Background: Symptomatic phases in bipolar disorder (BD) were previously hypothesized to result from a hypersensitive behavioral activation system (BAS) being overly alert to potential rewards. However, studies on the neuronal underpinnings of reward anticipation in BD are scarce with contradictory findings and possibly confounded by effects of dopaminergic medication, necessitating further research on dysfunctional motivation as possible endophenotype for BD. Moreover, its role as a vulnerability marker for BD is also unclear. Methods: Neural activation during reward anticipation was assessed in 16 BD-I patients and 19 healthy first-degree relatives and compared to respective control groups. Further, reward proneness, using the BIS/BAS questionnaire, and its relationship to neural reward anticipation was being investigated. Results: BD-I patients displayed greater anterior cingulate cortex (ACC) activity during reward anticipation and an elevated BIS total score compared to controls, with a positive relationship between the two measures. There were no neuronal or self-report group differences between relatives and controls. Limitations: Due to the experimental design the role of the ACC during receipt of reward remains unknown, sample sizes were rather small, and patients were not naïve to dopaminergic drugs, making an exclusion of medication effects on findings impossible. Conclusions: Our findings give new insights on reward anticipation in BD. BD-I patients showed larger recruitment of the ACC rather than ventral striatum compared to controls during reward anticipation, possibly to down-regulate hyperactive limbic reward regions. This activation seems to be a consequence of rather than a vulnerability marker for the disorder.

Feedback: this study has a number of strengths. Conceptually, the role of impulsivity in bipolar disorder has been broadly investigated but we still don’t know whether it is a consequence or vulnerability marker of the disease. Additionally, impulsivity is often viewed as a unidimensional, rather than a multifaceted concept. Correlations between self-rated impulsivity and behavioral measures of impulsivity are often inconclusive, and the neural correlates of reward-related impulsivity are poorly investigated. I have a few methodological questions and comments regarding the discussion section that should be addressed to improve the understanding and interpretation of these findings.

-Introduction: could you please clarify what a high BIS scores means in BD. How does the BIS/BAS scale compare to the widely used BIS scale (Barratt Impulsivity scale). Swann et al.’s work on impulsivity and bipolar disorder is based on this scale. how do you interpret these findings? please mention or address this in your introduction.

-fMRI task on pages 3 and 4. Please provide a list of regions that were activated in Starke et al. ‘s task. In figure 1 please provide times of presentation of each component of the task and overall duration of the task. How were participants’ responses recorded e.g. button box, could answer using 1 or 2 hands etc. ). Which software did you use to present the task in the scanner (e.g. eprime, matlab). Did you have a practice task training prior to the scanning session?

-could you please clarify if your task was presented using a block paradigm, and when you mention that “ the response window could be enlarged to 1.5s”, do you mean that the task RTs varied depending on individuals’ responses? If so how did you collect data (e.g.how did you synchronize the behavioral tasks with the scanning?).

-1.3..1 please explain why you conducted t-tests and not ANOVAs when comparing behavior and fMRI data across groups. Why did you compare BD to HC, and relatives to their HCs and not all together? why did you use 2 different control group populations? I am not sure how to compare/intepret the findings given that the control populations were not the same and we are not comparing groups simultaneously.

-which covariates did you use? e.g. age, gender? Alternatively, if you didn’t could you please explain why

-could you please clarify how you created your masks (not sure why you refer to the VS mask only). Did you create them based on activation observed in HCs and then extracted beta parameters for all the groups? or did you base them on comparisons between BD vs HC? please provide additional details.

-Did you define multiple a priori ROIs, and then used small volume corrections to correct for multiple comparisons only in these predefined regions. Or did you analyze the data whole-brain (i.e. without ROIs), then saw some significant clusters and corrected for your p-values for FWE?

-could you please provide a statistical map (figure) comparing BD vs HC, and BD relatives vs HC.

-I am also unsure whether you entered BIS/BAS as a regressor? Or did you correlate BIS/BAS scores to the betas of your ROIs.

-A related question is: did you consider comparing BD with high BIS/BAS scores to BD with low scores? Please address this in your discussion.

-did you correlate BIS/BAS scores with latencies/accuracy on the task? Please address this.

-could you please provide RTs and mean budget across groups, along with effect sizes.

-could you please clarify what you mean on page 10 when you state “carried a genetic risk…rather than having a risk due to their behavioral styles”. I assume “behavioral style” refers to impulsivity/performance on the reward task? Please consider reformulating.

-table 3. Could you please provide the cluster size of your ROIs? Did you define it to start with or not? Please clarify in your manuscript.

-you mention that biofeedback may help to “upregulate ACC”. Is there evidence that this works? and isn’t this neurofeedback rather than biofeedback (e.g. heart rate, skin conductance?).

Minor comments

-“Highlights” should include one sentence referring to relatives and comparisons with bipolar patients

-abstract: it doesn’t mention fMRI, age group, and whether the control groups were age/gender matched. Mention of primary fMRI analyses that were performed and software (SPM) may be helpful. Also it should be defined that patients were “euthymic BD”, not medicated at the time of testing”. BIS/BAS is not properly explained (BAS is, but not BIS).

-typo in 1.1. patients were (i) age… “ replace with aged

-page 9. You mention that you divided 0.05 by 3 (0.05/3) but not sure why. Is 3 referring to the number of groups? I thought you performed separate analyses.

-table 2 I noticed that you have individuals with early/late BD onset and remission times that ranged from .17 to 22.08. did you consider covarying for or looking at BOLD differences related to these clinical measures.