Decreased Amygdala Reactivity to Parent Cues Protects Against Anxiety Following Early Adversity: An Examination Across 3 Years

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ABSTRACT

BACKGROUND: The human brain remains highly plastic for a protracted developmental period. Thus, although early caregiving adversities that alter amygdala development can result in enduring emotion regulation difficulties, these trajectories should respond to subsequent enriched caregiving. Exposure to high-quality parenting can regulate (i.e., decrease) children’s amygdala reactivity, a process that, over the long-term, is hypothesized to enhance emotion regulation. We tested the hypothesis that even following adversity, the parent–child relationship would be associated with decreases in amygdala reactivity to parent cues, which would in turn predict lower future anxiety.

METHODS: Participants were 102 children (6–10 years of age) and adolescents (11–17 years of age), for whom data were collected at one or two time points and who either had experienced institutional care before adoption (n = 45) or had lived always with their biological parents (comparison; n = 57). We examined how amygdala reactivity to visual cues of the parent at time 1 predicted longitudinal change (from time 1 to time 2) in parent-reported child anxiety across 3 years.

RESULTS: At time 1, on average, amygdala reactivity decrements to parent cues were not seen in children who had received institutional care but were seen in children in the comparison group. However, some children who previously experienced institutional care did show decreased amygdala reactivity to parent cues (~40%), which was associated with greater child-reported feelings of security with their parent. Amygdala decreases at time 1 were followed by steeper anxiety reductions from time 1 to time 2 (i.e., 3 years).

CONCLUSIONS: These data provide a neurobiological mechanism by which the parent–child relationship can increase resilience, even in children at significant risk for anxiety symptoms.

Keywords: Amygdala, Buffering, fMRI, Parent, Parental deprivation, Previously institutionalized

https://doi.org/10.1016/j.bpsc.2019.02.001

Neuroaffective processes contribute to mental health across the life span, and parental caregiving lays the foundation for their construction. Whereas stability, warmth, and support promote emotion regulation development (1), caregiving adversities are risk factors, contributing to more than a third of mental illnesses (e.g., anxiety and mood disorders) (2,3) and increasing developmental risk to associated neurobiology (e.g., amygdala–cortical circuitry) (4,5).

Across many species, high-quality parenting has a powerful regulatory effect on an offspring’s stress and emotional reactivity, particularly during the juvenile period. Parents reduce distress, block stress hormone release, and modulate emotional behavior, effects collectively known as “parental buffering” (6–13). Rodent models implicate the amygdala as one part of the complex neurobiology involved in such buffering effects [see Eisenberger (14) for a review of extra-amygdala regions involved in social buffering effects]. That is, in the presence of parent cues (visual, tactile, or olfactory), the amygdala often exhibits decreased activation. For example, parental presence (or a learned maternal odor cue) blocks glucocorticoid elevations and decreases amygdala reactivity in rat pups, thereby decreasing aversive learning (15,16). In humans, too, amygdala reactivity is decreased by parent cues (e.g., parent photographs) during childhood (13), suggesting that the amygdala may be part of the mechanism for parental regulation of child emotions also. Childhood has been posited as a “sensitive period” for parental influence on the developing amygdala, when parents attenuate amygdala reactivity and at the same time help to shape the strength and nature of amygdala–cortical connectivity development, which supports future affective self-regulation (17,18). Hence, amygdala reactivity to parent cues during childhood is a strong candidate mechanism for linking early caregiving experiences with long-term mental health.

Parental buffering of stress responses can be compromised by early adversity exposure. For example, parental buffering of...
amygdala buffering to parent cues decreases after adversity.
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parents, n = 89 children). Parents (n = 72) completed questionnaires again at time 2 (year 3); the mean (SD) interval = 2.43 years (± 0.58 years). Attrition was not associated with variables of interest (see the Supplement).

Questionnaires

Revised Child Anxiety and Depression Scale–Parent Version. Youth anxiety was measured using the Revised Child Anxiety and Depression Scale (37), which has good internal consistency (Cronbach’s α = .84) and requires parents to rate the frequency with which their child displays specific emotional behaviors. The scale has been validated for children and adolescents, including youths with a history of institutional care (38). We focused on total anxiety symptoms across all categories.

The Security Scale. The Security Scale (39), which has good internal consistency (Cronbach’s α = .93), assesses the child or adolescent’s reported security in the parent–child relationship in the domains of parent responsibility and/or availability, reliability during times of stress, and interest in communicating with the parent; higher scores indicate greater feelings of security in the parent–child relationship. This measure was collected at time 1 only (comparison group, 3.16 ± 0.58; PI group, 3.15 ± 0.44) and was not different between groups, t87 = 0.06, p = .951. Prior studies have reported high convergent validity of this measure with other observed and reported measures of attachment security from infancy (40,41).

Imaging

Parent/Stranger fMRI Task. In the scanner, participants were presented with eight alternating blocks (28 seconds each, total time 4.34 minutes) of color photographs of their own parent or another child’s parent (stranger; matched for ethnicity and sex) with smiling and neutral facial expressions (see the Supplement for more details). Parent sex was mostly female (82%–93% female across groups), and parent sex was not associated with amygdala buffering (t99 = −0.33, p = .745). This design was intended to provide participants with blocks of their parent’s image alternating with blocks of the stranger’s image. The happy and neutral expressions were included to provide a behavioral task to ensure attention, but there was no expectation that this behavior would be meaningfully related to buffering (nonetheless, see Supplemental Results for analyses of these behavioral data).

Image Acquisition. Images were acquired with a Siemens Trio 3T fMRI scanner (Siemens Corp., Erlangen, Germany). A whole-brain, high-resolution, T1-weighted anatomical scan (magnetization prepared rapid gradient echo; 256 × 256 in-plane resolution, 256-mm field of view, 192 × 1-mm sagittal slices) was used for transformation and localization of each subject’s functional data into Talairach space (42). For the functional task, T2*-weighted echo-planar images (34 slices) were acquired using an oblique angle of ~30° from each subject’s position, 4-mm slice thickness (skip = 0), repetition time 2000 ms, echo time 30 ms, flip 90°, matrix 64 × 64.

fMRI Preprocessing. Functional imaging data were preprocessed and analyzed with the Analysis of Functional Neuroimages (AFNI version 16.1.28) software package (43). Volumes with excessive absolute motion (>0.5 voxel from reference volume) were censored. Preprocessing steps included slice-timing correction, image registration to the first volume, smoothing with an anisotropic 6-mm Gaussian kernel (full width at half maximum), time series normalization, and transformation into Talairach space (see the Supplement for more details).

Statistical Analysis

Right Amygdala Region of Interest. Based on prior findings (13), we had an a priori hypothesis that we would see changes in the right anatomical amygdala in children (Talairach–Tournoux Atlas in AFNI) when viewing pictures of the parent (but see the Supplement for right and left amygdala signal broken down by subnuclei [central medial, superficial, and basolateral]).

A 2 × 2 analysis of covariance was performed in SPSS (version 25; IBM Corp., Armonk, NY) to test for effects of age group (children vs. adolescents) and caregiving group (comparison vs. PI) on right amygdala β weights (for the parent–stranger contrast; see the Supplement for the analysis of variance outcomes where age was treated continuously). As there was a slight overrepresentation of girls in the PI group (see Supplemental Table S1), participant sex was included in all analyses.

Longitudinal Associations Between Amygdala Reactivity and Anxiety. Longitudinal associations between decreased amygdala reactivity to parent and anxiety symptoms across time were analyzed using a linear mixed model in SPSS with maximum likelihood estimation to accommodate the nested structure of the data (individual change in anxiety symptoms from time 1 to time 2). This method captures individual variance while allowing for missing data points, thus dealing with the attrition we had at time 2 (but see the Supplement for a model that includes only participants who contributed two data points). We used separate linear regressions to assess associations between amygdala buffering and age of adoption on reported security in the attachment relationship, controlling for age and sex. The α value was set at .05 for all analyses, and unless specified, two-sided t tests were used.

RESULTS

Response in Right Anatomical Amygdala Region of Interest (Parent–Stranger Contrast)

There was a significant caregiving group × age group interaction, F1,93 = 5.63, p = .020, ηp2 = .06 (Figure 2; see Supplemental Figure S2 for the effect broken down into parent and stranger contrasts). Post hoc t tests showed that children in the PI group did not exhibit decreased amygdala reactivity to pictures of the parent, t22 = 0.61, p = .726, and Bayesian analyses (one-sided, one-sample t test) in JASP (44) indicated that the data from the children in the PI group were 6.82 times more likely to be observed under the null hypothesis (i.e., no difference in amygdala response to parent vs. stranger pictures) than under the alternative hypothesis (i.e., lower
Figure 2. Results for the right amygdala response analysis. The graph shows the mean extracted $\beta$ weights from the right amygdala in the parent condition relative to those in the stranger condition across both caregiving groups (comparison [COMP] and previous institutional care [PI]) and age groups (children and adolescents). Error bars show ±1 SEM. The image of the brain represents the region of interest from which the $\beta$ weight values were extracted in each subject (Montreal Neurological Institute coordinate $y = -4$). **Significant difference from zero. *Significant difference between groups, $p < .05$. L, left; ns, nonsignificant; R, right.

amygdala reactivity to parent pictures relative to reactivity to stranger pictures). In contrast, children in the comparison group showed lower amygdala reactivity to parent than to stranger pictures, $t_{26} = 1.84, p = .039$ (one-sided t test) as shown previously (13), but comparison group adolescents did not, $p$ values > .05 (see the Supplement for post hoc Bayesian analyses in the comparison group youths and adolescents in the PI group). Post hoc tests of the simple effects indicated no age-related change in amygdala responses to parent cues in the PI group, $F_{1,93} = 0.40, p = .529, \eta^2_p = .004$, whereas age-related change was seen in the comparisons (i.e., decreases in amygdala reactivity to parent cues for children, but not adolescents), $F_{1,93} = 8, p = .005, \eta^2_p = .08$. There were no other main effects or interactions, largest $F_{1,93} = 0.693, p = .407, \eta^2_p = .01$.

**Amygdala Reactivity Decreases to Parent Cues Predicting Future Anxiety Symptoms**

Although at the group level, children in the PI group did not exhibit lower amygdala reactivity to parent cues than to stranger cues, 43% of children in the PI group and 36% of adolescents in the PI group (compared with 55% of children in the comparison group and 33% of adolescents in the comparison group) did show decreased amygdala reactivity to parent cues, which could have important implications for long-term anxiety. There were no differences in baseline anxiety (i.e., time 1) between participants who showed amygdala reactivity decreases to parent cues and those who did not (controlling for participant age, sex, and caregiving group), $\beta = 2.17, p = .332, d = 0.19$.

We tested the change in anxiety symptoms across time (time 1 to time 2) as a function of amygdala reactivity decreases to parental images in youths in the PI and comparison groups using a mixed linear model, with caregiving condition (comparison vs. PI), age group (child vs. adolescent), sex (male vs. female), time (time 1 vs. time 2), and amygdala response status (categorical: where amygdala $\beta$ values that were lower in response to pictures of parent than to those of stranger were considered as “decreased to parent”) as fixed effects predictors of Revised Child Anxiety and Depression Scale scores, with random slope and intercept between individuals (total $n = 101$ with anxiety data at either time 1 or time 2, or both; time 1: $n = 99$; time 1 and time 2: $n = 70$, time 2 only: $n = 2$). As hypothesized, there was a significant time × caregiving group × amygdala signal interaction, $F_{1,75.67} = 5.90, p = .018$, $\eta^2_p = .07$, whereby youths in the PI group (both children and adolescents) who exhibited amygdala reactivity decreases to parental stimuli at time 1 showed a sharper decline in anxiety symptoms between time 1 and time 2 than youths in the PI group who did not exhibit such amygdala reactivity decreases, and comparison youths (Figure 3). Post hoc tests on the estimated marginal means from the model showed that youths in the PI group who did and those who did not exhibit decreased amygdala reactivity to parent cues did not significantly differ in anxiety symptoms at time 1, $F_{1,89.44} = 0.006, p = .937, \eta^2_p = 0$, but their scores did differ at time 2, $F_{1,97.72} = 4.53, p = .036, \eta^2_p = .04$. Comparison youths who did, and did not, exhibit lower amygdala reactivity to parent than to stranger cues did not differ from each other at either time 1, $F_{1,100.25} = 0.25, p = .618, \eta^2_p = 0$, or time 2, $F_{1,101.17} = 0.004, p = .951, \eta^2_p = 0$. See the Supplement for the remaining main effects and interactions.

**Associations With Age of Adoption, Time With Adoptive Family, and Child-Reported Security in the Attachment Relationship**

Within the PI group, 15 children were adopted before 12 months of age, and 29 children were adopted after 1 year of age (data were missing for 1 child). There was no association between age at adoption and amygdala responses (controlling for age at scan and sex) in children and adolescents in the PI group, $\beta = .003, t_{40} = 1.02, p = .316, d = 0.14$. Decreased amygdala reactivity to parent cues was also not associated with the amount of time that youths in the PI group had spent with their adoptive family (controlling for age group and sex), $t_{40} = 0.58, p = .563, d = 0.18$, suggesting that caregiving group differences in amygdala response to parent cues were not related to familiarity with the parent stimulus. However, child- and/or adolescent-reported security with the adoptive parent did predict whether amygdala reactivity decreases occurred, with higher security scores being associated with lower amygdala reactivity to parent than to stranger cues, $\beta = .415, t_{36} = 2.44, p = .019, d = 0.38$ (Figure 4); see the Supplement for child-reported security in the attachment relationship and amygdala responses in the comparison children.

**DISCUSSION**

We tested three hypotheses generated from the neuro-environmental loop model (17). First, we tested whether, on average, early caregiver deprivation would reduce the likelihood of children’s right amygdala showing decreased reactivity to parental stimuli. Second, we examined within the PI group whether more secure parent–child relationships (characterized by higher child-reported feelings of security in the attachment relationship) were associated with amygdala
reactivity decreases to parent cues. Finally, we asked whether individual differences in amygdala response to parent cues predicted anxiety across time. We found support for all of these hypotheses. First, we found that children from the PI group were less likely to show decreased amygdala reactivity to parent cues, exhibiting amygdala responses that on average paralleled those seen in adolescents. This finding was unlike that for the comparison children, who exhibited a relative decrease in amygdala activity when viewing pictures of their parent compared with amygdala response when viewing images of a stranger, as we have previously shown (13). Secondly, despite these group differences, inspection of individual data within the PI group indicated that some individuals (~40%), including both children and adolescents, did exhibit decreases in amygdala reactivity to pictures of their adoptive parent. Finally, amygdala reactivity decreases to parent cues predicted change in anxiety symptoms across time. Decreased amygdala reactivity to parental stimuli at time 1 was associated with a greater decrease in anxiety symptoms across time in youths from the PI group. Importantly, those individuals who exhibited amygdala reactivity decreases to parent cues did not differ in initial anxiety scores (time 1) from those who did not; instead, associations between amygdala response and anxiety symptoms revealed themselves across time, when change from baseline to follow-up was examined. In other words, regardless of within-group variation in initial anxiety levels, amygdala reactivity was predictive of intrindividual, long-term anxiety reductions (i.e., the anxiety slope). That we saw caregiving group differences in anxiety at time 2, but not time 1, likely reflects the fact that we are observing a phenomenon that emerges across development as children live with their parents. Despite our hypotheses that this effect would be specific to children, the association between amygdala reactivity to parent or stranger cues and anxiety symptom reductions was present for adolescents as well as children, suggesting that amygdala reactivity decreases to parent cues at any time in childhood or adolescence is protective against elevated anxiety for youths exposed to early caregiving adversity. That finding has important implications, suggesting that there is capacity for some youths (particularly in the context of high relationship security) to retain childlike plasticity in this circuit (i.e., amygdala reactivity decreases to parent cues), despite adversity exposure.

The group-level findings are consistent with previous studies in both rodents and humans (16,20,21,29,31) suggesting that early parental deprivation changes amygdala development and may even do so through acceleration. In the current study, at the group level, amygdala responses to parent cues in children with a history of institutional care were more similar to adolescents’ responses. Such data are also, at
least conceptually, consistent with life course models, which postulate that certain early environments (e.g., instability or threat) favor accelerated development (45). These outcomes support the idea that early exposure to adverse environments may recruit the activity of certain neurobiological systems (e.g., those involved in affective processes) at earlier ages, abbreviating the period of developmental plasticity and shifting individuals toward a more adultlike, less plastic state (30,31).

Such abbreviated plasticity could result in a vulnerability to anxiety as neural circuits have less time to adapt to the environment across development (17).

The within-subject association between child-reported security in the attachment relationship and decreases in amygdala reactivity to adoptive parent stimuli was a particularly important finding in the current data set. Several studies have demonstrated the importance of attachment security in the emergence of resilience following institutional care (32,33,46). For example, in the Bucharest Early Intervention Project (32), establishment of a secure attachment mediated improvements of an experimental foster care intervention on internalizing disorders. The current findings provide a potential neurobiological mechanism for that effect. Specifically, we have shown that decreased amygdala reactivity to parent cues, which serves a protective function against long-term anxiety symptoms, occurs more frequently in the context of a secure relationship with the attachment figure. These data suggest that interventions targeting children’s feelings of security in the attachment relationship, which has been shown to protect against child internalizing disorders (47,48), might enhance parental regulation of the amygdala. The fact that the association between security and amygdala reactivity to parent cues did not exist in the comparison group (see the Supplement) is interpreted to mean not that security is inconsequential in the comparison children but that individual differences in security might be particularly important following early caregiving adversity. Indeed, such findings are consistent with data demonstrating the critical importance of attachment security for resilience within populations that have experienced early institutional caregiving (32,33,49). Interestingly, as there was no association between right amygdala reactivity and adoption timing variables, these data further emphasize the importance of the postadoption environment (such as feelings of security with the parent), rather than the age at adoption, in amygdala reactivity. Indeed, as youths in this study were in the middle childhood to adolescent age, there has been ample time for the postadoption environment to exert its effects on amygdala development. In contrast, left amygdala signal amplification to parent cues was not associated with child-reported security in the attachment relationship (50).

Although the sample examined here overlaps with those of prior reports (13,50), the novel longitudinal contributions and different analytic approaches used here innovate the work and merit reporting. Specifically, after the finding on left amygdala response amplification to parent cues reported in Olasvsky et al. (50) was published, in Gee et al. (13) we revisited this task with a renewed hypothesis [motivated by findings in rodent development (15)] that children should exhibit a different amygdala response to parental stimuli from that of adolescents. To address this question, we used age group as a variable of interest (children vs. adolescents) and specifically probed the right amygdala (anatomically defined). This report showed that if children were considered separately from adolescents, the right amygdala exhibited a relative decrease in reactivity to parental stimuli. The current study sought to apply this hypothesis-driven approach to the PI sample and again specifically examined age groups (children vs. adolescents) in the right (anatomically defined) amygdala. Additionally, the current study includes the more recently acquired longitudinal follow-up data, demonstrating a novel, and clinically important, association between amygdala responses to parents and long-term emotional functioning in humans.

A major strength of the current study was the use of a longitudinal design to assess how amygdala reactivity decreases to parent cues predicts future anxiety phenotypes. However, there were some important limitations. First, the use of parental images, rather than physical parental presence, limits the ecological validity of the findings, which will have to be interrogated in future research. Nonetheless, cues such as maternal odors in rodent studies (16) or pictures of social support figures in humans (51) are frequently used in buffering studies, and many seminal studies examining the effect of the parent on brain function do not attempt to induce fear to examine parent effects (52). Further, the familiarity of parents versus strangers was not controlled in this study. However, considering that adolescents have greater familiarity with parental stimuli than children do, that youths in the PI group had been with the family for many years (i.e., parents were familiar to all subjects), and that time with the adoptive family was not associated with amygdala reactivity decreases to parent cues, simple familiarity is unlikely to have influenced the current study outcomes. Also, in line with several studies examining developmental transitions in emotion circuitry (12,13,53), and because we did not expect to see linear changes in amygdala response with months of age, we chose to examine age as a categorical variable. In addition, though anxiety was assessed longitudinally in this study, fMRI data from this task were available at only one point, leaving developmental differences in amygdala reactivity in the task to be interpreted on the basis of cross-sectional data. As we had limited preadoption information for children in the PI group (including preadoption mental health), we cannot address the influence of preadoption factors. Also, as the levels of anxiety were not clinically significant in the majority of participants, the findings reported here may not generalize to clinical populations, although they are compatible with the Research Domain Criteria objectives to assess psychological factors continuously. Finally, as parent reports of child anxiety can be influenced by the parent’s own anxiety symptoms, it is possible that the change in child anxiety across time may instead have reflected change in parent anxiety across time. Though we did not measure parent anxiety at time 2, at time 1 it was moderately correlated with child and/or adolescent anxiety in both groups (comparison r = .44, PI r = .33). However, while we saw change in youth anxiety across time, we have no reason to suspect that parent anxiety would change. Despite these limitations, finding that the quality of the post-adoption relationship was a good predictor of amygdala reactivity to parent cues, and that the amygdala response was associated with long-term mental health, emphasizes the value of postadoption factors in promoting children’s emotional health.
Amygdala Buffering to Parent Cues Decreases After Adversity

ACKNOWLEDGMENTS AND DISCLOSURES
This research was supported by National Institute of Mental Health (Grant No. R01MH081864 [to NT] and Grant No. 1K99MH113821 [to BLC]), the Dana Foundation [to NT], the National Science Foundation (Conference Grant No. BCS-1439258 [to NT and coinvestigators Megan Gunnar, Regina Sullivan, Mar Sanchez, and Camelia Hostinar]), the National Health and Medical Research Council (Early Career Fellowship No. 1091571 [to BLC]), the American Australian Association (to BLC), and the Brain Behavior Research Foundation (National Alliance for Research in Schizophrenia and Affective Disorders Grant No. 24739 [to BLC]).

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Nov 11, 2018; revised Jan 15, 2019; accepted Feb 5, 2019. Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2019.02.001.

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