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Variation in Rostral Anterior Cingulate Functional Connectivity with Amygdala and Caudate during First-Manic Episode Distinguish Bipolar Young Adults who do not Remit Following Treatment

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Abstract

OBJECTIVES: Altered activity in the ventrolateral prefrontal and anterior cingulate cortices, as well as subcortical and amygdala projection sites, were previously reported during a first manic episode in youth with bipolar disorder and observed to be associated with treatment response. To extend these findings, we investigated functional connectivity among these regions in first-episode manic participants who remitted after eight weeks of treatment compared to those that did not.

METHODS: Forty-two participants with bipolar disorder (60% female) during their first manic episode were recruited and received eight weeks of treatment. Twenty-one remitted following treatment. 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) received fMRI evaluations at the same intervals. Differences in functional connectivity of the amygdala and caudate with the rostral anterior cingulate and ventrolateral prefrontal cortices at baseline (and changes in functional connectivity following treatment) were modeled between groups.

RESULTS: At baseline, non-remitters showed an increase in positive connectivity between right anterior cingulate and caudate and a loss of negative connectivity between right anterior cingulate

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Data Sharing
The data that support the findings of this study are available from the corresponding author upon reasonable request.

and amygdala, compared to healthy participants. Individuals who remitted following treatment showed an increase in negative connectivity between amygdala and left anterior cingulate eight weeks following treatment.

CONCLUSIONS: Results provide evidence of alterations in anterior cingulate-amygdala and caudate functional connectivity in bipolar disorder non-remitters during a first manic episode and changes in anterior cingulate functional connectivity associated with remission suggesting targets to predict treatment response.

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Keywords

bipolar disorder; functional connectivity; mania; anterior cingulate cortex; lithium; quetiapine

INTRODUCTION

Bipolar I disorder is defined by the occurrence of mania. Following a first manic episode, up to 80% of individuals will then experience lifelong recurring mood episodes (1). Additionally, if left untreated mood episodes become more frequent with a more pernicious clinical course over time (2–5). Early intervention is therefore critical. Yet, our ability to identify the best treatment early in the course of illness remains difficult. Following a first manic episode pharmacological regimens proceed through trial and error in order to optimize individual treatment to stabilize mood (6–9); this process can take months or even years in some individuals since we do not yet have reliable markers of treatment response to personalize prescribing. Biological markers with the power to inform treatment are therefore critically needed. While few, studies are beginning to emerge suggesting neural biomarkers are associated with treatment response (10, 11).

Bipolar disorder is associated with disruption of ventral prefrontal modulation of threat and reward systems, specifically centered on amygdala and striatum, respectively (12). While it is unknown if disruption in these systems are a driver of illness onset, findings converge to suggest blunted ventrolateral prefrontal cortex, increased rostral anterior cingulate cortex, and increased striatum and limbic activity underlie mania (13–21), although conflicting findings are also reported (18, 22, 23). Baseline activity in the ventrolateral prefrontal and anterior cingulate cortices may predict manic symptom improvement following treatment, although the number of studies are few and have not typically looked longitudinally at neural responses to treatment (21, 24, 25). Adding to activation studies, investigations are emerging that suggest mania is related to disruptions in functional coupling between the ventral prefrontal and anterior cingulate cortices with amygdala (26–28) and striatum (29, 30). How these differences relate to treatment response in bipolar I disorder is not known.

This report is a secondary analysis of a previously published dataset that identified neural activation differences in subcortical and amygdala regions between individuals with bipolar disorder who did, compared to those who did not, achieve remission following eight

weeks of treatment. Individuals were imaged during their first manic episode and then pseudo-randomized to open-label treatment with either quetiapine or lithium (21). This report extends the prior publication as it evaluates functional connectivity among regions of interest, rather than activation. Specifically, the aim of the current analysis was to assess differences in amygdala and caudate functional connectivity with anterior cingulate and ventrolateral prefrontal cortices while viewing negative emotional stimuli and then determine if differences distinguished individuals who did or did not remit with treatment. Participants completed the Continuous Performance fMRI Task with Emotional and Neutral Distractors (CPT-END) at baseline and following eight weeks of treatment (31). We used the CPT-END as our paradigm of interest as the emotional distractors have been reliably shown to elicit responses in ventral emotional networks of interest, in which we hypothesize alterations in these networks relate to the emergence of mania (12, 21). Specific regions of interest (ROIs) were chosen based on the activation analysis results (18, 21). The primary goal of this secondary analysis was to identify differences in connectivity to emotional distractors that may relate to variation in treatment response. Studying treatment response following a first-manic episode has many strengths including avoiding disease-related confounds (e.g. multiple mood episodes contributing to neural differences) and minimizing disease heterogeneity of the sample. Based on the considerations reviewed, we hypothesized that mania would be associated with decreased amygdala and striatal functional connectivity with the anterior cingulate cortex and the ventrolateral prefrontal cortex, suggesting decreased prefrontal modulation of limbic and striatum structures, with remitters showing greater baseline and recovery of functional connectivity (i.e. less loss of functional connectivity and more prefrontal modulation of amygdala and caudate) compared to non-remitters.

MATERIALS AND METHODS

Participants

As previously described [13], participants in the bipolar group were recruited during their first manic or mixed episode through the University of Cincinnati Bipolar Disorder Imaging and Treatment Research Center and identified from hospitalizations and, rarely, outpatient assessments. Diagnostic assessments and mood state were conducted using the Structured Clinical Interview for DSM-IV, Patient version (SCID-P, (32)) or the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS, (33)). Additional assessments included the Addiction Severity Index to further assess substance use (34), Family Interview for Genetic Studies to assess family history (35), and the Young Mania Rating Scale (YMRS, (36)) and the Hamilton Depression Rating Scale (HDRS, (37)) to assess past week manic and depression symptoms, respectively. Participants with bipolar disorder met DSM-IV criteria for bipolar I disorder, were currently experiencing their first manic or mixed mood state, had ≤2 past depression episodes, had no prior psychiatric hospitalizations, had <3 months of lifetime psychotropic medication use (except for a few cases of longer stimulant exposure), and were not taking active psychotropic medication for at least two weeks prior to study enrollment. Healthy comparison participants had no history of an Axis I psychiatric disorder and no first-degree relative with bipolar or psychotic disorders. Across all participants, there was no history

of substance dependence within 3 months prior to enrollment, no presence/history of medical or neurological disorders that could impact fMRI, no contraindications to having a MRI scan, and no history of developmental delays with all participants having a full-scale IQ score ≥85. All participants provided written informed consent, or assent with parents providing written informed consent in participants <18 years of age. A total of 68 participants were identified as bipolar disorder type I experiencing their first manic episode. As the aim of this study was to identify differences in functional connectivity at baseline between remitters and non-remitters, only those who completed eight weeks of treatment and the follow-up scan were included in the planned analysis. This left our final bipolar disorder group at 42 participants (14 to 35 years of age). Full description of this dataset is published (21). Key study details for this analysis are described subsequently.

Treatment and Longitudinal Follow-up Protocol

Participants with bipolar disorder were pseudo-randomized to open-label treatment with either quetiapine or lithium as previously described (21). These medications were chosen because they are US Food and Drug Administration-approved treatments for mania in children and adults. A randomization schedule was used to assign treatment. However, participants could refuse either treatment and continue to participate if they agreed to the other medication, or if there was a contraindication to one of the treatments, the other treatment was prescribed. Treatment was initiated during hospitalization (following clinical assessments and baseline MRI scans) and then continued following discharge for the duration of study (i.e., eight weeks). Doses were adjust based on serum drug levels (lithium only: target was 0.8–1.2 meq/L) and tolerability and treatment response to both drugs. Adherence was based on self-report, pill counts, and serum levels as needed. Mood symptoms were assessed at baseline (i.e. YMRS, HDSR) and were re-assessed at weeks 1, 2, 4, 6, and 8. Both YMRS and HDRS total scores ≤10 for at least one week at the final week eight visit was defined as remission (21).

Image Acquisition, Preprocessing and Functional Connectivity Analysis

All scans were conducted on the same 4.0 Tesla Varian Unity INOVA Whole Body MRI/MRS system (Varian Inc., Palo Alto, CA, USA) at the University of Cincinnati's Center for Imaging Research as previously described (21). A high-resolution T1-weighted, three-dimensional brain scan was obtained to provide anatomic localization (38). Participants completed the Continuous Performance fMRI Task with Emotional and Neutral Distractors (CPT-END). The CPT-END task is a visual odd-ball paradigm in which 70% of cues are colored squares, 10% are circles (targets), 10% are neutral pictures, and 10% are emotionally unpleasant pictures (emotional distractors). Circles, neutral, and emotional pictures are presented pseudorandomly. Neutral and emotional pictures were acquired from the International Affective Picture System (IAPS, University of Florida, Gainesville, FL, USA) with chosen pictures based on rating criteria developed by Yamasaki et al. (31). Targets require a unique response on a button box while all other stimuli (squares, neutral and emotional pictures) require the same response. Two runs were completed by participants, with 158 visual cues per run presented at three-second intervals with stimuli presented for two seconds and a fixation cross presented for one second between cues. Emotional distractors in this task have been shown to reliably activate ventral emotional

networks of interest, while targets do not, in healthy participants and those with bipolar disorder (18, 21, 31). Whole-brain images were acquired with a T2*-weighted gradient-echo echoplanar imaging (EPI) pulse sequence with the following parameters: TR=3000ms, TE=25ms, field of view=256×256mm^2, matrix=64×64, 35 slices, slice thickness=4mm, and flip angle=90°.

All anatomical and functional images were preprocessed in SPM12 through the CONN toolbox (www.nitrc.org/projects/conn, (39)) preprocessing utility (40, 41). Smoothing was performed during initial reconstruction with a 7mm FWHM Hamming filter. Volumes were examined for outliers using the Artifact Detection Tools toolbox contained in CONN. Thresholds were set for spikes in global signal equal to or greater than 3 SDs from the mean or subject motion of ≥3mm. Regions of interest (ROIs) were previously defined and included the bilateral amygdala, caudate, anterior cingulate cortex, and ventrolateral prefrontal cortex (21). Regions of interest used in this study came from the automatic anatomical labeling atlas in AFNI as previously described (18, 21). The ventrolateral prefrontal cortex included Brodmann's area 45/47. The anterior cingulate cortex corresponded to the rostral anterior cingulate cortex (Brodmann's area 24/32). These ROIs were chosen based on support that they contribute to mood state differences in bipolar disorder and prior publication suggesting differences in function may relate to treatment response. An ROI-to-ROI bivariate correlation was conducted using CONN. This approach uses the CompCor method to reduce noise in the BOLD signal (42). Included in our list of confounders were white matter, cerebrospinal fluid, movement parameters, scrubbing, and effects of circle, emotional, and neutral stimuli. Quadratic detrending and a high-pass filter was applied at 0.008Hz to remove global low-frequency signals. Functional connectivity in response to emotional distractors was modeled at the first level. The Fisher-transformed correlation coefficients between each pair of ROIs were then extracted to a text file for further statistical analyses.

Statistical Analyses

Demographic and Clinical Characteristics—Detailed group comparisons in age, sex-ratio, comorbid diagnoses, mood symptoms at baseline and eight-week follow-up were previously published. For convenience these results are summarized in Table 1.

Neuroimaging Analyses

Baseline Functional Connectivity Analyses: A mixed model analysis was performed with group (remitter, non-remitter, healthy) as a between subject factor, amygdala hemisphere (left, right) as a repeated within subject factor, and age and sex included as covariates with interactions between covariates and group modeled in R studio (https://www.R-project.org/, (43)) using the linear mixed-effects models package (https://cran.r-project.org/web/packages/lme4/index.html). Dependent variables included the left and right rostral anterior cingulate cortex (modeled separately). A parallel mixed model analysis was conducted with the caudate as the seed region. There were no significant group by hemisphere interactions for either seed region and thus the interaction was subsequently removed from the models and the analyses repeated. Findings were considered significant at p≤0.025 [Bonferroni correction for two seed regions (amygdala and caudate)]. Following

a significant omnibus main effect of group, between group contrasts were performed to interpret the omnibus analysis. Between group results were considered significant at $p<0.05$, uncorrected. Identical analyses were conducted with the left and right ventrolateral prefrontal cortex as the dependent variables.

Remission-Associated Changes in Functional Connectivity Analyses: Change over time in functional connectivity among seed regions and dependent variables (bilateral rostral anterior cingulate and bilateral ventrolateral prefrontal cortex) was calculated for each participant (e.g. right caudate seed: right rostral anterior cingulate cortex week eight connectivity minus right caudate seed: right rostral baseline connectivity). Parallel models as conducted for the baseline comparison were repeated with change in connectivity as the dependent variable to investigate connectivity trajectories association with treatment response.

Exploratory Analysis Comparing Functional Connectivity Changes Associated with Lithium and Quetiapine Treatment: A mixed model analysis was performed in the bipolar disorder group, with group (remitter, non-remitter) and treatment (lithium, quetiapine) as between subject factors, amygdala hemisphere (left, right) as a repeated within subject factor, and age and sex included as covariates, and interactions between group and treatment modeled in R studio using the linear mixed-effects models package. Dependent variables included change over time in functional connectivity (calculated above) among the amygdala and the left and right rostral anterior cingulate cortex (modeled separately) as a significant remission-associated change in functional connectivity was observed between the amygdala and rostral anterior cingulate cortex. Significance was set as alpha≤0.05, uncorrected. Following a significant group by treatment interaction, post hoc analysis was conducted investigating effects of drug type in remitters and non-remitters separately).

Exploratory Analysis Comparing Relations between Functional Connectivity Differences (Baseline and Changes Over Time) with Mood Symptom Improvement: To explore predictors of mood symptom improvement, a mixed model analysis was conducted across participants in the bipolar disorder subgroups with amygdala-right rostral anterior cingulate cortex and caudate-right rostral anterior cingulate cortex at baseline along with amygdala-right rostral anterior cingulate cortex and amygdala-left rostral anterior cingulate cortex change over time as independent between subjects variables, hemisphere of seed region as a within subject repeated variable, and age and sex included as covariates. These independent variables were chosen following observing significant effects of remitter status at baseline in functional connectivity in these connections or significant effects of remission or treatment on change in functional connectivity between these connections from above analyses. For manic symptoms, baseline YMRS score was also included as an independent variable with follow-up YMRS scores as the dependent variable. For depression symptoms, baseline HDRS score was included as an additional independent variable with follow-up HDRS scores as the dependent variable. Results from these exploratory analyses were considered significant at alpha<0.05, uncorrected.

RESULTS

Demographic and Clinical Characteristics

Demographics and clinical characteristics were previously published (21) and are summarized in Table 1. Participants who remitted were younger than those who did not (d=1.1) and the bipolar group overall was younger than healthy participants (d=0.7), so age was covaried in analyses. Both remitter and non-remitter groups had similar YMRS and HDRS scores at baseline but significantly differed in scores at week eight; with remitters showing lower YMRS and HDRS scores by definition. There was no difference in presence of comorbidities (ADHD, anxiety disorders, or PTSD) or history of alcohol or substance abuse/dependence between bipolar disorder subgroups.

Neuroimaging Analyses

Baseline Functional Connectivity Data Analyses—A significant group effect was observed for caudate connectivity with the right rostral anterior cingulate cortex ($F_{(6,160)}$= 5.1, p=0.007, Figure 1A). When comparing subgroups, a medium effect size was noted between non-remitters and healthy subjects, in which non-remitters showed a significant increase in positive connectivity between the caudate and right rostral anterior cingulate cortex (d=0.5, p=0.002). Specifically, non-remitters showed greater positive functional coupling compared to healthy subjects who showed minimal functional connectivity between the caudate and right rostral anterior cingulate cortex. Other contrasts showed weak effects (non-remitters vs. remitters: d=0.2, p=0.16; remitters vs. healthy subjects: d=0.2, p=0.18). A significant effect of group was also observed for amygdala connectivity with the right rostral anterior cingulate cortex ($F_{(6,160)}$=4.2, p=0.017, Figure 1B). When comparing groups, a medium effect size was noted between non-remitters and healthy subjects, in which non-remitters showed a loss of negative connectivity between amygdala and right rostral anterior cingulate cortex (d=0.4, p=0.006) compared to healthy subjects, i.e. connectivity was closer to zero in non-remitters while controls show greater negative functional coupling. Other contrasts showed smaller effects (non-remitters vs. remitters: d=0.1, p=0.45; remitters vs. healthy subjects: d=0.3, p=0.09) compared to healthy subjects. There were no significant group by seed hemisphere interactions or significant effects of age or sex (for either seed region for the right rostral anterior cingulate cortex). There were no significant differences between groups or group by hemisphere interactions when investigating functional connectivity between amygdala or caudate with the left rostral anterior cingulate cortex (Figure 1 C,D) or the left or right vlPFC (see supplemental Figure 1).

Remission-Associated Changes in Functional Connectivity Analyses—An effect of group was observed for change in amygdala connectivity with the left rostral anterior cingulate cortex ($F_{(6,160)}$= 3.8, p=0.024, Figure 2). When comparing groups, a medium effect size was noted between remitters and healthy subjects (d=0.4, p=0.01), and between remitters and non-remitters (d=0.4, p=0.02), in which remitters showed an increase in negative connectivity over time. No other main effect of group or group by hemisphere interactions were observed when investigating change over time between seed regions and dependent variables.

Exploratory Analysis Comparing Functional Connectivity Changes Associated with Lithium and Quetiapine Treatment—A significant bipolar subgroup by drug interaction was observed for changes in amygdala connectivity with the right rostral anterior cingulate cortex ($F_{(5,77)}$= 6.1, p=0.02, Figure 3A). Specifically, in remitters quetiapine treatment was associated with an increase in negative connectivity compared to lithium treatment (d=1.5, p=0.009). There was no difference in change in functional connectivity between non-remitters taking lithium and quetiapine (p=0.14). A significant group by drug interaction was not observed for the left rostral anterior cingulate cortex ($F_{(5,77)}$= 4.0, p=0.06, Figure 3B).

Exploratory Analysis Comparing Relations between Functional Connectivity Differences (Baseline and Changes Over Time) with Mood Symptom Improvement—Lower follow-up YMRS score was associated with greater negative connectivity at baseline between the amygdala and the right rostral anterior cingulate cortex (β=10.2, p=0.04). Baseline YMRS score and caudate to right rostral anterior cingulate cortex functional connectivity at baseline, nor changes over time in amygdala functional connectivity with the left or right rostral anterior cingulate cortex, sex, or age was associated with follow-up YMRS score (all p's>0.1). Lower follow-up HDRS score was associated with lower positive functional coupling between the caudate and the right rostral anterior cingulate cortex (β=8.8, p=0.015). Baseline HDRS score and amygdala to right rostral anterior cingulate cortex functional connectivity at baseline, nor changes over time in amygdala functional connectivity with the left or right rostral anterior cingulate cortex, or sex was associated with follow-up HDRS score (all p's>0.1). However, lower age was associated with lower HDRS score at follow-up (β= 0.73, p=0.000002).

DISCUSSION

Findings support our hypothesis that mania is associated with loss of amygdala functional connectivity with the anterior cingulate cortex, possibly representing less modulation over limbic regions, but does not support the same hypothesis with ventrolateral prefrontal cortex. In this analysis, differences in rostral anterior cingulate cortex, but not ventrolateral prefrontal cortex, connectivity with caudate and amygdala were observed in individuals with bipolar disorder during their first acute manic episode, with differences being more pronounced in the non-remitter group. Contrary to our prediction, we observed increased functional connectivity between rostral anterior cingulate and caudate during mania with non-remitters driving this finding. This observation could represent an attentional bias towards reward stimuli and increased sensitivity in behavioral activation systems during mania that is greater when other compensation fails, i.e., leading to poor treatment improvement (44, 45). We hypothesized treatment would minimize differences in remitters compared to healthy comparison individuals, with remitters looking more like healthy comparison individuals following treatment as previously reported (46). Supporting our hypothesis, remitters showed an increase in negative connectivity between amygdala and left rostral anterior cingulate cortex with their connectivity pattern at week eight looking similar to the healthy comparison group's connectivity at baseline, suggesting neural trajectories that may be associated with symptom improvement. We previously reported differences in

activation of the ventrolateral prefrontal cortex in people with bipolar disorder during a first manic episode, with greater activation in the ventrolateral prefrontal cortex observed in remitters (21), possibly suggesting that greater prefrontal recruitment at baseline is associated with increased treatment response. We did not observed differences between groups in functional connectivity of ventrolateral prefrontal cortex with either amygdala or caudate. Some studies of treatment response in unipolar depression have identified greater functional connectivity, i.e. a functional connectivity pattern more similar to healthy comparison participants, relates to treatment response (47). Similarly, in the current study, remitters looked more similar to healthy comparison participants, as compared to non-remitters. This possibly suggests that despite activation differences previously reported in remitters (21), connectivity in the remitters remains largely intact—or may be compensating for regional activity differences, e.g. greater prefrontal recruitment to regulate limbic and striatal response—at this point in their illness. This may contribute to treatment responsiveness. More research is needed, with longer duration of follow-up (beyond eight weeks), to discern if greater treatment duration would create more responders over time so non-remitters would also trend to look more like the healthy comparison group.

Several limitations should be noted. As previously discussed (21), we were underpowered to investigate differences between treatments. Exploratory analysis suggests quetiapine, but not lithium, is associated with an increase in negative connectivity between the amygdala and rostral anterior cingulate cortex in the remitter group, but not the non-remitter group. This finding should be interpreted with extreme caution because treatment subgroups were small. Therefore, it is difficult to discern with certainty in the present sample whether one or the other treatment may be driving the observed connectivity effects. Likewise, while exploratory analysis suggested baseline differences in amygdala to right rostral anterior cingulate cortex and caudate to right rostral anterior cingulate cortex functional connectivity (i.e. functional connectivity patterns that looked more like the healthy comparison group) best predicted follow-up manic and depression symptoms, respectively, these results should be considered hypothesis generating. Future studies with greater power are needed to better understand interactions between treatment, baseline functional connectivity differences that may predict response, and changes in functional connectivity over time associated with remission. We hypothesize that functional connectivity during first episode mania coincides with differences in *a priori* regions that underlie emotional regulation. Therefore, we focused on emotional distractors in the CPT-END task and primary hypothesis testing did not include investigating differences in response to targets. While not shown, there were no significant differences between groups when exploring differences in functional connectivity to targets. This null finding could be biased by *a priori* ROIs. Future work is needed investigating functional connectivity during mania among alternate regions that contribute to higher order executive functioning. Additionally, there was a significant difference in age between groups, with remitters being younger than non-remitters. However, we do not think this contributed to the connectivity findings as age effects on key contrasts were minimal and the majority of subjects were older teenagers/young adults. Moreover, we controlled for age across all analyses. Finally, this study did not include a placebo control group which limits our interpretations of treatment response overall. Future studies specifically designed to examine the impact of development are warranted.

Despite these limitations, this study contributes to evidence suggesting response to treatment of the manic phase of bipolar I disorder results from changes in functional neural systems that subserve emotional regulation and reward processing. Differences in functional connectivity observed in bipolar individuals who did not remit following eight weeks of treatment suggests potential targets to predict treatment response. More longitudinal study is needed early in the course of bipolar disorder to improve our understanding of the brain basis of early disease course to inform treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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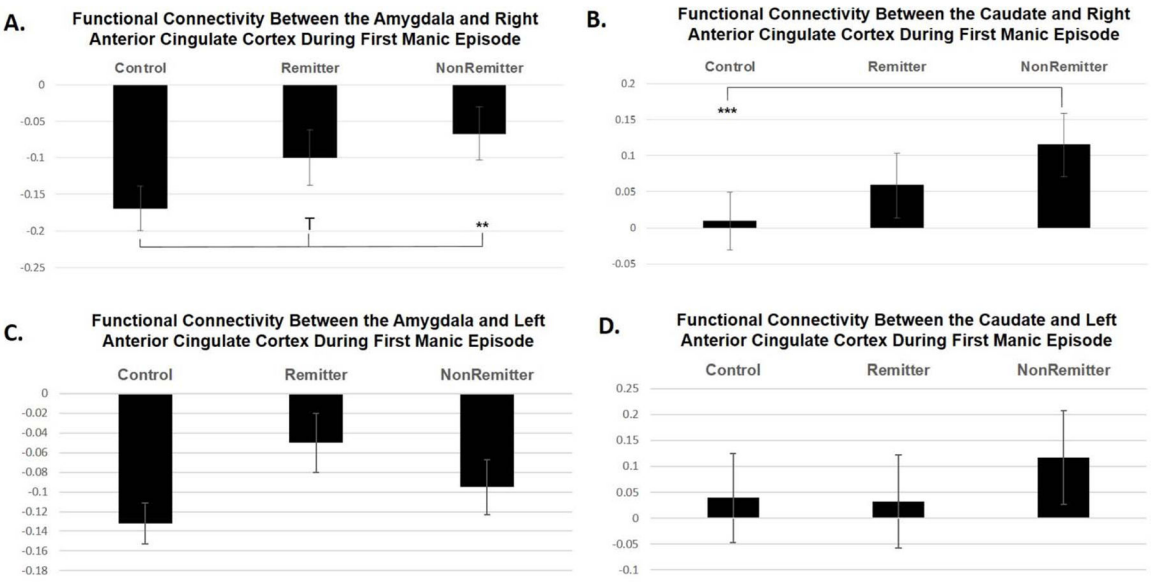

Figure 1.

Functional Connectivity of the Right Anterior Cingulate Cortex with the Caudate and Amygdala during Acute Mania Distinguishes Non-remitters. **(1A)** Non-remitters showed a loss of negative connectivity between the amygdala and right anterior cingulate cortex, compared to healthy comparison participants. Mean functional connectivity of the remitters fell between the non-remitters and healthy comparison participants, although remitters did not significantly differ from either group. **(1B)** Non-remitters showed an increase in positive connectivity between the caudate and right anterior cingulate cortex, compared to healthy comparison participants. Mean functional connectivity of the remitters fell between the non-remitters and healthy comparison participants, although remitters did not significantly differ from either group. There was no significant effect of group when comparing functional connectivity between the left anterior cingulate cortex and either the amygdala **(1C)** or the caudate **(1D)**. ** $p \leq 0.01$ uncorrected, *** $p \leq 0.005$ uncorrected, T $p=0.09$ uncorrected.

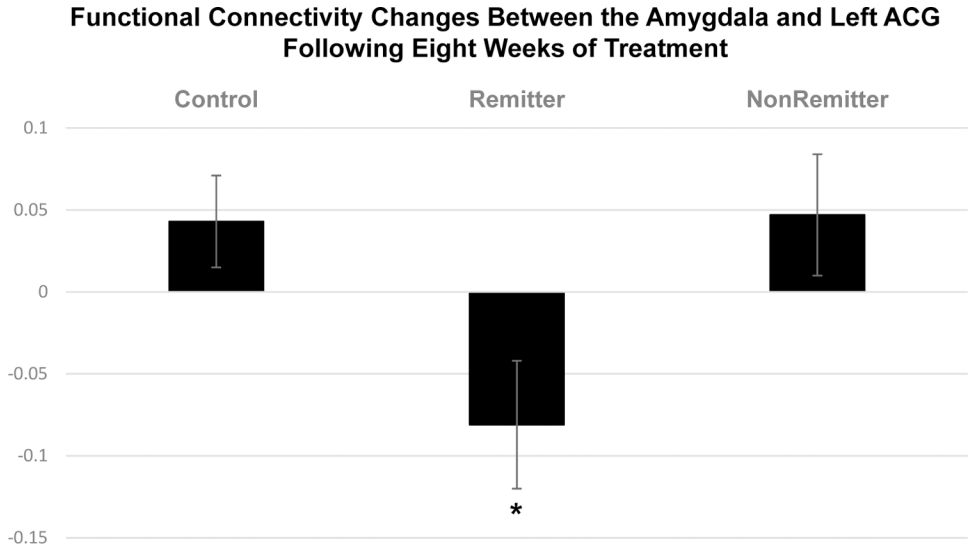

Figure 2.

Remitters differed in amygdala to the left anterior cingulate cortex functional connectivity changes (following eight weeks of treatment) compared to other groups. Specifically, when comparing change over time (week eight functional connectivity minus baseline functional connectivity) remitters showed an increase in negative connectivity. This was not observed in other groups. * $p \leq 0.05$ uncorrected, ** $p \leq 0.01$.

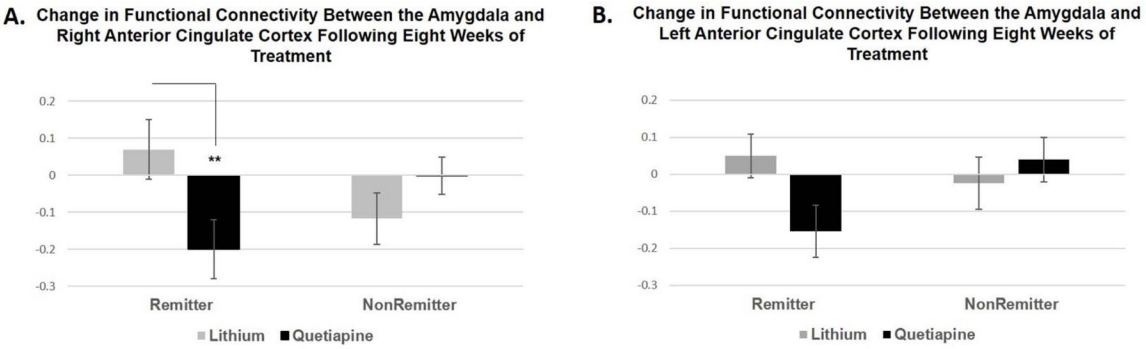

Figure 3.

In remitters quetiapine, compared to lithium, treatment was associated with an increase in negative connectivity between the amygdala and right rostral anterior cingulate cortex. There was no difference in change in functional connectivity between non-remitters taking lithium and quetiapine. Response to drugs did not differ between groups when investigating connectivity between the amygdala and left rostral anterior cingulate cortex. ** $p \leq 0.01$.

Table 1.

Demographic and Clinical Characteristics of 42 participants with bipolar disorder during their first manic/mixed episode, stratified by those who remitted, compared to those that did not, following eight weeks of treatment, and 41 healthy comparison participants.

	Bipolar Disorder		
Clinical Characteristics	**Remitted (n=21)**	**Nonremitted (n=21)**	**Healthy Participants (n=41)**
Age, years, mean (SD)[a,b]	16 (2)	21 (6)	22 (6)
Sex, male, n (%)	9 (43)	8 (38)	20 (49)
Comorbidities, n (%)[1]			
ADHD	8 (38)	3 (15)	-
PTSD	1 (5)	2 (10)	-
Separation Anxiety Disorder	1 (5)	0 (0)	-
History of Alcohol Dependence[2]	1 (5)	1 (5)	-
History Substance Abuse[2]	0 (0)	3 (15)	-
History of Substance Dependence[2]	1 (5)	0 (0)	-
Baseline YMRS, mean (SD)[c]	25 (5)	25 (5)	1 (1)
Week 8 YMRS, mean (SD)[c,d]	5 (3)	15 (8)	1 (1)
Baseline HDRS, mean (SD)[c]	13 (7)	15 (8)	1 (2)
Week 8 HDRS, mean (SD)[c,e]	4 (2)	14 (7)	1 (2)
Treatment assignment, n (%)			
Lithium	11 (52)	8 (38)	n/a
Quetapine	10 (48)	13 (62)	n/a

HDRS, 17-item Hamilton Depression Rating Scale total score; SD, standard deviation; YMRS, Young Mania Rating Scale total score.

[a]Signficant difference: remitted vs non remitted, t(40)=3.3, P=.002.

[b]Significant difference, bipolar disorder vs healthy participants, t(81)=3.2, P=.002.

[c]Significant difference, bipolar disorder vs healthy participants (by definition), t(81)=6.2, P<.0001.

[d]Significant difference, remitted vs non remitted, t(40)=5.0, P<.0001.

[e]Significant difference, remitted vs non remitted, t(40)=6.8, P<.0001.

[1]One participant in the Nonremitted group did not have data on comorbidities. Percentage reported is based on participants with comorbidity data.

[2]No participant had current alcohol or substance abuse/dependence.