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BRIEF COMMUNICATION

# Association between poor tolerability of antidepressant treatment and brain functional activation in youth at risk for bipolar disorder

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**Objective:** To investigate whether poor antidepressant tolerability is associated with functional brain changes in children and adolescents of parents with bipolar I disorder (at-risk youth).
**Methods:** Seventy-three at-risk youth (ages 9-20 years old) who participated in a prospective study and had an available baseline functional magnetic resonance imaging (fMRI) scan were included. Research records were reviewed for the incidence of adverse reactions related to antidepressant exposure during follow-up. The sample was divided among at-risk youth without antidepressant exposure (n=21), at-risk youth with antidepressant exposure and no adverse reaction (n=12), at-risk youth with antidepressant-related adverse reaction (n=21), and healthy controls (n=20). The fMRI task was a continuous performance test with emotional distracters. Region-of-interest mean activation in brain areas of the fronto-limbic emotional circuit was compared among groups.
**Results:** Right amygdala activation in response to emotional distracters significantly differed among groups ($F_{3,66} = 3.1$, $p = 0.03$). At-risk youth with an antidepressant-related adverse reaction had the lowest amygdala activation, while at-risk youth without antidepressant exposure had the highest activation ($p = 0.004$).
**Conclusions:** Decreased right amygdala activation in response to emotional distracters is associated with experiencing an antidepressant-related adverse reaction in at-risk youth. Further studies to determine whether amygdala activation is a useful biomarker for antidepressant-related adverse events are needed.

**Keywords:** Bipolar disorder; antidepressants; adverse events; functional magnetic resonance imaging; amygdala

## Introduction

Children whose parents have bipolar I disorder are at increased risk (at-risk youth) of developing the disorder themselves.[1] Clinical risk factors for the development of bipolar disorder among at-risk youth include a family history of mood disorders, anxiety, subthreshold manic symptoms, depressive symptoms, and minor depressive disorders.[2] Although these conditions often require psychopharmacological treatment, it is poorly understood whether antidepressants alter the risk of developing mood disorders among at-risk youth.

Antidepressants may accelerate the development of bipolar disorder among at-risk youth.[3] One study reported that antidepressant exposure was associated with a diagnosis of bipolar disorder among at-risk youth,[4] although another study found that antidepressant exposure was not associated with an earlier age of onset of bipolar disorder.[5] Further, we found that 57% of at-risk youth treated with antidepressants experienced psychiatric adverse reactions, including increased irritability, aggression, impulsivity, and psychosis, leading to treatment discontinuation, and that, the younger the age, the higher the risk of adverse reactions.[6]

At-risk youth may differ from low-risk youth in functional activation of several brain areas that mediate cognition and emotional regulation, such as the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, amygdala, insula, and parietal cortex.[7-9] However, it is unknown whether there are functional differences in brain regions that regulate mood and attention between at-risk youth who have psychiatric adverse reactions to antidepressants and at-risk youth who tolerate antidepressants. Thus, using a previously established dataset, we conducted this

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exploratory analysis of differences in brain activation among at-risk youth with and without antidepressant use to determine whether baseline brain activation is different in at-risk youth with a subsequent antidepressant-related adverse reaction.

## Methods

Our sample consisted of youth who participated in a naturalistic prospective study of children and adolescents at familial risk for bipolar disorder between 2008 and 2013.[10] Subjects were included if they were between 9 and 20 years old, had at least one parent diagnosed with bipolar disorder type I, and no personal history of major depressive disorder, bipolar disorder, or any psychotic disorder. All subjects provided assent, and their legal guardians provided written informed consent prior to enrollment. At-risk participants were assessed using the Washington University Kiddie-Schedule for Affective Disorders and Schizophrenia, the Hamilton Depression Rating Scale, and the Young Mania Rating Scale.[6,10] Details of the study, enrollment, additional exclusion criteria, and clinical assessments have been reported elsewhere.[6,10] The study was approved by the University of Cincinnati Institutional Review Board.

Treatment during the study was naturalistic and was provided either by board-certified child and adolescent psychiatrists (MPD, RPD, and JRS) or by community providers. Data on past or current antidepressant exposure was collected using a standardized form at each visit. Subjects treated with antidepressants for depressive or anxiety disorders (n=33) during follow-up were identified. This at-risk group was further categorized into two subgroups: those with (n=21) and without (n=12) an antidepressant-related adverse reaction. A treatment-related adverse reaction was defined as any reaction the treatment provider deemed to be associated with antidepressant treatment and that led to discontinuation of the antidepressant (i.e., increased irritability, impulsivity, hyperactivity, or aggression).[6] Twenty-one at-risk subjects without exposure to antidepressant treatment were matched to the 21 at-risk subjects who had treatment-related adverse reactions. We also group-matched healthy controls for age, sex, and race to provide estimates of normal parameters of functional activation.

The subjects were scanned at the University of Cincinnati's Center for Imaging Research using a 4 Tesla Varian, Unity INOVA Whole Body MRI/MRS System (Varian, Inc., Palo Alto, California). To provide anatomical localization, a high-resolution, T1-weighted, three-dimensional brain scan was obtained. Two functional magnetic resonance imaging (fMRI) scans with whole-brain images were acquired using a T2-weighted gradient-echo echo-planar imaging pulse sequence ($T_R/T_E$ = 3,000/29 msec, field of view = 208x208 mm, matrix 64x64 pixels, slice-thickness = 5 mm, flip angle = 75°) while subjects performed the Continuous Performance Task with Emotional and Neutral Distractors.

In this visual attention-demanding task, subjects must discriminate rare stimuli (cues) among frequent, standard stimuli.[11] Seventy percent of the cues are simple colored squares, 10% are simple colored circles, 10% are emotionally neutral pictures, and 10% are emotionally unpleasant pictures. Each visual cue requires a unique response: button 2 is pressed for circles, while button 1 is pressed for squares and pictures. Each imaging session consisted of two runs of 158 visual cues per run presented at 3-second intervals for 2 seconds each. Emotional and neutral pictures were presented pseudo-randomly. A fixation cross was presented for 150 ms between cues.

FMRI data were analyzed using Analysis of Functional NeuroImages software (http://afni.nimh.nih.gov/afni). Details of image reconstruction, co-registration, motion artifact correction, and anatomical and functional map transformation have been reported elsewhere.[9] After motion correction parameters were included as regressors of no interest, low frequency components of the signal were removed and smoothed using a 8 mm full-width at half-maximum Gaussian kernel, and the signals were converted to percent signal change. Event-related response functions were calculated for the emotional stimuli, with squares being the baseline against which hemodynamic responses were assessed.[9]

Region-of-interest (ROI) masks were created for regions pertaining to the fronto-limbic circuit of emotion processing and regulation, as reported elsewhere.[9] These masks were applied to each fMRI activation map to obtain activation measurements within ROIs for the emotional and square cues. Specific ROIs included the ventromedial prefrontal cortex (BA 10), ventrolateral prefrontal cortex (BA 45/57), subgenual anterior cingulate cortex (BA 24/32), anterior insula, and amygdala.

Statistical analyses were performed on the percent signal difference between the emotional and square stimulus. Chi-square and analysis of variance were used with demographic and clinical data to determine whether the groups significantly differed at baseline. Analysis of covariance was used with age and sex as covariates to compare mean activation changes to emotional stimuli among groups, with pairwise comparisons among the patient groups. Comparisons were considered statistically significant at an unadjusted $p < 0.05$. We also adjusted p-values for a total of 30 tests (3 among-group comparisons in each of five bilateral regions using the Westfall-Young stepdown permutation test procedure.[12]

## Results

Although the four groups were reasonably well matched in terms of sex and race, they significantly differed in mean age and IQ, with the at-risk with antidepressant-related adverse reaction group being older than the other groups, and the healthy controls (HC) having a higher IQ than other groups (Table 1). Baselines rates of anxiety disorders and depressive and manic symptom scores were higher in the at-risk with antidepressant use group than the at-risk without antidepressant group (Table 1).

Right amygdala activation to emotional stimuli significantly differed among groups ($F_{3,68} = 3.1$, $p = 0.02$). The at-risk with antidepressant-related adverse reaction group

**Table 1** Baseline demographic and clinical characteristics of the sample

| Characteristics | At-risk with antidepressant-related adverse reaction (n=21) | At-risk without antidepressant-related adverse reaction (n=12) | At-risk without antidepressant exposure (n=21) | Healthy controls (n=20) | p-values |
|---|---|---|---|---|---|
| Age in years, mean (SD) | 13.4 (2) | 15.3 (2) | 13.2 (2) | 13.0 (2) | 0.02 |
| Sex, male, n (%) | 7 (33) | 3 (25) | 8 (38) | 7 (35) | 0.93 |
| Race, white, n (%) | 15 (71) | 10 (83) | 17 (76) | 17 (85) | 0.77 |
| IQ, WAIS mean (SD) | 102 (11) | 103 (12) | 98 (13) | 107 (14) | 0.03 |
| Psychiatric conditions, n (%) | | | | | |
| Anxiety disorders | 2 (10) | 11 (92) | 2 (10) | - | 0.01 |
| Depressive disorders | 7 (33) | 11 (92) | 9 (45) | - | 0.41 |
| ADHD | 3 (14) | 9 (75) | 8 (40) | - | 0.88 |
| Mood rating scales, mean (SD) | | | | | |
| HAMD | 17.9 (7) | 15.3 (7) | 10.0 (8) | - | 0.005 |
| YMRS | 11.0 (6) | 10.0 (4) | 7.3 (5) | - | 0.08 |

ADHD = attention deficit/hyperactivity disorder; HAMD = Hamilton Depression Rating Scale; IQ = intelligence quotient; SD = standard deviation; WAIS = Wechsler Adult Intelligence Scale, YMRS = Young Mania Rating Scale.

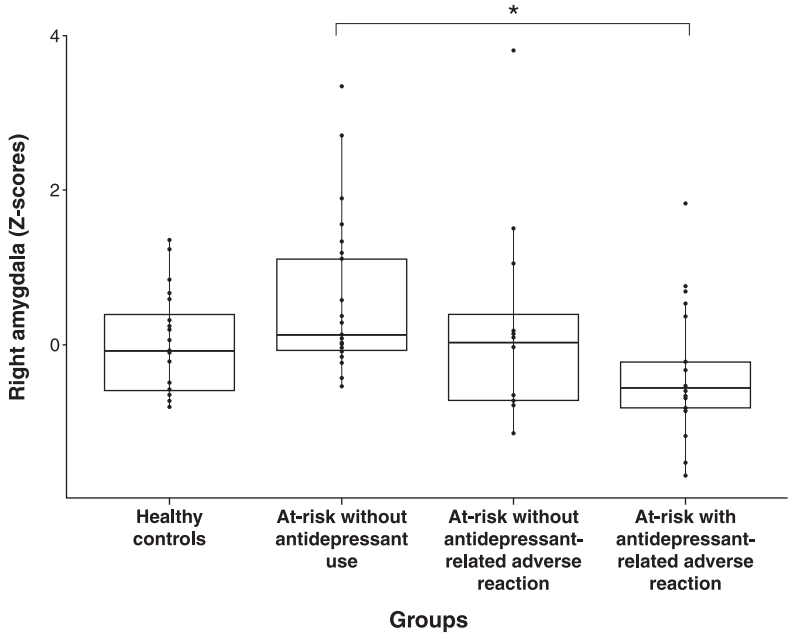


**Figure 1** Mean activation in the right amygdala of at-risk youth with and without antidepressant-related adverse reaction, at-risk without antidepressant use, and healthy controls.*p = 0.003, unadjusted; p = 0.06, adjusted for multiple comparisons.

had the lowest right amygdala activation (0.25±0.18), followed by the at-risk without antidepressant exposure group (0.44±0.23), the at-risk without antidepressant-related adverse reaction group (0.35±0.3), and the HC group (0.33±0.14). Pairwise comparisons showed that the difference between the at-risk with antidepressant-related adverse reaction group and the at-risk without antidepressant exposure group was statistically significant (unadjusted p = 0.003) (Figure 1). This difference was found to be just above the threshold for adjusted significance using the Westfall-Young procedure (p = 0.06). There was no difference in amygdala activation between the at-risk with antidepressant-related adverse reaction group and the at-risk without antidepressant-related adverse reaction group (unadjusted p = 0.06) nor between the at-risk with antidepressant-related adverse reaction group and HCs (unadjusted p = 0.23). Post-hoc analysis showed that there were no significant correlations between right amygdala activation and baseline depressive (r = -0.03, p = 0.8) and manic symptom scores (r = -0.03, p = 0.5), or significant differences in right amygdala activation between at-risk subjects with or without baseline anxiety disorders (p = 0.5) or depressive disorders (p = 0.8).

No other group differences were detected in the other ROIs, including the ventrolateral and ventromedial prefrontal cortices, and the anterior cingulate cortex (F values $< 2.1$, $p > 0.11$). The mean and standard deviation values of these ROIs are shown in Table S1, available as online-only supplementary material.

## Discussion

In this study, we found that at-risk youth with an antidepressant-related adverse reaction had significantly lower right amygdala activation to emotional stimuli than at-risk youth without antidepressant use. These two groups were matched for possible confounders, such as age, sex, and diagnosis of anxiety or depressive disorders, although the at-risk youth with an antidepressant-related adverse reaction had higher baseline depressive and manic symptom scores than at-risk youth without antidepressant use. Higher depression or anxiety have been associated with increased right amygdala activation to emotional stimuli in fMRI studies of at-risk youth.[13-15] Therefore, we would also expect higher rather than lower baseline right amygdala activation in at-risk youth with antidepressant-related adverse reactions. Right amygdala activation in at-risk youth without antidepressant use was higher than in the HC group, which is in line with previous fMRI studies in at-risk youth.[13-15] An inspection of mean activation values suggested no specific prefrontal cortex patterns in response to emotional stimuli (Table S1, online-only supplementary material). A recent meta-analysis of fMRI studies in at-risk individuals reported increased activity in the prefrontal cortex in cognitive but not in emotional processing tasks.[16]

The prefrontal cortex areas investigated in this study, in connection with the amygdala, play a key role in cognitive control of negative emotional regulation.[17] One fMRI study using effective connectivity has shown that the strength of functional connectivity between the prefrontal cortex and the amygdala is positively correlated with the intensity of negative affect, suggesting that a higher connectivity between these areas leads to better emotional regulation.[18] On the other hand, studies in adults and youth suggest that antidepressants exert their therapeutic effects by normalizing an aberrant pattern of top-down prefrontal regulation of limbic hyperactivity associated with abnormal emotional arousal.[19,20] Antidepressants, such as selective serotonin reuptake inhibitors, are shown to initially increase amygdala activity, causing an increase in agitation and anxiety during early treatment.[21,22] Therefore, we speculate whether the decreased baseline activation in the right amygdala might indicate a primary amygdala dysfunction that worsens with antidepressant treatment and fails to be compensated or adequately modulated by the prefrontal cortex, leading to antidepressant-related adverse behavioral reactions, such as increased aggressiveness, impulsivity, and irritability. Future research using psychophysiological approaches, such as effective functional connectivity studies, could examine changes in the interaction between the prefrontal cortex and the amygdala in the context of antidepressant treatment in at-risk youth before and after treatment.

Limitations of this study include the small subgroup sizes and the multiple statistical comparisons, which might have increased the possibility of a type I error. Given that this was an exploratory, hypothesis-generating study, we opted to report the unadjusted p-values. If adjusted for 30 comparisons, the positive amygdala results would no longer be significant. The post-hoc nature of the data analysis is another limitation. In addition, the observed adverse events were heterogeneous. Different neural substrates may underlie different treatment-emergent adverse events, such as psychosis, mania, or suicidality. Finally, this was an exploratory study using a unique dataset to generate hypotheses regarding which functional brain abnormalities underlie antidepressant-related psychiatric adverse reactions in at-risk youth. Thus, our findings should be considered preliminary.

In conclusion, decreased right amygdala activity might serve as a useful predictor of antidepressant-related adverse reaction in at-risk youth. Prospective studies examining neurofunctional changes in at-risk youth exposed to antidepressants are necessary to confirm these findings.

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