Amygdala and Caudate Connectivity with the Anterior Cingulate during a First-Manic Episode in Bipolar Disorder: Distinguishing Remitters and Nonremitters Following Eight Weeks of Treatment.

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BACKGROUND: Participants with bipolar disorder, during their first manic episode, showed altered activity in the prefrontal cortex (PFC), including the ventrolateral PFC and the anterior cingulate cortex (ACC), and PFC subcortical and amygdala projection sites, with differences in activity associated with treatment response. To extend these findings to better understand the functional neuroanatomy of bipolar disorder, we investigated functional connectivity among these regions in first-episode manic participants who remitted, compared to those that did not remit, after eight weeks of treatment.

METHODS: Participants with bipolar disorder during their first manic episode were recruited (n=42, $Age_{mean} \pm stdev$= 19$\pm$5 years, 60% females) and pseudo-randomized to open-label lithium or quetiapine. Participants completed fMRI scans, at baseline and following eight weeks of treatment, while performing a continuous performance task with emotional and neutral distractors. A healthy comparison group (n=41, $Age_{mean} \pm stdev$= 22$\pm$6 years, 51% females) received fMRI scans at the same intervals. Participants with bipolar disorder were stratified into those who remitted after eight weeks of treatment (n=21; total scores on both Young Mania Rating Scale and Hamilton Depression Rating Scales $\leq$10 for at least one week at week eight visit) compared to those who did not (n=21). The amygdala and caudate were defined as seeds and functional connectivity among seeds and the ACC and ventrolateral PFC to emotional distractors was calculated at baseline and following eight weeks of treatment. A 3-group (healthy, remitter, nonremitter) by seed hemisphere (left, right) analysis of covariance was conducted, covarying age and sex, with hemisphere as a repeated within-subject factor and baseline connectivity between the ACC and the amygdala or caudate as the dependent variables. Parallel models were conducted with baseline connectivity among seed regions and the ventrolateral PFC as the dependent variable. Significance was defined as $p<0.05$, corrected (standard Bonferroni correction for four models). Change overtime in connectivity (week eight minus baseline) was also calculated among seed regions and the vlPFC and ACC, with parallel models repeated with change in connectivity as the dependent variable to investigate connectivity trajectories association with treatment response.

RESULTS: At baseline, nonremitters showed a loss of negative connectivity between the right ACC and bilateral amygdala seed regions and increased positive connectivity between the right ACC and bilateral caudate seed regions, compared to both the remitters and healthy participants. Remitters did not significantly differ from healthy participants. Changes in ACC connectivity following treatment was not observed between groups.

CONCLUSIONS: These results provide evidence of alterations in ACC-caudate and ACC-amygdala functional connectivity in people with bipolar disorder during a first manic episode, and specifically in those who do not remit following eight weeks of treatment.