experiences, SES was controlled for in the analysis. A cumulative SES risk index, derived at T3 of the parent study, was created based on a composite of six parent-reported items: poverty status, parental education, perceived adequacy of income, parent employment, and government assistance. Intervention status was coded as 1 for participants involved in the intervention trial ($n = 59$) and 0 for participants in the control trial ($n = 57$).

Experimental Design and Statistical Analysis

MRI acquisition.—Imaging data were collected at the University of Georgia's Bio-Imaging Research Center using a GE Signa HDx 3-Tesla scanner. Participants were instructed to lie still with their eyes closed for five minutes during the structural scan. Structural imaging consisted of a high-resolution T1-weighted, fast-spoiled gradient echo scan (repetition time = 7.8 ms, echo time = 3.1 ms, flip angle = 20°; field of view = 25.6 cm, matrix = 256 × 256, 160 contiguous 1 mm axial slices, voxel size = 1 mm³). While not analyzed in this particular study, the scanning protocol also included functional MRI paradigms. The full scanning protocol was approximately 50 minutes in duration.

Image analysis.—The standard FreeSurfer pipeline (Fischl et al., 2004) was utilized to process the MRI data and to derive intracranial volume (ICV) for use in this study. Amygdalar subfield segmentation was derived using the new automated algorithm available in FreeSurfer 6.0 (Saygin et al., 2017). This method utilizes a refined probabilistic atlas constructed by three independent neuroanatomists from 10 *ex vivo* brains and 39 *in vivo* brains using both manual and automated methods. Using Bayesian inference, the atlas is used to automatically segment the amygdala into 9 bilateral nuclei (i.e., 18 total segments). This procedure has been validated on datasets of 374 individuals with and without Alzheimer's disease and 262 individuals with and without Autism Spectrum Disorder,

demonstrating greater accuracy in identifying individuals from these special populations than had prior versions of FreeSurfer.

Statistical analysis.—Hypotheses were tested using the statistical software Mplus 7.4 (Muthén & Muthén, 2010) with maximum likelihood estimator. Missing data were estimated using the full-information maximum likelihood as the data met missing-at-random assumptions (Little & Rubin, 2002). Based on recommended statistical fit criteria (Hu & Bentler, 1999), the chi-square test of model fit, the comparative fit index (CFI), and the standardized root mean square residual (SRMR) were utilized to assess model fit. First, two path analysis models were run to test the effect of ACEs, reflected by the total score of the ACE measure, on the volume of left and right amygdala segments, separately. Then, exploratory factor analysis (EFA) was used to construct the factor structure of amygdala segments based on the nine subregions in each lateral portion. The criteria to determine the number of factors in EFA were relative (i.e., the most optimal among the resultant solution) based on the oblique rotation, Eigenvalue > 1, and assessment of a parallel process scree plot (Figure S1 in the supplemental materials). Then, the factor structures obtained from EFA were confirmed by the confirmatory factor analyses (CFA). Next, a structural equation model was used to examine the associations among ACE, amygdala segment factors, affective problems including anxiety and depression, and alcohol use problems. ICV, intervention status, gender, and SES risk were controlled. Indirect effects were tested using RMediation techniques, which produce a confidence interval for the product of two normal random variables using three methods: the distribution of the product of coefficients, Monte Carlo, and asymptotic normal theory with the multivariate-delta standard error (asymptotic-delta) method (Tofighi & MacKinnon, 2011). All statistical tests conducted were two-tailed.

Results

ACEs Associations with Bilateral Amygdalar Subregions

Supplemental Table S1 presents the descriptive statistics, bivariate correlations of study variables, and partial correlations among ACEs, right and left amygdala volumes, and psychopathology, controlling for ICV, intervention status, gender, and SES risk. Zero-order and partial correlations were in expected directions. The hypotheses were tested in path analyses models in which the volumetric measurement each of the 9 amygdalar sub-regions previously reported (Solano-Castiella et al., 2010) were regressed on ACEs. Models were run separately for the left and the right amygdala. Results indicated a significant association of ACEs on the volume of 6 of 9 regions of the right amygdala, but no significant effects on the volume of regions of the left amygdala (Figure 1.) Thus, left amygdaloid regions were not included in subsequent models. Given the significant covariation of these subregions in the right amygdala, we then ran an exploratory factor analysis to identify factors that could commonly account for covariation of these right amygdalar regions.

EFA and CFA were conducted to assess the dimensionality and factor structure of right amygdala segments. Geomin rotation was used for the EFA. Results of EFA of right amygdala supported two-factor solutions. The EFA showed adequate model fit indices ($\chi^2(19) = 103.92$ ($p < .001$), CFI = .94, SRMR = .03). Substantive evaluation of the items

suggested that in the right amygdala factor structure models, the first factor represented basolateral amygdala segments and the second one represented central-medial amygdala segments. As expected, CFA further substantiated the two-factor structures of the right amygdala (Figure 2), yielding good model fit indices ($\chi^2(20) = 90.96$ ($p < .001$), CFI = .95, SRMR = .07) and large loading coefficients ($\lambda > .65$; Brown, 2015).

Relationships to Affective and Alcohol Outcomes

SEM was used to test the associations among ACE, right amygdala segment factors, affective problems including anxiety and depression, and alcohol use problems. ICV, intervention status, gender, and SES risk were controlled. Table 1 and Figure 3 present this SEM model. Overall, the SEM model exhibited good fit indices: $\chi^2(79) = 119.34$ ($p = .002$), CFI = .97, SRMR = .04. ACE was found to be associated with smaller basolateral ($\beta = -.190$, $p = .026$) and central-medial ($\beta = -.144$, $p = .049$) right amygdala factors. Further, a smaller right basolateral factor was associated with more severe anxiety ($\beta = -.255$, $p = .026$), depression ($\beta = -.227$, $p = .026$), and alcohol use ($\beta = -.321$, $p = .026$) problems. However, a smaller right central-medial factor was not significantly associated with anxiety ($\beta = .042$, $p = .531$), depression ($\beta = .102$, $p = .104$), or AUDIT scores ($\beta = .016$, $p = .817$). Per Figure 3, RMediation analyses suggested a significant indirect effect from ACE on anxiety ($\alpha*\beta = .049$, 95% CI [.01, .21]), depression ($\alpha*\beta = .043$, 95% CI [.002, .194]), and alcohol use ($\alpha*\beta = .061$, 95% CI [.02, 1.14]) problems through basolateral right amygdala segment factor.

Discussion

The present study utilized high-resolution characterization of amygdalar subnuclei to better understand the impact of ACEs in an at-risk sample of young adults. Specifically, we mapped the relationships among the subnuclei to adverse childhood events, and, in turn, whether the associations between adversity and amygdalar subnuclei morphology mediated the link between childhood adversity and adult psychopathology. Because the findings from the present study are based on SEM, examination of variance-covariance matrixes permitted constructing latent factors that represent concurrent covariations of the nine nuclei in the segmentation (Saygin et al., 2017). Specifically, EFA and CFA supported previous studies' morphometric classification of the nine amygdalar nuclei into two bilateral main subregions: the central-medial and basolateral (Solano-Castiella et al., 2010). The main findings suggest that ACE severity is significantly associated with reduced right amygdalar volume in both of these subregions. Lastly, the findings suggest that reduction in volume of the basolateral subregions in the right amygdala is associated with increased symptoms of anxiety and depression, and alcohol use.

This is the first study in humans to examine the effect of ACEs on amygdalar subnuclei based on the improved segmentation strategy. As such, it contributes to the literature to date showing mixed and inconclusive reports on the effect of ACEs on amygdalar volume. In the present study, the latest version of Freesurfer was used to segment high resolution T1-weighted images of the amygdala, a method that adds automation and within-subject segmentation (rather than normalization to a template). The results are consistent with other

methods (fiber orientations within the amygdala) that were used to classify the amygdalar structure into two subregions, centromedial and basolateral (Solano-Castiella et al., 2010). Similarly, the separation of nuclei into two factors, the basolateral and central-medial, was consistent bilaterally and fits well into prior research identifying unique function and neural connections among these two divisions. The resulting morphological typology in the present study is also corroborated by its unique associations with psychopathology. These findings are supported by the body of research linking reduced amygdalar volume to general risk for psychopathology (Goodkind et al., 2015; Pardini et al., 2014) and the basolateral subregions with a risk for anxiety (Etkin et al., 2004; Qin et al., 2014).

In the present study, the association between ACEs and amygdaloid volume reduction is consistent with theory and research on the effect of stress associated with ACEs on the brain. Based on the allostatic load model and growing neuroscience research, early life stress is processed by the brain and ushers in alldynamic adaptation that includes neurobiological changes, including in the amygdala. Specifically, animal studies on the effect of early stress exposure on the amygdala and hippocampus evidences remodeling of brain circuitry, including reduction and shortening of dendrites, apoptosis, and degeneration of spine synapses, as well as neurogenesis suppression up to young adulthood (Eiland, Ramroop, Hill, Manley, & McEwen, 2012; Howell et al., 2014). Similarly, growing neuroimaging research in humans suggests that the amygdala is involved in mediating forms of peripheral or alldynamic stress reactivity that have been linked to psychopathological outcomes (McEwen, Nasca, & Gray, 2016). For example, in a recent study of institutionalized orphaned youth, early deprivation was linked to volumetric changes in the left amygdala (Mehta et al., 2009). After correcting for difference in brain volume, the institutionalized group had greater amygdala volumes, especially on the right, but no differences were observed in hippocampal volume or mid-sagittal corpus callosum (Mehta et al., 2009).

The reports of shrunken amygdalae as a result of ACEs are in contrast to studies that documented larger amygdalae among children exposed to maltreatment-like experiences (Lupien et al., 2011), as well as those who showed no differences (Woon & Hedges, 2008). These reported differences may have stemmed from methodological (e.g., loose measure of ACEs, sample size) and demographic variability. For example, some studies showing a link between ACEs and amygdalar volume had examined youth who experienced deprived rearing environments (Mehta et al., 2009), while others had focused on challenges in more abusive parenting environments (Hanson et al., 2015). Furthermore, variability in the age that ACEs occurred and the timing of the scan is important because the effect of early life stress on amygdalar volume is not linear across time (Merz, Tottenham, & Noble, 2018). Lastly, power problems are increasingly recognized as contributing to inconsistent findings in the neuroimaging literature (Button et al., 2013) and previous studies on the impact of ACEs on amygdalar volume had typically had fewer than fifty participants. The present study's use of a widely validated measure of ACEs, advanced software to segment the amygdala, and a comparatively large sample size, addresses some of these methodological challenges.

Findings from the present investigation highlight the centrality of the right basolateral segment of the amygdala in mediating the association between ACEs and psychopathology

risk. These findings are supportive of growing evidence on the role of the basolateral amygdala in the fear response (Morris, Öhman, & Dolan, 1999) and reward valuation and addiction (Wassum & Izquierdo, 2015), as well as its role in conditioning of the fear response, a significant risk factor for anxiety-related disorders (Fanselow & LeDoux, 1999). It is possible that youth who have experienced ACEs have developed an attentional bias toward fearful stimuli, leading to emotion regulation problems that dispose them toward anxiety and depressive symptoms. Similarly, basic research suggests that the basal amygdala has an abundance of [glutamatergic](#) neurons, which have been documented for their role of sending projections to the [nucleus accumbens \(NAc\)](#). The activation of these projections is critical for processing [motivational salience](#) and is implicated in alcohol use problems (Koob & Kreek, 2007). The findings of the present study may also provide support to models and research on the connection between amygdalar structure and function with fear, emotional regulation, and substance use risk (Glahn, Lovallo, & Fox, 2007; Hill et al., 2001; Phelps et al., 2001; Phillips & LeDoux, 1992). Specifically, the connection between ACEs and reduced volume in the right basolateral amygdala may suggest that the emotional regulation neural architecture has been affected. According to these models, individuals with diminished affect regulation are at risk for heavy drinking (Lovallo, 2013; Oshri, Rogosch, & Cicchetti, 2013). The motivation for drinking is purported to stem from an attempt to curb or numb unpleasant emotional states. Specifically, the behavioral risk is governed by negative reinforcement in response to aversive stimuli, such as fear, experienced by having negative affect and being highly emotionally reactive. An acquired sensitivity to unpleasant emotional states and drive for negative reinforcement has been referred to as the “dark side” of addiction (Koob, 2013), in contrast to positive reinforcement-driven motivation.

The present study has some limitations that bear consideration. First, most of the findings in the present study range from small to medium effect sizes. Such effect sizes suggest that further replication of these findings is needed before firm conclusions are drawn about the indirect associations between ACEs, amygdalar volume, and attendant psychiatric symptomatology. However, these effect sizes may also suggest that some youth experience substantial effects while others may not. This variability can stem from unexamined moderators that lead to small and medium overall effect sizes. Second, the study is partly based on cross-sectional analyses to assess for ACEs, meaning that it could be affected by recall bias. Equally, the cross-sectional assessment did not allow for identification of ACEs during specific age ranges where the effects of early life stress may be particularly impactful on amygdalar development. Nonetheless, the ACE is a retrospective measure that has been widely studied as a robust predictor of physical and mental health problems (Anda et al., 2006), mitigating this issue to an extent. However, an additional limitation is that the ACE questionnaire indexes a broad measure of childhood adversity and thus does not enable us to account for the differential influence of specific types of adversity. Specifically, there is evidence that different types of adversity (e.g., traumatic events, physical abuse, or neglect) yield distinct effects on children’s cognitive and emotional outcomes (Lambert, King, Monahan, & McLaughlin, 2017). It would be important for future studies to examine the distinct influence of different types of adversity on amygdalar volume and related psychopathology. Similarly, the present study focused on the association between a total score of ACEs and reduced amygdalar volume. A remaining limitation and goal for future

research would be to examine what other types of adverse experiences are associated with change in amygdalar volume.

Lastly, this investigation focused on a sample of African-American youth from the rural Southeastern United States, possibly limiting the generalizability of the findings. However, there is a long history of focusing specifically on high-risk populations, such as children who were raised in institutions or given up for adoption (Mehta et al., 2009), extending that tradition of investigating special populations that are disproportionately exposed to adversity. From this perspective, although generalizability may be lower, the relationships between adversity and the brain may be brought into sharper relief and in turn extended to more typical populations. Furthermore, African Americans in the Southeastern US are not a trivial population demographic: according to the last U.S. Census, 55% of the African American population lived in the South, meaning even narrow generalizability to this population reflects a sizable number of people.

The present study has several clinical and prevention implications. For practitioners who actively work with youth who have experienced ACEs, it will be important to consider that the effects of ACEs include lasting biological impacts on brain structure that may be one basis for the presenting psychopathology. The unique associations between ACEs and the basolateral segments of the amygdala suggest that individuals with a history of ACEs may exhibit fear, anxiety, or deficits in emotional processing (De Bellis & Zisk, 2014; Hackman, Farah, & Meaney, 2010). Similarly, the effects on the basolateral amygdala may lead victims of ACEs to respond more emotionally to stress or to exhibit greater reward valuation (Wassum & Izquierdo, 2015), thereby conferring greater vulnerability to addiction. Together, these findings suggest that prevention and intervention efforts for individuals who report ACEs might be specifically focused on more effectively managing altered emotional processing and developing effective and adaptive emotional regulation skills. In contrast, cognitive techniques that rely on higher-order cognitive strategies may be less efficacious for individuals exposed to ACEs if these techniques do not account for altered emotional processing. Our study supports emerging literature suggesting that biology is not destiny when it comes to the adverse consequences of ACEs, as interventions may mitigate the neurobiological effects that ACEs have on the amygdala and associated pathways (see review by Dutcher & Creswell, 2018). For example, a recent randomized prevention trial showed that a parenting intervention attenuated the association between poverty and hippocampal and amygdalar volumes, an effect that may be generalizable to youth with ACEs (Brody et al. 2017). Brody et al.'s findings also underscore the importance of early intervention for individuals exposed to ACEs. By intervening early in childhood and adolescence while brain maturation processes (e.g., pruning and myelination) are still ongoing, practitioners can more effectively capitalize on neuroplasticity to abate the neurobiological impacts of early life adversity.

Going forward, research priorities include the use of studies with longitudinal designs to track the possible suppression of neurogenesis among youth exposed to ACEs and developing a clearer understanding of the dose-response relationship. In addition, more research is needed to gauge how much exposure to adversity leads to measurable negative consequences for the amygdala, particularly in terms of whether this association is linear.

Similarly, more research is needed to decipher whether certain types of exposures are selectively more impactful than others. Specifically, research is needed that examines exposure to specific types of childhood maltreatment in relation to youth neurodevelopment. Clarifying the mechanisms by which adversity confers developmental risk and identifying resilience factors that protect against these effects are critical for the development of psychiatric preventive and intervention programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Centromedial and Basolateral Regions Volume Predicted by ACE Total Score.

Note. The centromedial and basolateral regions were informed by Saygin et al. (2017). ICV and intervention status was controlled for in the model. Standardized coefficients of only significant paths are presented in the figure. $^\dagger p < .10$, $*p < .05$.

Figure 2.

Measurement Model (CFA) of Right Amygdala Segments.

Note. Model fit is good. Right amygdala: $\chi^2(20) = 90.96$ ($p < .001$), CFI = .95, SRMR = .

08. Standardized coefficients are presented in the model. ** $p < .01$, *** $p < .001$.

Figure 3.

Mediation Model of the Effect of ACE on Affect Problems and Alcohol Use problems through Right Amygdala Segments. ICV, intervention status, gender, and SES risk are used as covariates throughout the model.

Note. Model fit is good: $\chi^2(79) = 119.34$ ($p = .002$), CFI = .97, SRMR = .04. Standardized coefficients are presented in the model. ICV, intervention status, SES risk at T3, and gender are controlled. $^*p < .05$, $^{**}p < .01$, $^{***}p < .001$.

Table 1.

Model of the Associations Between Adverse Childhood Experiences, Right Amygdalar Volume, and Psychopathology

Paths	<i>B (SE)</i>	β	95%CI of <i>B</i>	<i>p</i>
Direct effects				
ACE → Basolateral	-.336 (.151)	-.190	[-.633, -.040] *	.026
ACE → Central-medial	-.269 (.136)	-.144	[-.536, -.002] *	.049
ACE → Anxiety	.299 (.132)	.209	[.041, .557] *	.023
ACE → Depression	.558 (.121)	.389	[.321, .795] ***	<.001
ACE → Alcohol	.336 (.742)	.043	[-1.118, 1.790]	.651
Basolateral → Anxiety	-.206 (.094)	-.255	[-.391, -.021] *	.029
Basolateral → Depression	-.184 (.087)	-.227	[-.355, -.012] *	.035
Basolateral → Alcohol	-1.412 (.534)	-.321	[-2.458, -.366] **	.008
Central-medial → Anxiety	.032 (.051)	.042	[-.068, .132]	.531
Central-medial → Depression	.079 (.049)	.102	[-.016, .174]	.104
Central-medial → Alcohol	.068 (.292)	.016	[-.505, .641]	.817
Indirect Effect				
ACE → Basolateral → Anxiety	.086 (.050)	.049	[.008, .206] *	--
ACE → Basolateral → Depression	.074 (.050)	.043	[.002, .194] *	--
ACE → Basolateral → Alcohol	.474 (.290)	.061	[.024, 1.141] *	--
ACE → Central-medial → Anxiety	-.007 (.016)	-.037	[-.049, .021]	--
ACE → Central-medial → Depression	-.025 (.024)	-.033	[-.093, .007]	--
ACE → Central-medial → Alcohol	-.023 (.108)	-.046	[-.293, .226]	--
Control				
ICV → Basolateral	.127 (.060)	.253	[.010, .244] *	.034
Intervention → Basolateral	-.060 (.164)	-.031	[-.382, .262]	.716
Gender → Basolateral	-.490 (.232)	-.252	[-.946, -.035] *	.035
SES Risk → Basolateral	.161 (.179)	.077	[-.189, .511]	.368
ICV → Central-medial	.058 (.054)	.110	[-.048, .164]	.283
Intervention → Central-medial	-.051 (.146)	-.025	[-.338, .236]	.726
Gender → Central-medial	-.441 (.209)	-.215	[-.850, -.032] *	.035
SES Risk → Central-medial	.115 (.160)	.053	[-.100, .429]	.472
ICV → Anxiety	.031 (.052)	.075	[-.072, .133]	.558
Intervention → Anxiety	-.234 (.141)	-.150	[-.510, .041]	.096
Gender → Anxiety	.190 (.205)	.121	[-.212, .591]	.354
SES Risk → Anxiety	.117 (.152)	.070	[-.182, .416]	.442
ICV → Depression	.090 (.048)	.221	[-.004, .183]	.060
Intervention → Depression	-.214 (.129)	-.137	[-.467, .039]	.098
Gender → Depression	.497 (.186)	.315	[.132, .861] **	.008

Paths	<i>B (SE)</i>	β	95% <i>CI of B</i>	<i>p</i>
SES Risk → Depression	.154 (.140)	.092	[−.121, .428]	.272
ICV → Alcohol	.188 (.294)	.086	[−.388, .765]	.522
Intervention → Alcohol	.126 (.792)	.015	[−1.425, 1.678]	.873
Gender → Alcohol	−1.360 (1.161)	−.159	[−3.636, .915]	.241
SES Risk → Alcohol	−.255 (.152)	−.028	[−1.937, 1.428]	.767

Note. ACE = Adverse childhood experiences, Basolateral = Basolateral right amygdala regions, Central-medial = Central-medial right amygdala regions. Intervention status was coded as 0 for no and 1 for yes. Gender was coded as 0 for male and 1 for female. Model fit is good: $\chi^2(79) = 119.34$ ($p = .002$), CFI = .97, SRMR = .04.

*
 $p < .05$,

**
 $p < .01$,

 $p < .001$