Amygdala-Function Perturbations in Healthy Mid-Adolescents With Familial Liability for Depression

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Objective: Functional magnetic resonance imaging (fMRI) studies have identified increased amygdala responses to negative stimuli as a risk marker of depression in adults, and as a state marker of depression in adults and adolescents. Hyperreactivity of the amygdala has been linked to negatively biased emotional processing in depression. However, no study has elucidated whether similar amygdala perturbations can be found in healthy mid-adolescents with familial liability for depression. We hypothesized that healthy 14-year-olds with relatives with depression would demonstrate increased amygdala responses to negative stimuli, as compared with their peers with no family history of mental disorders. **Method:** We investigated a community-based sample of 164 typically developing 14-year-olds without record of past or current mental disorders. Of these individuals, 28 fulfilled criteria for family history of depression, and 136 served as controls. Groups did not differ with regard to cognitive ability, depressive symptomatology, and anxiety. During fMRI they performed a perceptual discrimination task in which visual target and distractor stimuli varied systematically with regard to emotional valence. **Results:** Both a hypothesis-driven region-of-interest analysis and a whole-brain analysis of variance revealed that negative distractors elicited greater amygdala activation in adolescents with a family history of depression compared to controls. Amygdala responses also differed during the processing of negative target stimuli, but effects were reversed. **Conclusion:** Our study demonstrates that familial liability for depression is associated with correlates of negatively biased emotional processing in healthy adolescents. Amygdala perturbations during the processing of negative stimuli might reflect an early and subtle risk marker for depression. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(5):559–568. **Key Words:** amygdala, family history of depression, adolescence, fMRI

Amygdala-function perturbations were demonstrated in manifest adult[1] and child[2] major depression (MD) by functional magnetic resonance imaging (fMRI) studies. Increased amygdala activity during perception of negative stimuli, typically found in patients with depression, is supposed to bias emotional processing.[3] Differentiating this negative processing bias, Beck[4] suggested that increased amygdala activity mirrors prepotent bottom-up, that is, stimulus-driven processing that cannot be compensated by counter-directional goal-directed processes, or top-down mechanisms resulting in a dysbalanced cognitive control. Hence, such dysbalance might be associated with negatively biased attention and further negative cognitive distortions that progress into engagement of the hypothalamic–pituitary–adrenal-axis maintaining mechanisms of MD.[4] In adults, elevated amygdala responses to negative compared to positive stimuli[5] or geometric forms[6] have also been linked to neuroticism, a predictor of depression. Moreover, studies indicate that increased risk for MD because of genetic factors might be mirrored on the neural level. Carrying the SLC6A4 short allele of the

This article is discussed in an editorial by Dr. Deanna M. Barch on page 497.

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serotonin transporter gene has been associated with increased amygdala reactivity toward aversive[7] and not pleasant[8] pictures in healthy adults.

Most relevant for our approach, studies have also focused on participants with a family history of depression (FHD). One study[9] investigated 10- to 18-year-old offspring of parents with MD during processing of facial expressions gradually varying from happy over neutral to fearful. Amygdala activation of participants with positive FHD (FHD+) was higher compared to that in controls when stimuli were maximal fearful and attention was unconstrained, that is, during passive viewing. Nevertheless, more than half of individuals with FHD+ and 15% of controls had experienced an anxiety disorder in the past, limiting the study's conclusions,[1] particularly the explanatory power to disentangle whether altered amygdala responses reflected a trait marker of anxiety disorders or a risk marker for depression.

In addition to these limitations, variations in the focus of attention may have contributed to the discrepancies between studies. Amygdala activation varied depending on whether emotional processing was explicit (attention constrained to emotional aspects) or implicit (attention constrained to nonemotional aspects) or unconstrained (passive viewing). The significance of attentional modulation was emphasized by Beesdo *et al.*,[10] who demonstrated that adolescents with depression and anxiety showed amygdala hyperactivation to fearful faces when attention was constrained to subjective fear. In contrast, adolescents with MD showed hypoactivation of the amygdala compared to the healthy controls in the passive viewing condition. The authors concluded that attention modulates the degree to which altered amygdala function manifests in patients with depression. Another reason for diverging findings might be the use of different baseline categories for assessing neural increase at processing of negative stimuli, given that genetic susceptibility mechanisms for depression have also been linked to differential amygdala activation to neutral stimuli.[11]

Summarizing previous research, it seems that altered amygdala functioning during the processing of negative stimuli is a neural state marker of depression and anxiety in adults and adolescents and is also associated with increased risk of depression in adults. No study has demonstrated, however, whether altered amygdala responses to negative stimuli reflect an early risk marker emerging in mid-adolescents with familial liability for depression in which no psychopathology has manifested so far. This is particularly crucial, given that mid-adolescents are considered at the border of a core incidence phase for affective disorders,[12] and preventive strategies for those at risk for developing a mental disorder are highly sought. With this in mind, we investigated neural markers of familial liability for depression in a large community-based cohort of typically developing adolescents at the age of 14 years with no record of past or current mental disorders. Thereby we tried to avoid confounding variables by early manifestation of psychopathology, in contrast to most previous studies.

We used an fMRI paradigm, systematically varying the factors emotional valence and focus of attention, constraining attention either to emotional targets while also presenting nonemotional distractors, or constraining attention to nonemotional targets and showing emotional distractors. This allowed us to investigate the balance between top-down and bottom-up processing, especially in the latter condition, because of the well-described attentional capture effect by emotional stimuli.[13] In this condition, top-down processing is pivotal to focusing attention on nonemotional targets and to inhibiting bottom-up processes elicited by negative distractors.[14] We followed 2 analytical strategies. First, we hypothesized that negative stimuli would generally elicit greater amygdala responses in individuals with FHD+ compared to controls, that is, in both attentional conditions. Second, given the evidence that amygdala activity depends on the attentional focus towards stimuli, we explored whether differences in amygdala responses to negative stimuli between individuals with FHD+ and control participants are modulated by attention.

METHOD

Sample

Data acquisition was part of The Adolescent Brain Project,[15] which is funded by the German Federal Ministry of Education and Research. Monetary compensation was provided for participation. Informed consent was obtained from each participant and from 1 of his or her legal guardians. The local ethics committee approved the study. Adolescents were recruited via local school visits. Exclusion criteria were presence of a serious medical condition, history of mental disorders such as schizophrenia or bipolar disorder, and any history of head trauma with unconsciousness. A urine test ensured that there was no drug use on the day of assessment. Participants with a high probability for a mental disorder identified by the Development and