**Article Title:** State Dependent Cortico-Amygdala Circuit Dysfunction in Bipolar Disorder

This study tests the hypothesis that bipolar mania is associated with altered connectivity between cortical regions thought to regulate emotion and subcortical structures such as the amygdala. 28 subjects with bipolar disorder in a manic state, 24 different bipolar subjects in a euthymic state, and 23 matched healthy comparison subjects underwent resting state fMRI scans. Bipolar mania was differentiated from euthymia by decreased functional connectivity between the amygdala and anterior cingulate cortex (ACC). Increased connectivity was observed between amygdala and dorsal frontal cortical structures that are normally anti-correlated in emotion regulation tasks. Compared to bipolar subjects in a euthymic state, subjects in the manic state demonstrate disrupted functional connectivity between brain regions involved in "top-down" regulation of emotion and the amygdala. This disruption of activity in neural circuits involved in emotion may underlie the emotional dysregulation inherent to a bipolar manic episode.

*Overall comment:* At the moment an increasing number of papers are looking at functional connectivity in bipolar disorder as this feature may act as a potential neural marker of bipolar disorder. As the authors point out, so far studies have looked at state-dependent resting state measures but have not compared connectivity measures across phases of bipolar disease (as the authors did in this study). Despite this novel component this study does not provide direct evidence that reduced connectivity is indeed linked to reduced emotional regulation. This could have been easily achieved by collecting behavioral data outside the scanner e.g. administering a cognitive task assessing emotional regulation in participants who are euthymic, manic and depressed. This finding would have informed us on whether 1. Connectivity is mood dependent but does not affect the behavioral output, 2. Mood affects cognition and has an impact on connectivity.

I would suggest that the authors consider/address the following points.

1. A better definition of emotional regulation/mood regulation. For instance, are they talking about internally and/or externally induced mood changes and how the individuals cope with it? They could add references to studies focusing on mood induction for instance.
2. If we want to study the neural network involved in emotional regulation, it is necessary to study the task state fMRI too. If the authors do not have task related fMRI measures it would be important to at the very least discuss this limitation. Further there may be individual differences in the activation of the resting networks underlying emotional regulation. How do the authors cope with this? Please discuss further.
3. The authors do not mention whether they assessed the individuals’ mental state (e.g. tired, excited) during the neuroimaging evaluation as it could have affected functional connectivity too. Once again how did the authors cope with this and could they discuss this further in the discussion.
4. A very last problem is related to the cognitive status of the participants (e.g. memory) as we don’t know whether and/or to what extent participants were cognitively impaired. By this I am referring to neuropsychological/pen-paper tasks and not only IQ estimates.