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Research paper

Reward sensitivity and the course of bipolar disorder: A survival analysis in a treatment seeking sample

Janet W. Kwan[a], Isabelle E. Bauer[a], Martin Hautzinger[b], Thomas D. Meyer[a,*]

[a] Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center, Houston, TX, United States
[b] Department of Psychology and Psychotherapy, Eberhard Karls University, Tübingen, Germany

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ABSTRACT

Objectives: Reward sensitivity is suggested to be an influence on the onset and reoccurrence of bipolar disorder (BD) in observational longitudinal studies. The current study examined whether reward sensitivity predicted the recurrence of mood episodes in a treatment seeking sample. We also explored if reward sensitivity moderated treatment outcomes of psychosocial treatment.

Methods: Seventy-six euthymic adult patients with BD were randomly assigned to either Cognitive Behavioral Therapy (CBT) or Supportive Therapy (ST) and followed up for 2 years after completing therapy (Meyer and Hautzinger, 2012). The primary outcome measure was recurrence of mood episodes. The final multivariate Cox regression models included potential covariates, therapy conditions, BAS reward sensitivity, and the interaction between BAS and therapy conditions.

Results: BAS emerged as the only significant predictor of time till recurrence of mania, but not depression, but the overall model did not reach significance. There was no interaction between treatment and BAS reward sensitivity. Interestingly, a diagnosis of BD II predicted time till recurrence of depression.

Conclusion: The main result regarding BAS partially confirms prior studies linking BAS and mania, but power and the specific sample seeking psychosocial treatment might have reduced the effect.

1. Introduction

Bipolar disorder (BD) is characterized by episodes of elevated, expansive, or irritable mood, which can be classified as mania or hypomania based on severity. Due to the symptom frequency, severity, and likelihood to reoccur, BD is often associated with high morbidity, approximately three times more than that of the general population and the majority (82.9%) of the adult BD population present with serious impairment (Gitlin and Miklowitz, 2017; Martino et al., 2017). Genetic and physiological components have been cited to be strong risk factors for BD, but environmental factors and stress have a significant impact on the course of BD (see Lex et al., 2017). From subthreshold symptoms of bipolar spectrum disorder to BD-II, then BD-I, there is a proportional increase in age of onset, suicidal behaviors, history of suicide attempts, and number of lifetime episodes (Merikangas et al., 2007, 2011). On average, approximately 10–15% of individuals with BD will experience over 10 episodes of mania in their lifetime (Muller-Oerlinghausen et al., 2002). Given its pervasiveness and impairing nature, BD continues to require further research to better understand factors that impact the course of the disorder.

1.1. Behavioral Activation System, reward sensitivity, and bipolar disorder

The Behavioral Activation System (BAS; Carver and White, 1994) is theorized to be underlying motivation, and Carver and White (1994) differentiated three aspects of the BAS: drive, fun seeking and reward sensitivity.

Individuals with lower BAS sensitivity are thought to be prone to experience more depressive symptoms, especially when considering anhedonic symptomology (McFarland et al., 2006). On the contrary, higher BAS sensitivity has been associated with substance use and impulsive behaviors, as they are more sensitive and susceptible to pursuing the perceived reward (Abbasi et al., 2016; Newman et al., 2005). Depue and Iacono (1989) were among the first ones to describe the theoretical and empirical link between the BAS and bipolar disorder, as a crucial element of this disorder is the difficulty regulating response to desire and pleasure (i.e., (hypo-) mania). Across studies, researchers have found those with BD exhibit higher BAS scores when compared to

* Corresponding author at: Department of Psychiatry and Behavioral Science, McGovern Medical School, University of Texas Health Science Center at Houston, 1941 East Road (BBSB 3118), 77054 Houston, TX, USA.
E-mail address: Thomas.D.Meyer@uth.tmc.edu (T.D. Meyer).

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a control group even at a euthymic state; moreover, one's BAS scores is associated with likelihood of meeting diagnostic criteria for BD (e.g. Alloy et al., 2008; Fulford et al., 2015; Johnson et al., 2012; Meyer et al., 2001). Considering the course of BD, BAS sensitivity has not only been shown to be predictive of onset of hypomanic or manic episodes, it is also shown to predict worse manic symptoms, and higher likelihood of hypomanic or manic episode reoccurrence (Alloy et al., 2008). Looking at the research evidence, such as that achieving personally relevant goals increases the risk for mania (e.g. Johnson et al., 2008), it suggests that an easily dysregulated reward sensitivity, a facet of the BAS, underlies the vulnerability to bipolar spectrum disorders (for a review: Alloy et al., 2015)

1.2. Current study

Given research supporting specifically the impact of one's reward sensitivity on a course of BD, the current study aimed to further examine this link within a German, treatment seeking sample to assess cross-cultural validity of the association. It aimed to assess whether the 'BAS reward sensitivity subscale' (Carver and White, 1994) prospectively predicts survival time until onset of mood episodes over the course of almost 3 years, while controlling for potential covariates. Furthermore, it is the first study in which a treatment seeking sample of patients with BD is prospectively assessed with regards to whether BAS reward sensitivity predicts the course and perhaps even interacts with treatment allocation.

2. Methods

2.1. Participants

Participants were recruited at the University of Tübingen in Germany, Department of Psychology as part of a randomized controlled trial to evaluate the efficacy of psychotherapy for BD (for details see Meyer and Hautzinger, 2012; Meyer et al., 2018). Of the 147 adults who were referred from surrounding hospitals and psychiatrists or self-referred through local advertisements, 107 participants completed the baseline assessment. Within those participants, nine withdrew from the study (n = 9), 20 were excluded as they did not meet diagnostic criteria for BD (n = 20), and two were excluded due to a current opiate or alcohol dependency (n = 2). Thus, 76 participants' data were used in the current study's analysis. The sample consisted of an equal number of female (n = 38) and male (n = 38) participants, with age ranging from 19 to 65 (M_{age} = 44, SD = 11.8). Upon an initial screening session, participants were further recruited given the following inclusion criteria: (*a*) primary diagnosis of BD according to the DSM-IV (APA, 1994); (*b*) age ranged between 18 and 65; (*c*) open to starting medication treatment if none existed. Participants were excluded from the study given the following criteria: (*a*) primary diagnosis is a non-affective disorder, (*b*) participant's current affective episode is depressed, mixed, or manic according to SCID-I and Bech-Rafaelsen Melancholia Scale (BRMS; Bech and Rafaelsen (1980); score greater than 14), or Bech-Rafaelsen Mania Rating Scale (BRMAS; Bech et al., 1978); greater than 9), (*c*) affective disorder induced by substance use or due to medical condition, (*d*) substance dependence currently requires detoxification, (*e*) IQ below 80, and (*f*) currently engaged in other psychological treatment. Each participant was randomized into cognitive behavior therapy (CBT) or supportive therapy (ST) given a stratified randomization strategy that controlled for gender, age of onset before or after the age of 20 years, and bipolar I or II disorder (Meyer and Hautzinger, 2012).

2.2. Procedure and measures

Clinical psychologists administered the SCID-I and SCID-II to assess for mental health symptoms at baseline and follow-up sessions. Any symptom combination that met the DSM-IV criteria for a mood episode were considered a relapse. The BRMS, BRMAS, and Global Assessment Scale (GAS; Endicott et al., 1976) were used to examine continuous symptom severity and functioning. Additional self-rating measures included the Beck Depression Inventory (BDI; Beck and Steer, 1987) and Self-Rating Mania Inventory (SRMI; Shugar et al., 1992). Further, hospitalizations and mood episodes were documented in clinicians' notes and participants' mood diaries. Data were collected at baseline, immediately following treatment, and post-treatment (i.e., every 3 months during the first year and 2 years after the end of treatment).

2.2.1. Behavioral Activation System (BAS; Carver and White, 1994)

The BAS is a 24-item self-report questionnaire that assesses an individual's tendency to activate behavioral systems when anticipating reward or punishment. The scale consists of three subscales, of which the current study is only examining Reward Responsiveness. Individuals rate each statement on a 4 point Likert scale, from "*very true for me*" to "*very false for me*." The current study consisted of a German translation of this scale (Meyer and Hofmann, 2005) and excluded four filler questions., i.e. only containing the 13 BAS related and 7 BIS related items. All items, except two, are reverse-scored. That is, the higher the BAS Reward Responsiveness score, the more sensitive one is to a reward possibility.

2.2.2. Beck Depression Inventory (BDI; Beck and Steer, 1987)

The BDI is a 21-item self-report assessment that assesses the presence and severity of depressive symptoms. Each question requires an individual to select one of four statements that is most representative of their current state. Scores range from 0 to 63, with higher scores suggestive of more severe symptoms of depression. Other studies have shown high internal consistency within psychiatric (α = 0.86) and non-psychiatric (α = 0.81) populations (Beck et al., 1988).

2.2.3. Self-Rating mania inventory (SRMI; Shugar et al., 1992)

The SRMI is a 48 item true-false self-report questionnaire that examines the presence and severity of manic symptoms. Previous studies suggest SRMI is a reliable, valid, and sensitive screening diagnostic tool (Bräunig et al., 1996; Cooke et al., 1996). While patients had to be considered remitted to be included into the RCT, we used this scale to assess subsyndromal manic-like symptoms.

2.2.4. Structured clinical interview for DSM-IV Axis I and Axis II disorders (SCID-I, SCID-II) (German version; Wittchen et al., 1997)

This is a clinician-administered semi-structured interview that is widely used to assess the presence and severity of axis I and II disorders, based on the DSM-IV diagnostic criteria. If participants endorsed any symptom combination that met the DSM-IV criteria for a mood episode (i.e., distinctive period of atypically expansive, elevated, or irritable mood for at least 1 week; 5 or more depressive symptoms during the same 2-week period; symptom presentation cause clinically significant distress or impairment in various areas of functioning), it was considered a recurrence. Inter-rater reliability were shown to be excellent for BD I (κ = 0.93) and BD II (κ = 0.89).

2.3. Statistical analyses

Survival analyses were conducted to examine whether relapse (i.e., the time until a DSM-IV depressive, mixed or [hypo]manic episode occurred) would be predicted by reward sensitivity and its interaction with treatment modality after controlling for covariates. The first survival analysis examined recurrence of depressive episodes, which consisted of age of onset, sex, and diagnosis of BD I or II as covariates (block 1), therapy condition (block 2), reward sensitivity (block 3), and an interaction of therapy condition and reward sensitivity (block 4). The second survival analysis examined recurrence of (hypo)manic episodes, which included the same variables in each block, with the

Table 1
Descriptive data of patients receiving Cognitive Behavioral Therapy (CBT) and Supportive Therapy (ST).

	CBT (n = 38)	ST (n = 38)
Age	44.39 ± 10.97	43.53 ± 12.73
Gender (n women)	18	20
Age of onset	26.63 ± 9.24	29.84 ± 12.44
Bipolar I disorder (%)	30 (78.90)	30 (78.90)
Bipolar II disorder (%)	8 (21.10)	8 (21.10)
BDI	13.53 ± 9.23	11.03 ± 7.60
SRMI	17.65 ± 10.98	18.99 ± 11.19
BAS reward sensitivity	10.05 ± 1.99	9.66 ± 1.82

addition of SRMI as a covariate (block 1). The SRMI needed to be included as a covariate because in a prior, related paper we found that self-rated manic symptoms at baseline predicted recurrence of mania (see Bauer et al., 2017). Additional post-hoc crosstabulation analyses were conducted to examine how reward sensitivity at low and high values as well as diagnosis of BD I and II were associated with the frequency of recurrences of a depressive or (hypo)manic mood episode. The odds ratio of each model provided an estimated ratio of reoccurrence rate in the CBT and ST groups.

3. Results

As discussed in Meyer and Hautzinger's original study, participant demographics were similar across CBT and ST groups in terms of age, gender, age of onset of the disease, and severity of depressive and manic symptoms (Meyer and Hautzinger, 2012, see Table 1 for descriptives). Across the sample, BAS reward sensitivity scores ranged from 11 to 19 (M = 15.15, SD = 1.90), and there were no significant differences in BAS reward sensitivity scores between CBT (M = 14.95, SD = 1.99) and ST (M = 15.34, SD = 1.82) conditions, $t(74) = -0.903$, $p = 0.369$.

3.1. Testing for recurrence of depressive episodes

The first Cox regression analysis examined whether our model would predict the time until recurrence of a depressive episode (Table 2). Block 1 consisted of covariates sex, age at first onset of a mood episode, and diagnosis of BD I and II; this was overall significant (χ^2 (3) = 13.463, $p = 0.004$). A diagnosis of BD I versus II was a significant predictor for time until reoccurrence of depressive mood episodes. Although the overall model remained significant, adding treatment condition in Block 2 did not significantly improve the prediction of survival time ($\Delta\chi^2$ (1) = 0.020, *n.s.;* χ^2 (4) = 13.492, $p = 0.009$). Similarly, BAS reward sensitivity in Block 3 did not significantly improve the model ($\Delta\chi^2(1) = 0.001$, $p = 0.977$) while the overall model remained significant ($\chi^2(5) = 13.493$, $p = 0.019$). Adding the interaction of treatment condition and BAS reward sensitivity in Block 4 also did not significantly increase the prediction of time till a recurrence of depression ($\Delta\chi^2$ (1) = 0.013, $p = 0.910$) but again the overall model remained significant (χ^2 (6) = 13.494, $p = 0.036$).

Additionally, post-hoc crosstabulation analysis indicated that the diagnosis is significantly associated with the recurrence of depressive episode ($X^2(1) = 6.207$, $p = 0.013$). Participants diagnosed with BD I had a less often rate of depressive episode reoccurrence (40%) than those diagnosed with BD II (75%).

3.2. Testing for recurrence of manic episodes

The second Cox regression analysis examined the same variables with the addition of SRMI in predicting time until recurrence of (hypo) manic episodes, given prior literature supporting SRMI as a significant predictor of manic relapse (Bauer et al., 2017). In Block 1, the covariates did not predict time till recurrence (χ^2 (4) = 5.887, $p = 0.208$). Similarly, the addition of treatment condition in Block 2 did not significantly improve the model ($\Delta\chi^2$ (1) = 1.232, $p = 0.267$) and the overall model was not significant either (χ^2 (5) = 7.200, $p = 0.206$). At Block 3, with the addition of BAS reward sensitivity, the overall model was trending towards significance (χ^2 (6) = 10.596, $p = 0.102$), and the same was true for the improvement in the model by adding BAS ($\Delta\chi^{2\ (1)} = 2.984$, $df = 6$, $p = 0.084$). When the interaction of BAS reward sensitivity and treatment was added in Block 4, this did not significantly improve the model ($\Delta\chi^2$ (1) = 1.363, $p = 0.243$) but the overall model was still approaching significance (χ^2 (7) = 12.405, $p = 0.088$). However, the direction of the prediction of recurrence of mania by BAS reward sensitivity was consistent with literature.

Table 2
Cox regression survival analysis: Models testing predictors of recurrence of mood episodes in bipolar disorder.

Variables	B	Wald	p-value	Odds ratio	95% CI Lower	95% CI Upper
Depressive episodes						
Block 1						
Sex	−0.414	1.373	0.241	0.611	0.330	1.322
Age at first onset	0.021	1.777	0.183	1.021	0.990	1.054
Diagnosis Axis 1	−1.034	7.988	0.005	0.356	0.174	0.728
Block 2						
Treatment condition	−0.265	0.009	0.925	0.767	0.003	18.120
Block 3						
BAS reward sensitivity	0.032	0.014	0.907	1.032	0.604	1.764
Block 4						
BAS Reward* Treatment	−0.021	0.013	0.910	0.980	0.685	1.401
Manic episodes						
Block 1						
Sex	−0.024	0.004	0.952	1.024	0.468	2.241
Age of first onset	−0.008	0.164	0.992	0.987	0.955	1.031
Diagnosis Axis 1	−0.686	2.316	0.128	0.504	0.208	1.218
SRMI	0.031	2.828	0.092	1.032	0.995	1.070
Block 2						
Treatment condition	−3.339	0.973	0.324	0.035	0.000	27.020
Block 3						
BAS reward sensitivity	0.526	2.812	0.094	1.692	0.915	3.129
Block 4						
BAS reward* Treatment	−0.251	1.344	0.246	0.778	0.508	1.190

Notes: BAS = Behavioral Activation System, SRMI = Self Rating Mania Inventory; the statistics reported are the ones obtained for final model 4 including all predictors.

While our focus was on BAS reward sensitivity as a predictor of recurrence, we also explored whether it changed over time because it was assessed at baseline and t4 (i.e. 15 months later). Looking at the intent-to-treat sample, assumptions of homogeneity of variance and sphericity were tested and upheld. There was no significant change in mean BAS reward sensitivity scores over time ($F(1,73) = 0.06$, *n.s.*), and also no interaction of treatment condition and time ($F(1,73) = 0.82$, *n.s.*).

4. Discussion

Previous research supports an association between BAS sensitivity, reaching and achieving high goals on the one hand and course of BD on the other hand, specifically in regards to the onset and reoccurrence of hypomanic or manic episodes (e.g. Alloy et al., 2009; Johnson et al., 2008, 2000). However, this has mainly been examined amongst American populations and in samples who were not specifically seeking psychosocial treatments. Thus, this study examined whether the BAS reward sensitivity scale predicts survival time until onset of mood

episodes within a German treatment seeking population to assess for cross-cultural variability.

Our results indicated a diagnosis of BD II was a significant predictor for time until reoccurrence of depressive mood episodes. This is consistent with previous studies showing that individuals with BD II experience more depressive episodes (Baek et al., 2011; Rosa et al., 2010; Vinberg et al., 2017). In our model to predict time until reoccurrence of (hypo)manic episodes, results were trending towards significance when BAS reward sensitivity and its interaction with treatment were added. This trend is consistent with literature suggesting BAS reward sensitivity is associated with proneness to hypomanic symptoms and first onset of bipolar spectrum disorder (Alloy et al., 2006, 2012). The non-significance of explaining sufficient variance by this model is likely due to the small sample size and associated limited power.

Originally the Behavioral Activation System, sometimes also referred to as the Behavioral Facilitation System or Approach System (e.g. Depue and Iacono, 1989; Johnson, 2005) was thought to relate to both mania and depression, with high sensitivity being characteristic for mania and low sensitivity being characteristic for depression. However, there is less evidence for the latter in bipolar disorder. Most of the cited studies found evidence that high BAS sensitivity, especially reward related, is predicting mania or changes in mania but not bipolar depression. Since mania and bipolar depression are associated with different risk factors, for example differential effects of social support or psychotherapy on the course of bipolar disorder or differences in heritability (e.g. Johnson et al., 1999; McGuffin et al., 2003; Merikangas et al., 2014), this led to the question of whether mania and depression are true opposites poles of the same dimension or independent but often co-occurring (e.g. Angst, 2015; Johnson et al., 2008). Our results are partially consistent with the idea that the risk factors for mania and bipolar depression are different: while BAS rewards sensitivity was found to be a significant predictor of recurrence of mania despite the overall non-significance of the regression model, this was not the case for depressive episodes.

From a cross-cultural point of view, it is worth pointing out that the BAS reward sensitivity mean score in this adult German sample of patients with BD (15.15 (SD = 1.90) is within the range reported by other studies and populations in the Western world (Dempsey et al., 2017; Fletcher et al., 2013; Meyer and Hofmann, 2005; Quilty et al., 2014). This means that the BAS subscale reward sensitivity taps into a construct that at least within the Western world seems to have cross-cultural validity.

While the focus of the analyses was not whether there were any changes in BAS reward sensitivity over time, it is worth mentioning that this characteristic remained stable over time and did not change during treatment. This supports the notion that the BAS reward sensitivity scales assesses a stable trait or temperament dimension that is also listed as a core construct of the Positive Valence System of the NIMH Research Domain Criteria (e.g. Nelson et al., 2013; Woody and Gbb, 2015).

Looking at limitations of the current study, the main limitation is that the analyses were post hoc, which limited power because the sample size was originally not powered to specifically test for predictors or moderators. Furthermore, we cannot rule out a self-selection bias because all patients were seeking psychological treatment and were willing to be randomized into a trial. Last but not least, we only focused on BAS reward sensitivity and used a self-report. However, this facet of BAS has the strongest empirical support for being involved in BD (e.g. Alloy et al., 2015), which led us to restrict the analysis to this from a theoretical and empirical point of view.

In conclusion, despite these limitations, our results looking at BAS reward sensitivity as a predictor of course in a German treatment-seeking sample is partially consistent with the previous literature about the role of reward sensitivity in BD. Additionally, findings indicated that a diagnosis of BD II predicts shorter survival time of depressive mood episodes than a diagnosis of BD I. Future research might want to expand to Non-Western cultures because it seems that almost all research on the role of BAS in BD has been done in Western countries. Furthermore, one might wonder if BAS reward sensitivity will have a stronger moderating role when other psychosocial treatments are explored such as Behavioral Activation Therapy (Martell et al., 2010) which is focused on currently depressed patients while our treatment was focused on relapse prevention in euthymic patients.

Contributors

TDM and MH were the investigators of the study. JK and TDM ran the analyses and prepared the first draft of the paper, and IB helped with the methodolgy, revieweed adn edited drafts. All authors commented on earlier versions and approved the final manuscript

Declaration of Competing Interest

None of the authors are aware of any conflict of interest with regards to this research project.

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Supplementary materials

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