Manuscript Details

Manuscript number JAD_2016_1711

Title Reward anticipation revisited- evidence from an fMRI study in euthymic bipolar I patients and healthy first-degree relatives

Abstract

Background: Symptomatic phases in bipolar disorder (BD) are hypothesized to result from a hypersensitive behavioral activation system (BAS) being sensitive 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 in BD. Moreover, its role as vulnerability marker for BD is unclear. Methods: Functional imaging was conducted in16 euthymic BD-I patients free from dopaminergic medication and 19 healthy first-degree relatives using a monetary incentive delay task and compared to parallelized control groups. Further, reward proneness, using the BIS/BAS questionnaire, and its relationship to neural reward anticipation was investigated. Results: BD-I patients displayed greater anterior cingulate cortex (ACC) activity during reward anticipation and higher BIS total scores compared to controls, with a positive relationship between the two measures. There were no neural 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 rated themselves as more risk avoidant and 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.

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Adressing the reviewers' comments

Reviewer 1

Methods and Results

1. *The participants are well characterized, but in addition to calculating current medication load it would be helpful to have reported previous exposure to dopaminergic agents. The authors note that prior exposure could have influenced findings but more information as to the degree of prior exposure would be helpful in weighing this potential issue.*

Answer: This is an important remark. We fully agree with the reviewer that reporting this information might be helpful in interpreting results. However, it is very difficult to assess previous medication validly on the basis of the patients' self-reports. As we had no access to medical files of the patients from the hospital or treating physician, we do not have full information on previous medication for the patients and could therefore not include it in the study. However, we refer to this shortcoming in the discussion (page 13, lines 398-403).

2. *In addition, the authors note that substance use disorders were exclusionary but a measure of exposure to illicits that might not have met formal criteria for a disorder might be important—even sub-pathological use could potentially affect results. It would also be helpful to report nicotine (e.g. smoking) exposure.*

Answer: We assessed the regular usage of common drugs of abuse, namely cannabis, amphetamines, ecstasy, crack/cocaine, heroin, opioids/opiates, hallucinogens, inhalant drugs (e.g. paint, glue), and sleeping pills. In addition, the AUDIT and FTND questionnaires were being assessed. Information on patient's usage of alcohol, nicotine and caffeine consumption was added to table 1 and the questionnaire scores in table 2. We also added information on drug usage on page 9 (lines 250-261) and added information on the above mentioned questionnaires in the methods section of the manuscript (page 6, lines 160-174).

3. *The authors report that the affected relative of the individuals included in the first-degree relative group were "invited to a clinical assessment for diagnostic verification" but do not state how diagnoses in these individuals were verified*

Answer: Indeed, we did not clearly state how these patients were diagnose and now clarified this in the methods section on page 4, lines 101-102. These patients were assessed using the same observer-rated and self-report instruments as bipolar patients included in the study with the SCID I and II being the most important to verify the diagnosis.

4. *In table 3, the authors present data from the healthy subjects showing activation in several regions not included in the ROIs used for the between-group comparisons. As they note in the discussion, their task differs in some important ways from some previous studies; it might therefore make sense to use the data from their healthy subject analysis to at least partially drive their choice of regions.*

Answer: We agree with the reviewer that this is a common approach to analysing fMRI data of mainly unknown paradigms. The paradigm used in the current manuscript is a well-established MID task by Kirsch et al. and has been assessed in healthy participants before (e.g. Plichta, et al., 2012; Kirsch et al., 2006; Plichta et al., 2013). Therefore, we chose our

ROIs based on the activation clusters observed in previous studies using the same paradigm in healthy controls. Also, using the same controls for the analysis of regions of interest and later for the group comparisons would result in double dipping, biasing the obtained results. Therefore we decided to use the ROIs based on the previous, independent literature. We, however, included table 3 in the manuscript in order to prove the validity of the task in our study (using a different sample and different scanner than the references indicated above) in eliciting activations in the regions expected from the literature. We reformulated the paragraph describing our approach on page 8, lines 226-229, hoping that it thereby is formulated more clearly.

Discussion

5. *Their suggestion that greater ACC activation might be the result of conflict brought on by memories of the poor outcomes associated with impulsivity in other contexts seems to be a bit of a stretch assuming as it does that euthymic participants will equate their pressing buttons in a reward task to more dysfunctional activities undertaken while manic. The authors' alternate suggestion of top-down control of a hyperactive limbic network seems more reasonable—and is the explanation that they chose for the abstract.*

Answer: We adapted the respective paragraph of the discussion by removing the mentioned hypotheses and by reformulating it (page 11, lines 328-334).

6. *The authors might be more modest in their interpretation of the lack of findings with regard to the first-degree relatives. The fairly small sample size might have obscured differences if relatives of patients with bipolar disorder show smaller activation than individuals who have manifest the illness. Furthermore, the range of ages in the relatives recruited is sufficiently large to suggest that the group might be fairly heterogeneous, including individuals who have not yet experienced a first episode, as well as older individuals who did not inherit vulnerability genes.*

Answer: We fully agree with reviewer 1 and reformulated the paragraph on findings in first-degree relatives on p. 12, lines 386-388 in the manuscript.

Reviewer 2

Introduction

1. *Introduction: could you please clarify what a high BIS scores means in BD.*

Answer: According to the theory by Gray et al., 1991 the BIS is related to harm avoidance and a high trait BIS will result in more anxious behavior in animals and humans. However, there is no theoretical background with regard to the role of a high BIS in BD. The BAS dysregulation theory by Depue and Iacono, 1989, as well as the elaboration by Urosevic and colleagues from 2008 both do not make assumptions on the role of the BIS in BD and assume trait BIS levels to be "normal" in BD, not affecting motivational regulation in these patients. We included this clarification in the introduction of the revised manuscript (page 2, lines18-22). Further, this topic was picked up again in the discussion of the manuscript on page 12, lines 415-419.

2. *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.

Answer: We would like to thank the reviewer for this question and remark, which we addressed in the introduction (page 2, lines 23-30).

Methods

1. *fMRI task on pages 3 and 4. Please provide a list of regions that were activated in Starke et al. 's task.*

Answer: The task used by Stark et al. is the same one as applied in the current study. It is an adaptation of the original reward anticipation task by Kirsch et al., 2003 mentioned in the manuscript on page 5, lines 120-121, because it also contains a loss condition. We now added the regions activated in Stark et al.'s study which investigated individuals at risk for ADHD. These were similar regions for the win and loss condition (i.e. NAcc, ACC, OFC, thalamus) and only an activation in the NAcc for the verbal condition in Starke et al.'s paper, as indicated on page 5, line 121.

2. *In figure 1 please provide times of presentation of each component of the task and overall duration of the task.*

Answer: A revised version of figure 1 has been added to the manuscript.

3. *How were participants' responses recorded e.g. button box, could answer using 1 or 2 hands etc.)*

Answer: Thank you for pointing out this unclarity. We missed this information in the former version of the manuscript. We now added it on page 5, lines 126-127.

4. *Which software did you use to present the task in the scanner (e.g. eprime, matlab).*

Answer: This information has now been added on page 5, lines 122-123 of the manuscript.

5. *Did you have a practice task training prior to the scanning session?*

Answer: No, there was no practice trial prior to the scanning session, because the task is fairly simple and we did not want to possibly confound results with a practice effect on the task. This information has been added to the manuscript's method section, page 5, line 123.

6. *Could you please clarify if your task was presented using a block paradigm*

Answer: The task was presented using an event-related design, in which conditions were alternated in pseudo-randomized order. We clarified this in the methods section on page 4 (lines 132-133).

7. *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?).*

Answer: The task was adaptive in that the response window, within which participants had to make their response, was adapted depending on the RT of the previous trial. This response window started out at 300ms. If participants responded within these 300ms, the time to respond was reduced by 5% on the next trial, while it was increased by 5% if they took longer than 300ms to respond. This was done for all trials. Participants first saw an arrow indicating possible win, loss, verbal feedback or a neutral arrow, which served as baseline condition and did not require any action. This was followed by a flash for all arrows, except for the baseline condition. Participants were required to press a button as fast as possible upon presentation of the flash. The flash was an event programmed so that a button press would terminate it. There was a rule with regard to the feedback that would then be displayed depending on whether the event was terminated within the time frame or not. Thus, this RT window is important for the feedback, which will be given following a button press. Four events were modelled, including the onset times of the arrow in each condition namely the win condition, loss, verbal, and a neutral baseline condition. In addition, the occurrence of the flash light and 6 motion regressors were modelled as covariates of no interest in order to remove possible influences of the flash light and motion on the experimental paradigm. Onsets of these events were fit into the model in an event-related fashion. Onsets for each event were calculated in relation to the onset of the session. Events were synchronized to the scanner by a trigger box. The regressors were modelled using a canonical HRF convolved with the stimulus onsets.

We rewrote this paragraph accordingly (however, more shortly) in the manuscript on page 5, lines 127-133 and page 8, lines 219-225..

8. *please explain why you conducted t-tests and not ANOVAs when comparing behavior and fMRI data across groups.*

Answer: For the comparison of the behavioral data from the reward paradigm, repeated-measures ANOVAs were being used, since here the same participants participated in multiple conditions of the task (i.e. win, loss, verbal). Group differences in final budget, however, were analyzed using t-tests, since it was the final budget summed over all conditions in the experiment per participant. For all other comparisons, independent samples t-tests were being chosen. A repeated-measures ANOVA would be underpowered in a rather small sample size as the current one due to the higher amount of degrees of freedom, compared to t-tests. We therefore chose to analyse the fMRI data analogous to previous studies using the same experimental paradigm (e.g., Ubl et al., 2015). Further, our hypothesis was concerned with the win-baseline contrast, so that we applied an independent samples t-test for the analysis of group differences in this contrast.

9. *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.*

Answer: Since patients and relatives differed in mean age and the ratio between male and female participants (table 1), it was not possible to match a control group of similar size to the mean ages and gender of both groups. Therefore, we decided to analyze BD patients and relatives separately, each with a parallelized control group (page 4, lines 87-102). Analyzing all groups together, adjusting for age and gender as covariates, might still not fully address possible effects due to these possible confounds. Therefore, similar to previous studies of our lab (Linke et al., 2013; Wessa et al., 2015) we chose the current approach in an attempt to have more unbiased results (see also page 5, lines 112-115).

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

Answer: We did not use any covariates in the current manuscript, since the control participants were parallelized to the patients/relatives with regard to age, gender, IQ and education and there were also no group differences on these variables in both samples. We did, however, repeat the analyses with HAM-D scores as covariate, since there was a significant group difference in sample 1 on this variable. This did not alter the found results, as described in the manuscript (page 10, lines 308-309).

11. *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.*

Answer: ROIs were built based on an atlas implemented in SPM. Therefore, the size and location of the ROIs taken from this atlas are standardized. Using this atlas for ROI creation is a common approach in well-established paradigms. We chose for this a priori ROI creation in order to prevent double dipping, as would be the case when looking at differences between BD and HC, followed by a ROI analyses in the found regions with activation differences.
This information is provided in the manuscript on page 6, last paragraph (lines 226-240):

"Afterwards, group differences were being investigated on regions of interest **(ROI) masks defined in the Wake Forest PickAtlas toolbox v2.3** (Lancaster, J.L., Summerlin, J.L., Rainey, L., Freitas, C.S., Fox, P.T., 1997; Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003) using two-sample t-tests and small volume correction (threshold of $p < .05$ and Bonferroni corrected for multiple testing)."

12. *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?*

Answer: The former suggestion is correct. We defined multiple distinct a priori ROIs based on the regions known to be activated by the specific condition from the literature using this task. We then used small volume correction to correct for multiple comparisons only in the ROIs a priorily determined, since these were the regions, in which we assumed to find activation. This approach is more theory-driven, in that we do not need to correct for all voxels in the brain, but only for those voxels in the ROIs of importance for the current task. Later, we also corrected for multiple testing, since we investigated multiple ROIs per condition, by using a Bonferroni correction to determine the adapted significance levels of our findings.

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

Answer: There is a figure for the win-baseline contrast comparing BD vs. HC attached to this article (figure 2), including also a bar graph of the mean beta weights in the ACC for BD vs. HC. All other figures displaying relatives vs. HC or loss-baseline/verbal-baseline would be empty brains, since there were no group differences in any clusters surviving multiple comparison correction for this sample or conditions, respectively. Thus, we did not add a figure of them to the manuscript.

14. *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.*

Answer: We planned to enter BIS/BAS scores into a regression analysis in SPM, as was stated in the methods section of the manuscript (page 7, lines 241-242). Since we did not find group differences in BAS total or subscale scores, we only entered the significantly different BIS score into the regression analysis. Thus, the BIS score was entered as covariate of interest into a simple regression, which determines whether there is a correlation between this covariate and the signal change in the win-baseline contrast across participants in sample 1. In our case, this analysis is similar to extracting betas from the ROIs and correlating them with BIS scores in e.g. SPSS. However, since values are subject to slight value changes due to rounding effects when extracted, it is less precise to perform analyses in SPSS than in SPM directly. That is why we chose for the latter option. We also précised our approach in the manuscript on page 9, lines 303-308.

Results and Discussion

1. *did you consider comparing BD with high BIS/BAS scores to BD with low scores? Please address this in your discussion.*

Answer: This is an interesting approach, but hard to conduct with such a small sample of BD patients as in the current study. There are no pre-defined cut-offs for high or low BIS/BAS scores, hence we would need to establish this first in a large sample of BD patients by looking at the scores of those patients 2-3 SD above the mean as a definition of a high BIS/BAS and those 2-3 SD below the mean for a definition of a low score. However, this is not possible with the current sample, thus we would need to determine an arbitrary cut-off ourselves. This approach has also been addressed now in the discussion on page 12, lines 415-419.

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

Answer: Participants had to respond within a certain time window for a reward (win condition) or the avoidance of punishment (loss condition). As such, mean reaction times for these trials were being computed per condition and the final budget obtained at the end of the experiment, before dummy trials occurred. An accurate response is therefore a response within the response window of a certain condition. However, since the length of the response window is dependent on participant's performance on the previous trial, participant's accuracy is not independent from the task design. As such, it is not straightforward to correlate BIS/BAS scores with accuracy on this task. This is why we chose not to include it in the current manuscript.

With regard to latency, we calculated the mean latency per condition and participant, meaning the mean time passing between the onset of the flash and the button press, which in our paradigm equals the mean RT for the different conditions. We then calculated the correlation between the mean RT's per condition with the BIS/BAS scores. For the entire sample 1, there was a negative correlation between mean RT on loss trials and BAS drive ($r = -.325$, $p = 0.041$), indicating a faster response in order to prevent punishment in those participants with high drive for reward obtainment, though this correlation was not significant anymore when looking at the participant groups separately. Further, there was a positive correlation between mean RT on verbal trials and BIS total score ($r = .459$, $p = .003$), indicating that a higher BIS score resulted in slower responses in the verbal condition. This finding was driven by patients in this sample, since it was only significant in this participant group (patients: $r = .504$, $r = .047$; controls: $r = .229$, $p = 283$), when analyzing patients and controls separately in sample 1. Thus, the more punishment avoidant these patients were, the slower they were in the verbal condition, maybe as a consequence of fear of being judged. However, when correcting for multiple testing (applying a Bonferroni correction with an adjusted alpha level of $p < .008$ (.05/6 correlations)), only the correlation between mean

RT on verbal trials and BIS total score remains significant. Notably though, there was no difference in this sample in the verbal condition with regard to mean RT or BOLD responses, thus this significant correlation is unlikely to explain the current findings. Therefore, we decided to exclude this analysis from the manuscript.

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

Answer: Mean RTs for both samples and all three conditions have been added to the manuscript, as well as effect sizes, denoted as "r" (page 8, lines 275-279 and 286-291).

4. *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.*

Answer: Thank you for this remark and for pointing out the lack of clarity in this issue. This phrase was indeed formulated misleading. We were referring to a high trait BAS in those participants at risk for the disorder and stated this now also more clearly in the manuscript (page 11, line 375).

5. *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.*

Answer: This table does not indicate ROIs, but rather all the regions activated in a whole-brain analysis with FWE-correction in all healthy controls that participated in the experiment (from sample 1 **and** 2). The specific anatomical location or size of the regions activated in this sample were not used for further analyses. We included the cluster size of activated ROIs in the manuscript in table 3. For the win-baseline and verbal-baseline contrast, we applied the ventral striatum mask described in the method's section in line 215-216, since this region is too small to find activation in it on a whole-brain level. We point to using this method as well in table 3.

6. *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?).*

Answer: Thank you very much for this valuable remark. Indeed, we were referring to neurofeedback in this passage and adapted the formulation now in the manuscript (page 12, line 437). There is evidence that the activation of various parts of the ACC can be successfully up-regulated, resulting e.g. in an increase of positive affect (Gröne et al., 2015), depending on the part of the ACC being upregulated. However, there is no evidence yet, that upregulating ACC activity does specifically reduce activity in limbic reward-associated regions. This hypothesis needs further investigation by future studies, which we also highlighted in the manuscript (page 12, lines 437-439).

Minor comments

1. *"Highlights" should include one sentence referring to relatives and comparisons with bipolar patients*

Answer: We included absent group differences in sample 2 in BOLD activation and BIS/BAS scores in the highlights (bullet point no. 4). A bullet point with respect to a direct patient vs. relatives comparison cannot be made, since this comparison was not being performed in the present study.

2. *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).*

Answer: We adapted the abstract with regard to the information that was missing.

3. *typo in 1.1. patients were (i) age… " replace with aged*

Answer: Thank you for pointing this out to us. The typo has been fixed.

4. *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.*

Answer: This is to correct for multiple testing, since we investigated 3 ROIs in the win-baseline contrast (VS, ACC, OFC) as stated on page 9, lines 302-303. This information has also now been added in the Results section on page 11, first paragraph.

5. *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.*

Answer: Covarying out these variables is not feasible in SPM, since we would need to calculate a t-test between patients and controls, entering these values as nuisance variables. However, for controls, we do not have values for these variables, since they are not applicable to them, resulting in missing values. Thus, we would not be able to enter controls into the analysis due to missing values, which SPM cannot handle. We did split up the patient sample into those with an "early" onset (before 25 years of age) and late onset (> 25 years), resulting in 8 participants per group. Notably though, compared to other studies, our patients all had a rather late disease onset. Comparing these two patient groups on the win-baseline contrast did not result in significant group differences.

Using a simple regression in SPM, entering time in remission as covariate of interest and looking at a possible correlation with BOLD activation in the win-baseline condition in the patient sample only, did not result in any significant voxels. Applying small volume correction of the ACC or ventral striatum also did not result in significant voxels for this correlation. Thus, we did not include this analysis in the current manuscript.

Reward anticipation revisited- evidence from an fMRI study in euthymic bipolar I patients and healthy first-degree relatives

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This research was supported by the Deutsche Forschungsgemeinschaft (SFB636/C6).

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Abstract

Background: Symptomatic phases in bipolar disorder (BD) are hypothesized to result from a hypersensitive behavioral activation system (BAS) being sensitive 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 in BD. Moreover, its role as vulnerability marker for BD is unclear.

Methods: Functional imaging was conducted in16 euthymic BD-I patients free from dopaminergic medication and 19 healthy first-degree relatives using a monetary incentive delay task and compared to parallelized control groups. Further, reward proneness, using the BIS/BAS questionnaire, and its relationship to neural reward anticipation was investigated.

Results: BD-I patients displayed greater anterior cingulate cortex (ACC) activity during reward anticipation and higher BIS total scores compared to controls, with a positive relationship between the two measures. There were no neural 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 rated themselves as more risk avoidant and 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.

Keywords: reward anticipation, BIS/BAS, bipolar, first-degree relatives, fMRI

Introduction

Bipolar disorder I (BD-I) is characterized by intermittent episodes of depressive, manic, and euthymic mood states, accompanied by respective changes in emotional and motivational processes (American Psychiatric Association, 2000). Whereas altered emotional processing and its underlying neural

correlates have received substantial attention in bipolar disorder research (see e.g., (Wessa and Linke, 2009), investigations on motivational dysfunctions, particularly with respect to the neural underpinnings of reward and punishment processing, are still rare.

In the last decade, a model of BD-I has been postulated focusing on the motivational dysregulations in this disorder. The BAS hyperactivity model of bipolar disorder (BD) (Alloy and Abramson, 2010) is based on the behavioral inhibition/behavioral activation (BIS/BAS) system, underlying harm-avoidance and approach behavior in humans, respectively (Gray, 1991). It ascribes mood switches in BD to changes in patient's BAS system, being hypoactive during depressive episodes and hyperactive during manias (Depue and Iacono, 1989; Alloy and Abramson, 2010). Elevated BAS scores on the BIS/BAS questionnaire (Carver and White, 1994), pointing towards a BAS hyperactivity, persist into euthymic phases in BD and predicted a transition to bipolar spectrum disorders in healthy control participants, indicating its possible role as endophenotype and vulnerability marker for BD, respectively (Alloy et al., 2012; Fletcher et al., 2013). A high trait BIS, in turn, was hypothesized to result in more anxious behavior in animals and humans (Gray, 1991), but neither the original BAS dysregulation theory (Depue and Iacono, 1989) nor the elaborated version by Urosevic and colleagues (Urosevic et al., 2008) make assumptions with regard to the possible role of this system in bipolar patients. Therefore, it can be concluded that this system likely has no influence on motivational regulation in this disorder. In addition to heightened BAS scores on the BIS/BAS scale, BD patients have repeatedly been found to be more impulsive than control participants, indicated by higher scores on the behavioral inhibition scale (BIS-11, Barratt and Patton, 1983), also in euthymia (e.g. Swann et al., 2001). This impulsivity was also related to a worse course of the disorder (Swann et al., 2009). However, while the BIS-11 measures trait impulsivity, which is related to the initiation of actions (Barratt and Patton, 1983), namely risky and unplanned ones when scores are high, the BIS/BAS scale measures the underlying motivation to execute an action or not (Gray, 1970). Therefore, the two scales are related to each other, but still measure distinct symptomatic aspects of bipolar disorder. Nonetheless, questionnaires are always subject to response biases. Therefore, it appears important to investigate correlates of an overactive BAS system, e.g., reward sensitivity, on a more objective, neurobiological level. This is even more relevant when searching for potential vulnerability markers in individuals, prone to develop a particular disorder, but who do not show the respective phenotype, i.e., behavioral symptoms, yet.

Previously, the BAS has been linked to dopaminergic projections from the ventral tegmental area to striatal and limbic structures, particularly the caudate, putamen, nucleus accumbens and amygdala, and onwards to prefrontal areas (Depue and Iacono, 1989; Urosević et al., 2008; Alloy and Abramson, 2010). In line, large neuroimaging evidence has shown that a network comprising of the ventral striatum (VS), the mesial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), insula, and the thalamus is linked to reward processing, particularly the anticipation of

monetary rewards, and to a lesser degree to verbal incentives (Knutson et al., 2000; Knutson et al., 2001; Kirsch et al., 2003). Similar regions were found to be activated for the anticipation of monetary losses (i.e. caudate, thalamus, mPFC, putamen, and ACC) (Knutson et al., 2000).

However, studies on the neurobiological underpinnings of the BAS hypersensitivity model in euthymic BD-I patients and healthy relatives are rare. There are only two studies investigating reward anticipation in euthymic BD-I patients with oppositional findings. While the first study found significantly greater activity in the right VS and right OFC during reward anticipation in BD-I patients compared to healthy controls (Nusslock et al., 2012), the second one did not find any difference in neuronal activation between BD-I patients and healthy controls when anticipating a monetary reward (Caseras et al., 2013). Likewise, there is only one study on reward anticipation in BD-I relatives in an adolescent sample, which did not show altered VS or OFC activation during the anticipation of reward, but increased OFC activity in response to obtained rewards (Singh et al., 2014). This is in line with a recent study of our group, investigating neural response patterns to reward outcome, only, and observing increased OFC and amygdala activation in response to the receipt of reward in adult relatives of BD-I patients (Linke et al., 2012). However, the latter study did not allow for the investigation of reward and loss anticipation and whether the findings in adolescent relatives can be transferred to adult relatives of BD-I patients is questionable, as brain regions involved in reward anticipation are subject to change during brain maturation. Therefore, empirical evidence on reward sensitivity, and thus also BAS dysregulation, as vulnerability marker for bipolar disorder is still scarce.

Finally, the existing findings, investigating reward anticipation in euthymic patients, need to be interpreted with caution due to some confounding factors. In the previous studies, more than half of the included patients used antipsychotic medication or dopaminergic antidepressants, both influencing the dopamine system, which is also the crucial neurotransmitter in reward processing (Schott et al., 2008; Arias-Carrión et al., 2010), thereby biasing the obtained results (Phillips et al., 2008; Wessa and Linke, 2009). Further, previous studies also included patients with comorbid lifetime substance use or dependence, although substance dependence has been shown to have prolonged effects (Nery et al., 2011), possibly also on the brain's dopamine transmission, rendering findings in BD-I patients with such comorbidities unspecific to BD-I. Therefore, to elucidate the neural underpinnings of motivational dysregulation, particularly reward sensitivity, as a trait marker of BD-I patients, studies excluding the outlined confounding factors are needed.

Thus, the present study sought to shed light on the mixed findings of previous studies, while also eliminating possible confounding effects using a reward (and loss) anticipation task in the scanner. Further, relationships between neural activation patterns and self-rated reward proneness were investigated. In line with the BAS hyperactivity model and previous findings from our workgroup, we anticipated elevated ventral striatal and OFC activity during reward anticipation in BD-I patients compared to healthy controls. In support of an endophenotype for the disorder, we expected healthy

first-degree relatives of BD-I patients to show a comparable activation pattern. In both groups, differences in other reward-related brain regions (i.e., ACC, insula) as well as loss- and verbal incentive -related changes in neural activation patterns were investigated on an exploratory level. Finally, BD-I patients and relatives were hypothesized to report a higher BAS total and reward responsiveness score on the BIS/BAS questionnaire than their respective control group and these elevated scores were supposed to correlate with the blood oxygen level dependent (BOLD) signal in the VS and OFC.

Materials and Methods

1.1 Participants

Sample 1:

Participants were 16 euthymic BD-I patients and 24 parallelized healthy controls (see Table 1). Inclusion criteria for patients were (i) aged between 18-65 years, (ii) no antipsychotic medication or dopaminergic antidepressants for at least 2 months, (iii) stability on medication dosage and type for at least 2 months prior to testing, (iv) and euthymia for at least 2 months prior to testing. Euthymia at the day of testing was ensured with a score lower than seven on the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) and a score lower than six on the Young Mania Rating Scale (YMRS) (Young et al., 1978). Clinical diagnostics were assessed by two trained raters (VS, BK). The current medication load was being computed, adhering to the calculation described by Sackheim (Sackeim, 2001).

Sample 2:

Sample 2 comprised of 19 healthy first-degree relatives of BD-I patients and 17 parallelized healthy controls (see Table 1). First-degree relatives were unrelated to patients in sample 1 and only 1 relative per family was included, to rule out possible genetic effects. The affected patient was also invited to a clinical assessment for diagnosis verification using the SCID-I and SCID-II interview (Wittchen, Zaudig & Fydrich, 1997).

All participants were recruited through self-help groups, announcements on webpages or through the local residency registration office. Healthy controls and relatives were not allowed to have any mental disorder, while BD-I patients were not allowed to have any comorbidities on axis I or II on the SCID-I and SCID-II (Wittchen, Zaudig & Fydrich, 1997). All participants were eligible for study participation if they additionally did not meet any counter indications for MRI scanning.

All participants received a complete description of the study procedure, after which they gave written informed consent and received a monetary compensation upon completion of the study. The study adhered to the declaration of Helsinki and was approved by the ethical committee of the Heidelberg

University, Germany. Patients and relatives differed in mean age and gender ratio, so that it was not possible to match a control group of similar size to both experimental groups simultaneously. Adding age and gender as covariates into the analysis of samples 1 and 2 together, might not be sufficient to address possible effects resulting from these demographic differences. Therefore, samples 1 and 2 were analyzed separately in the current study.

1.2 Instruments

1.2.1 Reward anticipation paradigm

Reward anticipation was assessed with a modified version of the task developed by Kirsch and colleagues (Kirsch et al., 2003), which has been shown to reliably activate regions associated with reward processing, such as the NAcc, ACC, OFC, and thalamus (Stark et al., 2011). The task was programmed with the Presentation software package (Neurobehavioral systems, Albany, CA, www.neurobs.com) and conducted without a practice trial outside the scanner. Participants were confronted with one of four arrows, indicating different possible outcomes for 6sec (anticipation phase). Three of these arrows were followed by a flash for 100ms. Subjects were asked to respond as fast as possible when they saw the flash by pressing a button on a button box with their right index finger. The response window, within which participants were allowed to make their response, varied depending on their reaction time (RT) on the previous trial. The task started out with a response window of 300ms, within which participants were requested to respond by a button press. Reaction times within this response window led to a reduction of the RT threshold by 5% on the subsequent trial, while a RT longer than the current response window resulted in an enlargement of the RT threshold by 5% on the next trial. The response window could maximally be enlarged to 1.5sec. Button presses were followed by an outcome phase for 1.5sec, during which a monetary or verbal feedback was presented, followed by participant's current budget presented for 1.5sec. An arrow pointing upwards during the anticipation phase inferred a win of 2€, if participants pressed within the time frame and no budget change for a slow response (win condition). A downward arrow indicated a possible loss of 2€ for a slow response or no change in budget for a fast response (loss condition). An arrow pointing up-and downwards was a cue for verbal feedback, with a fast response resulting in the message "Fast response. Good job!" and a slow response resulting in the message "Unfortunately too slow!" on the screen (verbal condition). Verbal feedbacks were not accompanied by any change in participant's budget. A horizontal arrow, pointing left and right, served as baseline condition as it was not followed by a flash and did not require any response, nor did it result in any feedback (see Figure 1). There were 10 trials per condition, followed by dummy trials ensuring a total pay-off of 10€ for every participant. Trials were presented in pseudo random order, with no more than two repetitions of the same condition.

---------- Insert Figure 1 here ----------

1.2.2 BIS/BAS, cognitive abilities and usage of substances of abuse

The Behavioral Inhibition/Behavioral Activation Scale (BIS/BAS scale) (Strobel et al., 2001) is a 24-item self-rating trait questionnaire, assessing participant's urge to approach reward-related cues or to pursue goals (BAS) and their sensitivity to signals of punishment or non-reward (BIS). Its questions are assessed on a four-point Likert scale, ranging from 1 (strongly disagree) to 4 (strongly agree). The BIS scale consists of seven items, while the BAS total scale consists of 13 items. The BAS scale itself is subdivided into three smaller scales: Reward Responsiveness, Drive, and Fun-seeking.

In addition, all participants were tested on the German version of the Multiple Choice Word Vocabulary Test to rule out any effects due to differences in participant's general intelligence (Lehrl, 2005)German: Mehrfach-Wortschatz Intelligenztest (MWT-B)).

Also, participants in both samples were assessed on the Fagerström Test for Nicotine Dependence (Fagerström & Schneider, 1989). This self-rating questionnaire consists of six questions on smoking habits, assessed on a two- or four-point Likert scale, depending on the item, ranging from 0 to 3. Total scores are interpreted as follows: 0-2 points low dependency, 3-5 points medium dependency, 6-7 points strong dependency, 8-10 points very strong dependency. Further, the German version of the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) was being assessed, measuring current alcohol drinking habits and it can identify hazardous alcohol consumption. It is a self-rating questionnaire with 10 items, assessed on a five-point Likert scale, ranging from 0 (never) to 4 (daily or almost daily), with questions on drinking amount, frequency, and possible negative consequences of drinking. The cut-off for harmful drinking habits is a score of 8 or higher for men under 65 years, while the cut-off score is at a score of 7 for women and men older than 65 years. Moreover, all participants indicated, whether they used one or more of the following substances of abuse regularly within the last 12 months: alcohol, nicotine, caffeine, cannabis, crack/cocaine, amphetamines/ecstasy, hallucinogens, sleeping pills, substances that need to be inhaled (e.g. glue, paint), opiates/opioids, and heroin.

1.2.3 Image Acquisition

Functional images were acquired on a 3T Siemens Trio scanner using a single-shot echo planar sequence with parallel imaging GRAPPA (with an acceleration factor of 2) techniques with 40 slices per volume (repetition time (TR) = 2150ms, echo time (TE) = 22ms, flip angle = 90°, slice thickness =

2.3mm + 0.7mm gap, field of view = 220x220mm², matrix size = 96 x 96) and a 32-channel head coil. Slices were measured in descending order, with the phase-coding direction running from posterior to anterior (PC-AC orientation).

1.3 Analyses

1.3.1 Demographic, self-report and behavioral data

Demographic data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Group differences between BIS/BAS scores total scale and subscale scores and on the FTND, AUDIT, and regular use of substances of abuse questionnaires were tested using independent-samples t-tests for normally distributed data and Mann-Whitney U-tests for non-normally distributed scores.

Possible group differences in reaction times on the reward anticipation task during the different conditions were analyzed using repeated measures analyses of variance (ANOVA) with the respective condition (win, loss, verbal) as within-subjects factor and the groups (sample 1: patients versus healthy controls; sample 2: relatives versus healthy controls) as between-subjects factors. Significant main or interaction effects were analyzed using post hoc t-tests where applicable and Mann-Whitney U-tests or Wilcoxon signed-rank tests in case of non-normally distributed data. In case of a violation of the sphericity assumption, tested using Mauchly's test of sphericity, Greenhouse-Geisser values are reported. Differences in the final budget obtained were analyzed by means of independent-samples t-tests or Mann-Whitney U-tests, respectively. All tested differences were significant at $p < .05$.

1.3.2 Functional Image Analyses

Preprocessing

Image preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running on MATLAB2012b (The MathWorks Inc., Natick, MA). Participants were excluded if head movements exceeded 3mm or 3° in any direction. Remaining participant's data were corrected for technical artifacts, using the ArtRepair toolbox developed by Mazaika and colleagues (Mazaika P, Whitfield S, Cooper J, 2005). As proposed by the developers, a slice correction was performed using art_slice when 1-5% of the slices were categorized as bad slices. If the number of bad slices exceeded 5%, subjects were excluded from further analyses. Volumes were being repaired after preprocessing and participants with bad volumes after correction were excluded from first-and second-level analyses. In sample 1, four patients had to be excluded due to non-reparable bad data quality, resulting in 16 patients in the final sample. In sample 2, 2 relatives and 4 controls had to be excluded from further

analyses, resulting in a final sample of 19 relatives and 17 controls. The first four volumes were discarded in order to correct for T1-saturation effects. All images were realigned using a rigid body transformation, slice time corrected to the middle slice as reference slice and normalized to the EPI template provided in SPM 8. Afterwards, images were smoothed using a 6.8 x 6.8 x 9 mm Gaussian kernel.

First-level individual subject BOLD changes during the anticipation phase of the reward paradigm were calculated using a General linear model. The final model entailed 4 regressors (win, loss, verbal, and baseline) plus the flash light regressor and 6 motion regressors. A canonical haemodynamic response function was used to model the regressors and was convolved with the onset of the arrow in each condition. From these regressors, 3 contrasts were being computed: win minus baseline (main effect of win anticipation), loss minus baseline (main effect of loss anticipation), and verbal minus baseline (main effect of verbal feedback anticipation).

Second-level random-effects analyses first determined, whether activation patterns in regions related to the anticipation of reward, loss and verbal feedback found in previous studies using the same (Kirsch et al., 2003) or a fairly similar paradigm (Knutson et al., 2001) could be replicated in the present sample. For this matter, a one-sample t-test was being conducted over all control participants ($N = 41$), using whole-brain analyses. Activations were treated as significant when surviving a threshold of $p < .05$ family-wise error (FWE) corrected. In order to distinguish VS activity from larger clusters in the limbic system, we used a VS mask and conducted a region of interest (ROI) analysis for this region, using the same threshold. The VS mask resembled the one used by Nusslock and colleagues (Nusslock et al., 2012). Afterwards, group differences were being investigated on regions of interest (ROI) masks defined in the Wake Forest PickAtlas toolbox v2.3 (Lancaster, J.L., Summerlin, J.L., Rainey, L., Freitas, C.S., Fox, P.T., 1997; Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003) using two-sample t-tests and small volume correction (threshold of $p < .05$ and Bonferroni corrected for multiple testing). Defined ROI's were the orbitofrontal cortex (OFC), the insula, and the anterior cingulate cortex (ACC) for the loss contrast and the OFC, ACC, and VS for the win and verbal contrast, using the previously described mask for the VS.

Associations between participant's BIS/BAS score and BOLD responses were assessed using multiple regression in SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Correlations were significant at $p < .05$ FWE corrected using small volume correction.

Results

1. Demographic, self-report and behavioral data

We observed no group differences in any demographic variable, neither in sample 1 nor in sample 2. Further, participants did not differ in terms of IQ, years of education, or their scores on the YMRS.

However, patients had a significantly higher score on the HAM-D compared to healthy controls [U=101.50, p = .004; range patients: 0-4, range controls: 0-2]. Participants in sample 1 did not differ with regard to regular nicotine, alcohol or caffeine consumption within the last 12 months. In addition, patients' scores on the AUDIT ($M_{controls}$ = 2.88, SD = 2.56; $U_{patients\ vs\ controls}$ = 153.0, z = -.47, p = 67, r = -.08) and FTND ($M_{controls}$ = .14, SD = .66; $U_{patients\ vs\ controls}$ = 110.0, z = -.52, p = .85, r = -.09) did not differ from those of healthy controls in sample 1 and were below the aforementioned cut-off, indicating no harmful alcohol use or nicotine dependence, respectively (see Tables 1 and 2). Patients did not report the usage of any other drugs of abuse, except for one patient reporting regular usage of sleep alleviating medication other than benzodiazepines. Also in sample 2, participants neither differed in their AUDIT ($M_{relatives}$ = 4.33, SD = 4.16; $M_{controls}$ = 3.71, SD = 2.81; $U_{relatives\ vs\ controls}$ = 120.5, z = -.21, p = .84, r = -.04) or FTND scores ($M_{relatives}$ = 0, SD = 0; $M_{controls}$ = .23, SD = .83; $U_{relatives\ vs\ controls}$ = 66.0, z = -.92, p = .78, r = -.19), nor in their regular consumption of alcohol, caffeine or nicotine (see Table 1). Additionally, they did not report the usage of any other drugs of abuse.

----------Insert Tables 1 and 2 here----------

Regarding group differences on the BIS/BAS questionnaire, patients in sample 1 displayed a significantly higher BIS total score than healthy controls, while their BAS total score and BAS subscale scores were not significantly different.

In sample 2, first-degree relatives and respective control subjects did not differ on the BIS/BAS (see Table 1 for details).

Considering behavioral differences between groups on the reward anticipation paradigm, there was a trend for a main effect of condition [F(2,76) = 3.076, p = .052] and a significant main effect for group [F(1,38) = 8.74, p = .005], but no interaction effect between condition x group [F(2,76) = .895, p = .413] in sample 1. Hence, the two groups differed significantly in their reaction times on the reward paradigm, irrespective of the condition performed, with patients being slower in all three conditions compared to controls ($M_{patients\ win\ trials}$ = 332.29, SD = 159.1; $M_{controls\ win\ trials}$ = 263.85, SD = 37.04; $M_{patients\ loss}$ = 295.81, SD = 61.51; $M_{controls\ loss}$ = 269.06, SD = 54.51; $M_{patients\ verbal}$ = 357.66, SD = 88.30; $M_{controls\ verbal}$ = 292.35, SD = 79.44). Further, patients and healthy controls did not differ in their final budget obtained during the task ($M_{patients}$ = 4.25, SD = 4.89; $M_{controls}$ = 4.75, SD = 4.08) [U = 188.500, z = - .098, p = .922, r = - .02].

In Sample 2, there was a significant main effect for condition [F(2,68) = 7.61, p < .001], with participants being significantly faster on win (M_{win} = 252.68, SD = 35.14) and loss trials (M_{loss} = 247.31, SD = 51.09) compared to verbal trials (M_{verbal} = 282.47, SD = 49.85) [$T_{win\ versus\ verbal}$ = 99, p < .001, r = -.35; $T_{loss\ versus\ verbal}$ = 81, p < .001, r = -.38]. Furthermore, study participants were faster for loss compared to win trials [$T_{loss\ versus\ win}$ = 171.5, p = .011, r = -.24]. There was no significant main

effect of group [F(1,34) = .318, p = .58] ($M_{relatives\ win}$ = 260.06, SD = 37.91; $M_{controls\ win}$ = 244.43, SD = 30.79; $M_{relatives\ loss}$ = 245.44, SD = 37.71; $M_{controls\ loss}$ = 249.39, SD = 64.04; $M_{relatives\ verbal}$ = 285.49, SD = 58.55; $M_{controls\ verbal}$ = 279.09, SD = 39.47). There was also no significant group x condition interaction [F(2,68) = .512, p = .60]. Furthermore, the two groups did not differ with respect to their final budget earned ($M_{relatives}$ = 6.00€, SD = 3.46; $M_{controls}$ = 6.94€, SD = 3.01) [U = 140.500, z = -.679, p = .512, r = -.11].

2. Functional imaging analyses

The reward paradigm activated all regions previously shown to respond to the anticipation of reward, loss and verbal incentives in healthy control participants (see table 3 for details).

There were no significant group differences in either sample for FWE-corrected ROI based activation analyses of the VS during reward anticipation. Further, exploratory investigations of the OFC, insula and the VS did not show significant group differences in either sample. Interestingly, however, for the contrast win – baseline BD-I patients showed a significantly higher activation in the left and right ACC (left: x = -2, y = 31, z = -5, p < .031, Z = 3.80; right: x = 3, y = 31, z = -5, p < .016, Z = 4.00) compared to controls (see Figure 2). After multiple comparison correction using an adapted alpha-level of .05/3 = .016 to correct for the three tested ROIs in the win-baseline contrast (i.e. NAcc, OFC, ACC), activation in the right ACC remained significant. Additionally, there was a significant positive correlation between the activation in the left ACC (x = -11, y = 31, z = -2, p < .007, z = 4.22) during the contrast win-baseline and the BIS total scale score among participants in Sample 1, investigated by a simple regression in SPM. Comparing the regression slopes of the two groups, it became evident that this correlation was mainly driven by the patient group (patients: p < .028 FWE-corrected using small volume correction, z = 3.83; See also Graph 1 for details). Inserting participant's HAM-D score as nuisance variable into the model in sample 1 did not change the observed results. No significant group differences were found for any of the other contrasts.

There were no group differences in BOLD responses between participants in sample 2 for any of the investigated contrasts.

----------Insert Figure 2 here----------

----------Insert Graph 1 here----------

Discussion

The present study investigated, for the first time, the neural correlates of reward anticipation in euthymic non-comorbid BD-I patients, free of dopaminergic medication, as well as adult first-degree relatives of BD-I patients. In contrast to our hypotheses and results of a previous study (Nusslock et al., 2012), we did not observe significant group differences in both samples in ventral striatal and OFC

activation during reward anticipation. However, BD-I patients showed significantly stronger ACC activation than healthy controls when anticipating rewards. In accordance with our hypotheses and previous studies, there were no differences in neuronal activation during the anticipation of losses or verbal incentives (Nusslock et al., 2012).

The ventral ACC is a region related to affect regulation and response conflicts in task switching, with direct connections to the VS (Bush et al., 2000; Swainson et al., 2003). As such, heightened ACC activation observed in BD-I patients compared to controls during reward anticipation might indicate a top-down control on a hyperactive VS, either directly or via the prefrontal cortex, to regulate elicited positive emotions related to possible rewards (Rowe et al., 2008). This activation might be a disease rather than a vulnerability marker, as it was not observed in healthy first-degree relatives of BD-I patients. As such, it possibly developed over time due to exposure to the disorder. However, our data do not allow confirming a top-down regulating influence of the ACC on the VS directly. Future studies should further elucidate this potential mechanism in BD. Further, we observed elevated BIS scores in BD-I patients compared to controls, indicating a rather risk averse behavioral pattern, which was positively correlated with the observed ACC activity in these patients. Enhanced ACC activation and higher risk aversion might, in this sense, be interpreted as a compensational or counteracting activation.

While the absence of group differences in VS activation during reward anticipation in sample 1 is in line with a recent study, the observed elevation in ACC activity in patients in the present study is not (Caseras et al., 2013). One reason for that might be the different tasks applied. While the aforementioned study used a card guessing paradigm, equivalent to the one used in a previous study (Nusslock et al., 2012), the present study used a monetary incentive delay task (Knutson et al., 2000; Kirsch et al., 2003). In the former task, participants are first required to take an action (button press) followed by a cue indicating the anticipation quality (win or loss), while participants in the latter task first receive the cue upon which they build expectations about possible outcomes and then take action. As such, the task we used might be more close to actual reward-seeking behavior, in which an incentive is presented upon which necessary actions are executed in order to receive it. Notably though, both tasks focus on anticipation, not including a decision-making component. Executing a certain behavior *after* expectation formation might be a prerequisite for the elicitation of a response conflict, detected by the ACC, downregulating reward expectations in the current paradigm and possibly preventing behaviors with potentially negative consequences in real-life settings.

Another possible reason for the contrasting findings might be the differences in the study samples, most importantly the absence of antipsychotic medication, as well as substance use disorders in our patient group, both likely affecting activation in reward-related brain regions via the dopaminergic system. This is supported by studies on neural activation during reward anticipation in bipolar disorder II (BD-II) patients, which found conflicting results depending on whether patients took antipsychotic

medication or were drug-naïve at the time of testing (Caseras et al., 2013; Yip et al., 2015). Although patients in the present study were not naïve to dopaminergic medication, they were free from any dopamine affecting medication for at least 2 months prior to testing, limiting these medications' possible influence on reward anticipation at the time of testing.

Elevated BIS scores, found in BD-I patients compared to controls in the present study, might indicate mechanisms responsible for a down-regulation of reward-seeking behavior, while a higher BAS score would make BD-I patients more prone to elevated reward anticipation activation. The observed positive correlation between elevated BIS scores and ACC activity is in line with this hypothesis. Further, the observed BIS score elevation in euthymic BD-I patients of the current study are in line with a finding by Caseras et al. (Caseras et al., 2013), but contradict predictions made based on the BAS hypersensitivity model of BD (Depue and Iacono, 1989; Urosević et al., 2008). Reasons for differing findings might particularly involve the patient samples investigated in the different studies. Whereas most previous studies (Alloy et al., 2008; Alloy et al., 2009) investigated mixed samples of bipolar spectrum disorder, Caseras (Caseras et al., 2013) included only BD-II patients and – as in our study – BD-I patients during euthymia. Notwithstanding, they displayed greater BIS scores compared to healthy controls, indicating a persisting harm-avoidance. A high BIS score has previously been found to be associated with current depressive symptoms (Meyer et al., 2001). While patients in our study indeed displayed significantly more depressive symptoms, as reflected by higher HAM-D scores, absolute depressive symptoms were very low (see Table 2). Hence, subclinical depressive symptoms are an unlikely cause for this group's elevated BIS total scores. BAS scores were comparable to those of healthy controls, reflecting neural findings of comparable ventral striatal activation during reward anticipation in all experimental and control groups in the present study. High BIS scores do therefore not necessarily interfere with normal reward responsiveness.

As for BD-I patients, we did not observe elevated ventral striatal and OFC activity during the anticipation of a monetary reward in high-risk individuals, compared to healthy controls. These findings were also reflected on a behavioral level by no group differences in RT's in both samples. Nonetheless, in line with previous findings, all participants showed a faster response towards monetary compared to verbal incentives (Kirsch et al., 2003). Thus, a higher BOLD response in the VS, OFC or ACC during reward anticipation might not represent a vulnerability marker for BD, although this notion requires further investigation due to the small sample sizes in the present study.

Contrary to our hypothesis and the BAS dysregulation model of BD, first-degree relatives of BD-I patients did not show elevated BAS scores compared to their respective control group. Previous studies using the BIS/BAS questionnaire were successful in identifying individuals at risk for milder forms of BD, such as BD-NOS or BD-II in community or university samples (Alloy et al., 2008; Alloy and Abramson, 2010; Alloy et al., 2012). However, the high risk participants in the current study carried a genetic risk for a more severe form of the disorder regarding manic phases, rather than

having a risk for it due to a high trait BAS score . Their phenotype might differ from that of at risk groups in previous studies.

The results of the present study have to be interpreted in light of some limitations. First, and above all, study samples were rather small, increasing the probability of false negative findings. As already mentioned in the introduction, we aimed to exclude potential confounding factors, such as dopaminergic medication or substance use disorders, among BD-I patients at the expense of larger sample sizes. The strict exclusion criteria might also limit generalizability of results as exclusion of these confounds results in selective subsamples with potentially higher levels of functioning and rather modest courses of BD-I. Further, although patients in the current study did not take dopaminergic medication at the time of and at least two months prior to testing, lifetime exposure to dopaminergic agents was not assessed in the current study, since there was no access to patient's medical files and assessing this information via patient's self-report is prone to be less valid, especially for those patients with a long disorder history. Not taking these medications shortly before testing might not be sufficient to rule out possible effects on the reward system. Thus, future studies are challenged to investigate reward anticipation in patients naïve to dopaminergic medication. Third, the experiment was not designed to analyze neural responses to the receipt of reward during the outcome phase. The rational for the recruitment of the ACC during reward anticipation in BD-I patients might be better understood when knowing about the activation during the outcome phase. On a cautious note, it might be assumed that ACC activation during anticipation renders BD-I patients less prone for prediction errors in the win condition. However, this hypothesis requires further investigation, taking the outcome phase of a reward paradigm into account. Fourth, there might have been differences in BOLD activity between those patients with a rather high to those with low BIS scores. However, the relatively small sample size investigated in the present study did not allow for the comparison of BD-I patient subgroups with regard to their BIS score. Future studies are needed for direct comparisons of neural activity in patients with high to those with low BIS scores.

Nonetheless, the current study is an important addition to the growing literature on reward sensitivity in BD, in that it investigated reward anticipation for the first time in euthymic BD-I patients ruling out confounding factors common in studies on reward anticipation in BD-I and also taking adult participants at high risk for the disorder into account. Contrary to some previous findings, this study did not find neuronal or behavioral evidence for a hypersensitive reward system as a trait or vulnerability marker for bipolar disorder. Rather, we found elevated ACC activity during reward anticipation in BD-I patients, which was related to elevated BIS scores. Due to the role of the ACC in response conflict and affect regulation, an elevated ACC activity in BD-I patients might be the result of repeated experiences with the disorder and its potential negative consequences in the sense of a compensatory mechanism. Further, reported heightened BIS scores on the BIS/BAS scale in BD-I patients also point to this compensation, counteracting a hypersensitive BAS. The development of

such compensatory mechanisms indicates the importance of early diagnosis and effective treatment of BD, rendering compensatory mechanisms redundant. Future studies are needed, comparing BD-I patients with only one symptomatic phase to those with multiple episodes, to determine whether the ACC activity during reward anticipation in BD-I really is a counteracting mechanism, which develops over time. Also, longitudinal studies are needed in order to test whether this mechanism is sufficient to prevent future symptomatic episodes. If so, patients at an early disease stage might be trained to upregulate the ACC to prevent future episodes, e.g. by using neurofeedback. While the feasibility of upregulating ACC activity by neurofeedback is well established (e.g. Gröne et al., 2015), its specific usefulness in exerting control over hyperactive limbic regions requires investigation by future studies. Notably, in contrast to one of our previous studies (Linke et al., 2012), we only investigated the anticipation phase of reward processing in the current study. Further research is needed, using larger and drug naïve patient samples, to determine the role of the ACC in reward anticipation in BD and to elucidate the influence of ACC activation during reward anticipation on the outcome phase.

Table 1. Sample characteristics and BIS/BAS scale scores of the final samples

	Bipolar patients (N=16)	Controls of patients (N=24)	Test statistic	p-value		First-degree relatives (N=19)	Controls of relatives (N=17)	Test statistic	p-value
Age- mean (SD)	43.13(11.25)	42.73(10.16)	t=.12	.91		33.81(11.46)	32.79(12.82)	U=149.50	.70
Gender- m/f	6/10	12/12	X^2= .61	.44		9/10	8/9	X^2=.00	.99
Years of education-mean(SD)	16.56(2.45)	15.92(2.26)	U=160.50	.37		16.53(2.10)	16.63(2.47)	U=134.50	.95
IQ- mean (SD)[a]	104.13(12.47)	101.96(10.43)	t=.59	.56		105.74(13.26)	106.47(13.64)	U=161.00	.99
HAM-D – mean(SD)[b]	1.13(1.41)	.17(0.49)	U=101.50	.004*		.53(1.12)	.18(.53)	U=137.50	.27
YMRS- mean(SD)[c]	.19(.54)	.13(0.45)	U=184.00	.67		.68(1.15)	.06(.24)	U=126.50	.09
BIS total score-mean(SD)	19.50(3.65)	16.92(2.50)	t=2.66	.011*		18.74(2.66)	18.71(2.54)	U=160.00	.96
BAS total score-mean(SD)	38.75(4.31)	39.71(5.27)	t=-.60	.55		37.89(4.77)	39.94(3.72)	t=-1.42	.16
BAS reward responsiveness-mean(SD)	15.88(2.13)	16.38(2.73)	t=-.62	.54		15.58(2.04)	16.12(1.69)	t=-.86	.40
BAS drive-mean(SD)	11.69(2.12)	12.04(2.12)	t=-.52	.61		11.37(2.01)	12.06(1.65)	t=-1.10	.28
BAS fun-seeking – mean(SD)	11.19(1.87)	11.29(1.92)	t=-.17	.87		10.95(2.09)	11.94(1.48)	t=-1.63	.11
Regular alcohol consumption n(%)	6(37.5)	11(45.8)	X^2=3.585	.17		7(70)	5(41.7)	X^2=1.766	.18
Regular nicotine consumption n (%)	1(6.3)	2(8.3)	X^2=1.339	.51		0(0.0)	1(9.1)	X^2=1.048	.31
Regular caffeine consumption n (%)	9(56.8)	18(75.0)	X^2=2.222	.33		9(90)	9(100)	X^2=.950	.33

*significant at $p < .05$

[a]IQ assessed using the Mehrfach-Wortschatz Intelligenz Test version B (MWT-B)

[b]HAM-D: Hamilton Depression Rating scale

[c]YMRS: Young Mania Rating scale

Table 2. Clinical variables in the patient sample

	Mean	SD	Median	Range
Age at illness onset (years)	25.63	8.76	25.50	12-44
Number of hospitalizations	2.20	1.27	2.00	1-5
Number of lifetime episodes	7.57	7.46	6.00	2-32
Time in remission (in years)	4.81	5.78	3.21	.17-22.08
Medication load	2.38	1.82	3.00	0-5
AUDIT score	2.71	1.73	3.00	0-7
FTND score	.45	1.51	.00	0-5
	Number	Percentage %		
Quality first episode (D/M)	10/6	62.5/37.5		
Quality last episode (D/M)	11/5	68.8/31.3		
Medication				
unmedicated	5	31.3		
Lithium	9	56.3		
Valproaic Acid (VPA)	4	25.0		
Lithium & VPA	3	18.8		
Lamotrigin	2	12.5		
Lithium & Lamotrigin	1	6.3		
Lithium & SNRI	2	12.5		

D/M: ratio depression to (hypo)mania
AUDIT: Alcohol Use Disorders Identification Test
FTND: Fagerström Test for Nicotine Dependence
SNRI: serotonin-norepinephrine reuptake inhibitors, in this case Venlafaxine only

Table 3. Activated regions in one-sample t-tests for controls (N = 41)

Region	Hemisphere	MNI coordinates			z-score	p-value	Cluster size
		x	y	z			
Win anticipation > baseline							
Cuneus (BA 18)	R	25	-98	-8	7.48	.000	189
Postcentral gyrus (BA 3)	L	-34	-27	49	7.23	.000	7404
Precentral gyrus (BA 4)	L	-46	-15	55	7.07	.000	
SMA(BA 6)	R	3	-2	52	7.00	.000	
Inferior occipital gyrus (BA 18)	L	-27	-98	-8	6.39	.000	159
Insula (BA 13)	R	32	24	1	5.79	.000	283
Frontal inferior operculum	R	51	12	7	5.43	.002	
Vermis	R	5	-59	-20	5.63	.001	307
Cerebelum	R	21	-55	-23	5.49	.001	
Precentral gyrus	R	44	-4	46	5.85	.000	313
Middle frontal cortex	R	37	49	31	5.53	.001	271
Putamen	R	32	-20	-2	5.22	.004	12
Cerebelum	L	-30	-64	-20	5.18	.005	70
Postcentral gyrus	R	32	-27	49	4.90	.018	6
Middle frontal gyrus (BA 9)	L	-39	28	40	4.89	.018	7
Applying mask for ventral striatum[a]:							
Ventral striatum	L	-16	14	-2	6.84	.000	285
Ventral striatum	R	9	8	7	6.46	.000	282
Loss anticipation > baseline							
SMA	L	-4	-4	67	Inf	.000	11217
SMA	R	5	1	55	7.67	.000	
Inferior occipital cortex (BA 18)	R	25	-96	-8	6.71	.000	232
Vermis	R	3	-57	-17	6.20	.000	376
Cerebelum	R	23	-55	-23	5.69	.001	
Middle frontal gyrus (BA 6)	R	42	-2	52	6.15	.000	447
Precentral gyrus	R	37	-13	55	6.08	.000	
Supramarginal gyrus (BA 40)	R	60	-48	28	5.07	.010	10
Verbal anticipation > baseline							
SMA	L	-4	1	61	6.77	.000	933
Frontal superior medial	R	5	28	46	6.05	.000	
Precentral gyrus	L	-34	-15	67	6.68	.000	1068
Inferior occipital cortex (BA 18)	L	-27	-96	-8	6.53	.000	246
Inferior occipital cortex (BA 18)	R	39	-89	-5	6.15	.000	312
Putamen	L	-20	5	4	5.58	.001	165
Insula	L	-34	24	-2	5.53	.001	
Thalamus	L	-16	-15	4	5.30	.004	27
Caudate	R	9	5	7	5.18	.006	49
Middle orbitofrontal cortex (BA 10)	L	-34	54	-5	4.95	.018	6

Table 3 continued

Applying mask for ventral striatum[a]							
Ventral striatum	L	-20	5	4	5.58	.001	61
Ventral striatum	R	9	5	7	5.18	.006	27

[a] Applying ventral striatum mask described in method's section, in order to account for the small size of this region, significant at $p < .05$ FWE-corrected.
SMA: Supplementary motor area
R: right
L: left
BA: Brodmann area

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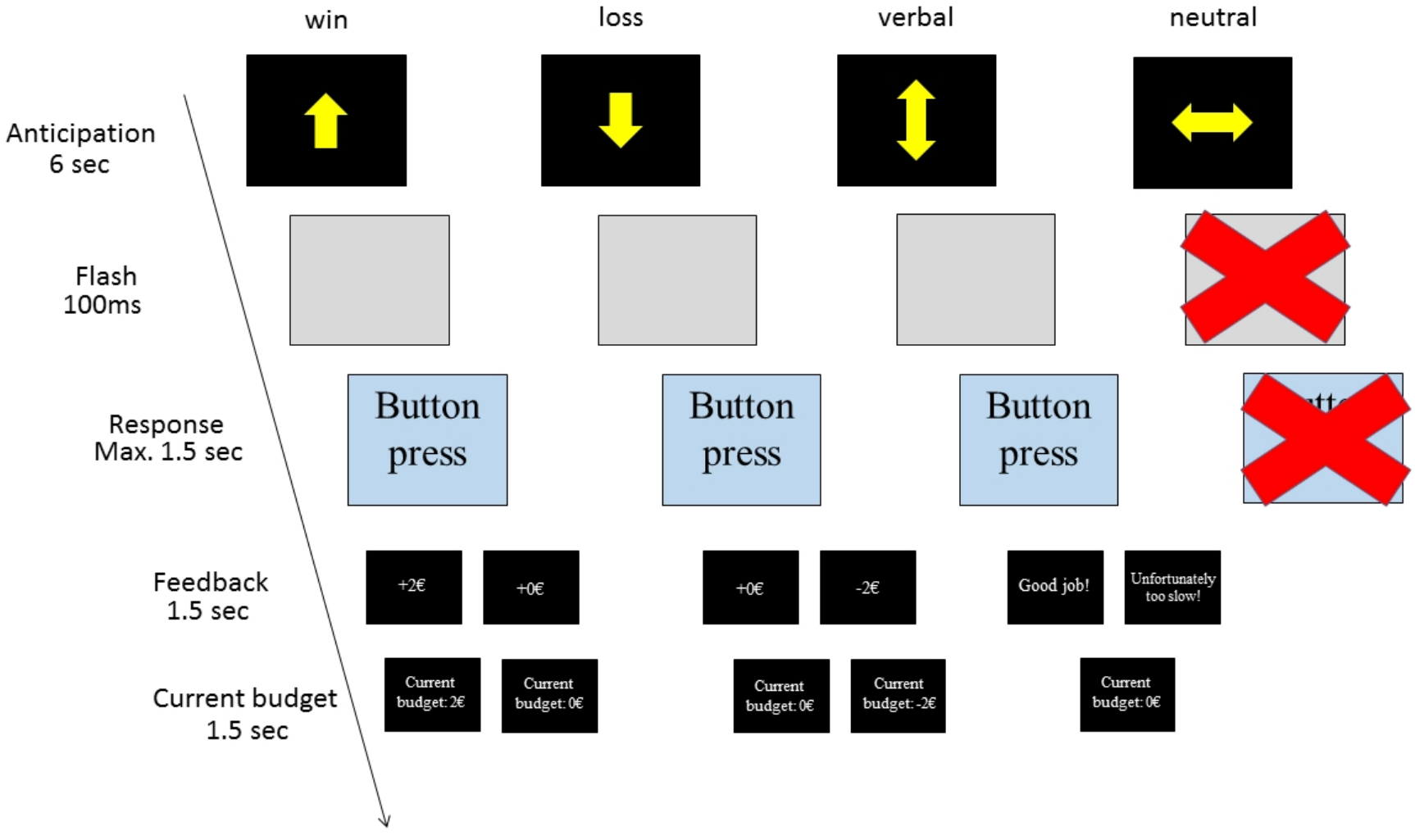
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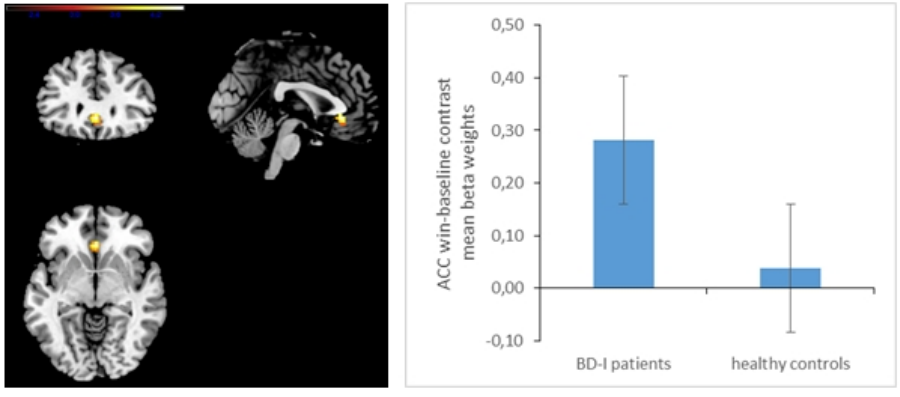
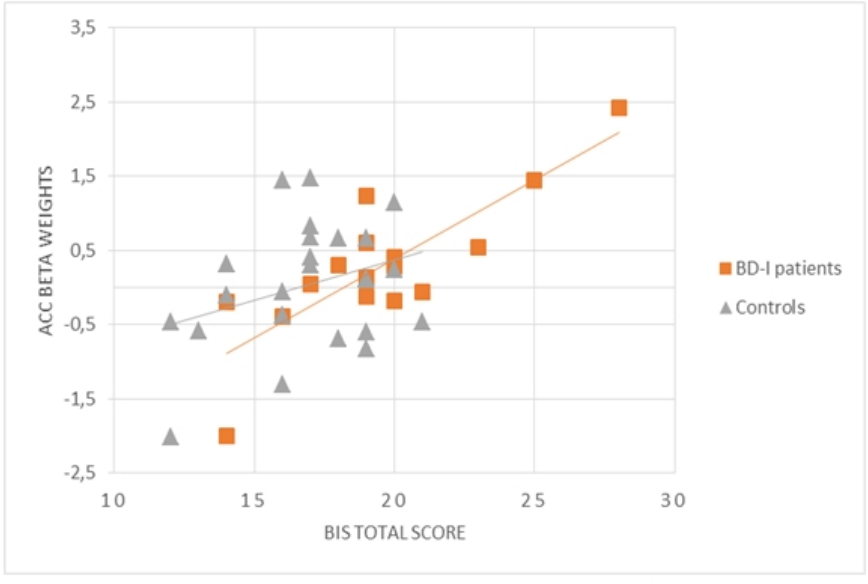


Figure 2. Win > baseline contrast comparing BD-I patients to healthy controls. ACC activity for this contrast, thresholded at $p<0.05$ FWE corrected using small volume correction (**A**). The color bar indicates T statistics. Mean beta weights for the same region in the same contrast (**B**). The bars indicate mean standard errors.



Graph 1. Correlation between beta weights extracted for the ACC during the win condition in patients versus healthy controls and participant's BIS total score on the BIS/BAS scale

Abstract

Background: Symptomatic phases in bipolar disorder (BD) are hypothesized to result from a hypersensitive behavioral activation system (BAS) being sensitive 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 in BD. Moreover, its role as vulnerability marker for BD is unclear.

Methods: Functional imaging was conducted in16 euthymic BD-I patients free from dopaminergic medication and 19 healthy first-degree relatives using a monetary incentive delay task and compared to parallelized control groups. Further, reward proneness, using the BIS/BAS questionnaire, and its relationship to neural reward anticipation was investigated.

Results: BD-I patients displayed greater anterior cingulate cortex (ACC) activity during reward anticipation and higher BIS total scores compared to controls, with a positive relationship between the two measures. There were no neural 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 rated themselves as more risk avoidant and 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.

Keywords: reward anticipation, BIS/BAS, bipolar, first-degree relatives, fMRI

Highlights

- Elevated ACC activation during reward anticipation in BD-I compared to controls
- Patients displayed also higher BIS scores than controls
- ACC activation and BIS scores correlated positively in these patients
- No differences in BOLD activation or BIS/BAS scores between relatives and controls
- These findings are rather a consequence of than a vulnerability marker for BD-I