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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