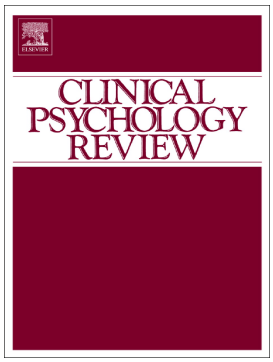

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The Dual-System Theory of Bipolar Spectrum Disorders: A Meta-Analysis

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The bipolar spectrum contains a set of related disorders characterized by the periodic experiencing of emotional extremes (American Psychiatric Association, 2013). Those who suffer from a bipolar spectrum disorder have typically experienced periods of abnormally elevated, energetic or irritable moods as well as periods of lethargy and anhedonia – sometimes rapidly cycling between both, and sometimes experiencing both simultaneously. Although a diagnosis of Bipolar I disorder (BP-I) requires only a manic episode (American Psychiatric Association,

2013), a recent, large-scale survey of those diagnosed with BP-I found that the vast majority have experienced at least one depressive episode as well (e.g., 94.2%; Karanti et al., 2020). A diagnosis of Bipolar II (BP-II), on the other hand, entails the history of a less severe manic episode along with a depressive episode (American Psychiatric Association, 2013). Cyclothymic disorder involves numerous cycles of subthreshold manic and depressive episodes. Final diagnosis often reflects the relative severity of each bipolar episode. Severe impairment due to mania/hypomania is somewhat more common among those with BP-I than with BP-II (e.g., 73.1% vs 64.6%), while severe impairment due to a depressive episode is slightly more likely among those with BP-II than in BP-I (e.g., 91.4% vs 89.3%, Merikangas et al., 2007). While the relative severities of each bipolar episode may shift based on disorder, bipolar spectrum disorders typically share the primary experience of alternating between extremes.

Much research has been devoted to considering what basic processes may lead to an upheaval of mood states (e.g., Alloy & Abramson, 2010; Berghorst et al., 2016; Hammen, 2009; Harmon-Jones et al., 2008). Gray's Reinforcement Sensitivity Theory (RST; J. A. Gray, 1970, 1987; J. A. Gray & McNaughton, 2000), has been used extensively as a framework for basic research aimed at answering this question (e.g., Alloy, Nusslock, & Boland, 2015; Bijttebier, Beck, Claes, & Vandereycken, 2009; R A Depue & Iacono, 1989; Johnson, Edge, Holmes, & Carver, 2012; Urosević, Abramson, Harmon-Jones, & Alloy, 2008; Zald & Treadway, 2017). According to the original version of RST (J.A. Gray, 1970, 1987), two neurological systems separately govern how reinforcing stimuli are processed: the Behavioral Approach System (BAS) governs processes related to appetitive stimuli and the Behavioral Inhibition System (BIS), on the other hand, processes aversive stimuli (Corr, 2008; Rutherford & Lindell, 2011). In 2000, RST was revised (J. A. Gray & McNaughton, 2000) with two main differences. First, the

system governing aversive processing was renamed from the BIS to the Fight/Flight/Freeze System (FFFS). The revised BIS was proposed to serve the purpose of resolving conflicts between multiple goals, particularly those between approach and avoidance (i.e., BAS/FFFS; Corr, 2008). Despite this revision in terminology, however, the bipolar literature has generally continued the terminology of the original RST, using BAS sensitivity to refer to appetitive sensitivity and BIS sensitivity to refer to aversive sensitivity (e.g., Alloy, Urošević, et al., 2012; Bijttebier et al., 2009; Carver & Johnson, 2009). The current meta-analysis therefore uses the terminology of the original RST – BAS and BIS – in its review of the literature, when describing appetitive and aversive processing, respectively.

BAS and BIS sensitivities impact responses to reward and punishment at multiple levels. They predict individual differences in basic processes, such as rates of physiological arousal in response to potential rewards or punishments (Blair, Peters, & Granger, 2004; Depue & Collins, 1999), as well as more complex processes, such as preferences for promotion vs prevention goals (Corr, 2013; Eddington, Majestic, & Silvia, 2012; Elliot & Thrash, 2010; Urošević et al., 2010). For this reason, positive and negative valence systems have been highlighted in the National Institute of Mental Health's Research Domain Criterial (RDoC) initiative as fertile interdisciplinary basic processes of interest (Insel et al., 2010).

Like most types of individual difference, reinforcement sensitivity falls across a range of levels, with moderate BAS and BIS sensitivities being the most common (Carver & White, 1994; J. A. Gray & McNaughton, 2000). Dysregulated reinforcement sensitivity, on the other hand, is associated with a range of affective psychological disorders both cross-sectionally and longitudinally (Bijttebier et al., 2009; Gonen et al., 2014; Johnson et al., 2003; Katz et al., 2020; Zald & Treadway, 2017; Zinbarg & Yoon, 2008). However, the role of reinforcement sensitivity

in bipolar disorder is complicated by the fact that the two emotional poles of mania and depression are associated with opposing reinforcement sensitivity profiles.

BAS hypersensitivity, or an increased responsiveness to appetitive stimuli, is noted for its salience to the manic experience (Johnson et al., 2012). Many manic symptoms, such as euphoria, disproportionate optimism, and excessive goal-directed behavior (American Psychiatric Association, 2013) are themselves extreme versions of normative BAS functioning (Johnson et al., 2012; Zald & Treadway, 2017). Other aspects of the manic emotional experience such as overly persistent positive emotionality (Gruber, 2011) further indicate abnormal BAS activation (Carl et al., 2013; Carver & Harmon-Jones, 2009; Whitton et al., 2015). Additional aspects, such as irritability and aggression, indicate BAS activation as well as BIS activation (Duek et al., 2014; Molz et al., 2013; Trew, 2011).

It is therefore unsurprising that BAS hypersensitivity is linked to the occurrence and severity of manic episodes (Johnson et al., 2012). Cross-sectionally, participants in a current manic state show greater BAS sensitivity than healthy controls (Van der Gucht et al., 2009). Longitudinally, greater BAS sensitivity has been found to predict sooner onsets of manic episodes among BP-II and cyclothymic participants (Alloy et al., 2008) and manic episodes of greater severity among BP-I patients (Meyer, Johnson, & Winters, 2001).

BIS sensitivity, on the other hand, does not appear to be associated with mania (B. Meyer et al., 2001). Indeed, the same bipolar participants in a manic state who showed greater BAS sensitivity than healthy controls were no different in terms of BIS sensitivity (Van der Gucht et al., 2009). Nor has BIS sensitivity been found to predict manic episodes longitudinally (Alloy et al., 2008; Salavert et al., 2007). Because manic symptom severity is a phenomenon unique to bipolar disorders, BAS hypersensitivity has been highlighted as a bipolar-specific risk factor

(Alloy, Bender, et al., 2012). As such, BAS sensitivity is often included as the central focus of empirical research (e.g., Fletcher et al., 2013; Hamaker et al., 2016; Pizzagalli et al., 2008) and narrative review (e.g., Alloy & Abramson, 2010; Bijttebier et al., 2009; Whitton et al., 2015) in bipolar research. On the other hand, because BIS sensitivity does not predict mania, some have argued that its role in bipolar disorder research is often downplayed relative to BAS sensitivity (Bijttebier et al., 2009). Indeed, when BIS sensitivity is included in bipolar research programs, it is most often in addition to measures of BAS sensitivity (e.g., Biuckians et al., 2007; Cuellar et al., 2005; Johnson et al., 2011; Quilty et al., 2014).

While manic episodes may be predominantly characterized by BAS hypersensitivity alone, depressive episodes show a very different reinforcement sensitivity profile (e.g., Whitton et al., 2015). Phenomenologically, depression is characterized by a mix of anhedonia and distress – the dulling of appetitive sensitivity alongside the sharpening of aversive sensitivity (Pizzagalli, 2014; Whitton et al., 2015; Zald & Treadway, 2017). Indeed, this has been found across meta-analyses of different constructs related to positive and negative valence systems, including extraversion/neuroticism (Kotov et al., 2010), temperament profiles (Zaninotto et al., 2016), and positive/negative emotionality (Bylsma et al., 2008; Khazanov & Ruscio, 2016). One recent meta-analysis directly examined reinforcement sensitivity in unipolar depression (Katz et al., 2020), finding a small, negative relationship with BAS sensitivity and a large, positive relationship with BIS sensitivity.

Bipolar depression appears to maintain similar reinforcement sensitivity patterns with regards to BIS sensitivity but not for BAS sensitivity. BIS sensitivity is associated with concurrent bipolar depressive symptoms – but not manic symptoms – when controlling for BAS sensitivity (Meyer et al., 1999, 2001; Van Meter & Youngstrom, 2015). Furthermore,

participants undergoing a bipolar depression episode report much greater BIS sensitivity than do healthy controls, though no differences are observed in BAS sensitivity (Sasayama et al., 2011; Van der Gucht et al., 2009). Among participants with bipolar disorder, higher levels of BIS sensitivity have been found to prospectively predict shorter times until the next depressive episode (Alloy et al., 2008), as well as the number and severity of depressive episodes overall (Zaninotto et al., 2015). Indeed, participants currently suffering from bipolar depression reported even greater BIS sensitivity than those suffering from current unipolar depression (Weinstock et al., 2018). Thus, unipolar depression is characterized by a combination of BAS hyposensitivity and BIS hypersensitivity. In bipolar depression, on the other hand, the current literature only finds differences in BIS hypersensitivity, though this may be the result of small sample sizes.

These distinct patterns of reinforcement sensitivity highlight the extent to which mania and depression function along independent dimensions within bipolar disorder. Although both mood states lie at opposite poles phenomenologically, they are better modeled as occurring along separate, independent dimensions (Cuellar et al., 2005; Johnson et al., 2011). Indeed, the possibility of "mixed states" provides a case study for how each bipolar dimension can occur without being suppressed by the other one (Swann et al., 2013). As separable dimensions, it is also likely that each bipolar mood state is caused by separable vulnerability factors (Johnson et al., 2011; Klein et al., 2011). The two forms of reinforcement sensitivity likely work in tandem to predict these phenomenologically opposing mood states, with BAS hypersensitivity playing the main role predicting manic states, and BIS hypersensitivity in predicting depressive states (Alloy et al., 2008). However, it remains unclear whether these patterns of reinforcement sensitivity characterize only the mood states themselves, or whether they are underlying factors at play in bipolar spectrum disorders, even when people are euthymic.

Current practices for forming bipolar groups, however, limit further inquiry in this direction. Major Depressive Disorder (MDD), for example, shows substantially larger effect sizes when participants are undergoing a current unipolar depressive episode than when they are euthymic or sampled from the general population (Clark et al., 2003; Katz et al., 2020). These effect sizes, however, change only in magnitude. The effect sizes grow larger while the general patterns of reinforcement sensitivity dysregulation remain the same. Bipolar episodes, on the other hand, are expected to be characterized by opposing effects on BAS and BIS sensitivities depending on whether participants are undergoing a manic or bipolar depressed episode (Van der Gucht et al., 2009; Weinstock et al., 2018). Most studies, however, assemble bipolar groups consisting of participants undergoing both mood states (e.g., Hayden et al., 2008; see Alloy, Titone, Ng, & Bart, 2018). Doing so severely undercuts the analysis of reinforcement sensitivity's role in bipolar disorders. Unless participants are grouped by current mood state (e.g., Van der Gucht et al., 2009), it is likely that any study's findings are a function of the specific sample's proportion of participants currently experiencing manic vs depressive symptoms (Fisher et al., 2020; Tohen et al., 2009). Other studies have taken steps to either group participants based on mood state (e.g., Brietzke et al., 2009) or separately track (hypo)manic and depressive symptoms among participants diagnosed with bipolar disorders (e.g., Johnson et al., 2011). However, these studies usually focus more on tracking the development of symptoms than on examining trait vulnerabilities that may be associated with each state. As such, they leave open the question of what vulnerability factors may be associated with each bipolar mood state and the possible role of reinforcement sensitivity in particular.

A second limitation in the current literature concerns the ways in which theoretical reviews have formulated the relationship between RST and bipolar disorders. Among the

available high-quality reviews on reinforcement sensitivity in bipolar disorders, none have quantified the role of reinforcement sensitivity across studies. Rather, these reviews have typically been narrative (e.g., Alloy et al., 2015), as opposed to meta-analytic. Narrative reviews, however, cannot adequately account for effects that are nonsignificant, unpublished, or secondary to the study at hand (Easterbrook et al., 1991; Rosenthal & DiMatteo, 2001; Sterne et al., 2000). Narrative reviews also tend to utilize a "vote counting" approach to literature, assessing previous research on the basis of their findings' statistical significance (Borenstein et al., 2009). Such an approach provides a strong argument in favor of a relationship overall. However, in order to establish a formal theory of reinforcement sensitivity in bipolar disorders, it is necessary to set out explanatory models that predict not only the presence of relationships, but also the size of such relationships as well (Borsboom et al., 2020). Furthermore, a large share of the reviews focus specifically on BAS sensitivity (e.g., Gruber, 2011; Whitton et al., 2015), and usually in relation to mania (e.g., Johnson et al., 2012; cf. Cuellers et al., 2005). These reviews have been important in establishing the role of BAS sensitivity in bipolar disorders. However, they do not quantify the size of this relationship, generally understate the role of BIS sensitivity, and often do not address reinforcement sensitivity patterns in bipolar disorders beyond the effects of mania (see Bijttebier et al., 2009).

Thus, taken together, the relationships between BAS sensitivity, BIS sensitivity and bipolar spectrum disorders remain unclear for a few reasons. First, most studies in the literature combine manic and bipolar depressive participants in the same group, bringing together opposing mood states' effects on reinforcement sensitivity. Second, the main theoretical work on the topic takes the form of narrative reviews and tends to focus most on the relationship between BAS sensitivity and mania. Doing so, however, neglects the underlying reinforcement sensitivity

profiles which characterizes bipolar disorder in general, and the role of BIS sensitivity in particular. In order to summarize the overall relationship between reinforcement sensitivity and bipolar disorders, it is necessary to perform a meta-analysis that quantifies the size of each type of reinforcement sensitivity's relationship with bipolar disorders, while also directly addressing the effects of bipolar mood states on reinforcement sensitivity measures (Alloy et al., 2018; Gonen et al., 2014; Greenebaum & Nierenberg, 2020; Kotov et al., 2017).

Current study

The present study aimed, for the first time, to quantify the relationships between both BAS and BIS sensitivity with bipolar disorders. It consisted of two sets of analyses with complementary goals. In the first set of analyses, we aimed to estimate the relationship between self-report measures of risk for (hypo)mania (e.g., Hypomanic Personality Scale (HPS); Eckblad & Chapman, 1986) with reinforcement sensitivity in the general population. Although reinforcement sensitivity's relationships with self-report depression has already been quantified elsewhere (Katz et al., 2020), its relationships with self-reported (hypo)manic risk remained unknown. This is a particularly significant gap in the literature. Although measures of (hypo)manic risk do not directly assess clinical symptoms as self-report measures of depression often do (Eckblad & Chapman, 1986; T. D. Meyer, 2002), they are nevertheless often utilized as the primary proxy for bipolar disorder in the general population (e.g., Pastor et al., 2007; Segarra et al., 2007; Sperry & Kwapil, 2020) or are used in combination with measures of depression (e.g., Applegate, El-Deredy, & Bentall, 2009; Dempsey et al., 2017).

In the second set of analyses, we considered, for the first time, the relationship between reinforcement sensitivity and diagnosed bipolar disorders across studies. This was done by performing a meta-analysis of group differences in reinforcement sensitivity between

participants diagnosed with bipolar disorder and healthy controls. Due to the considerable, opposing effects on reinforcement sensitivity imposed by mania and bipolar depression (Alloy et al., 2018; Clark et al., 2003; Van der Gucht et al., 2009), we only included participants in a currently euthymic state. While we considered including mood state as an additional moderator, we were able to find only four studies that provided reinforcement sensitivity effect sizes for isolated mood states. The vast majority of the bipolar literature that included participants with non-euthymic bipolar disorders grouped multiple mood states together (see Supplemental Table 1 for summary). Thus, it was impossible to quantitatively examine the relationships between the RST components and symptoms among participants currently undergoing manic or depressive episodes (see Method; Coding of Studies).

Operationalization of Reinforcement Sensitivity and Bipolar Pathology

Only self-report measures with prior validation were used to assess BAS and BIS sensitivity. These included measures directly derived from RST (e.g., BIS/BAS; Carver & White, 1994) as well as those with subscales developed to measure RST subsystems (e.g., Tridimensional Personality Questionnaire – Novelty Seeking and Harm Avoidance; Cloninger, 1987; Klein et al., 2011; for a comprehensive review, see Torrubia, Avila, & Caseras, 2008). Depending on the population, bipolar pathology was assessed either by self-report measures of risk for (hypo)mania (e.g., HPS; Eckblad & Chapman, 1986) or by a diagnosis of a bipolar spectrum disorder in a current euthymic state.

While behavioral measures of reinforcement sensitivity were also considered, they were ultimately not included. This primarily stemmed from the fact that many behavioral measures incorporate both BAS sensitivity and BIS sensitivity in calculating their final scores (see Matthews, 2008). Thus, reinforcement sensitivity was operationalized using only validated self-

report measures, which included subscales that were specific to BAS and BIS (see Torrubia et al., 2008 for review of self-report measures).

Hypotheses

Consistent with the BAS dysregulation model (Alloy et al., 2016), we expected to find a positive relationship between self-report measures of risk for (hypo)mania and measures of BAS sensitivity (Hypothesis 1). However, risk factors for (hypo)mania are not necessarily the same as those for depression (Alloy et al., 2008; Johnson et al., 2011). As such, we did not expect (hypo)manic risk to relate to BIS sensitivity in the general population.

However, we did expect to find diatheses for both manic and depressive states among participants diagnosed with bipolar spectrum disorder who are currently euthymic. As per the positive relationship between BAS sensitivity and mania (e.g., Alloy et al., 2016), we expected that euthymic bipolar patients should show greater BAS sensitivity than healthy controls (Hypothesis 2). On the other hand, considering the positive relationship between BIS sensitivity and depression (Katz et al., 2020), we also expected to find a positive relationship between BIS sensitivity and euthymic bipolar disorder (Hypothesis 3).

Additionally, we expected to find differences among bipolar disorders as a function of their general profiles of manic and depressive severity (Hypothesis 4). Specifically, owing to the greater impairment caused by manic episodes in BP-I (American Psychiatric Association, 2013; Merikangas et al., 2007), we expected to find greater effects for BAS sensitivity in BP-I disorder. In both sets of meta-analyses, we performed exploratory analyses of possible moderators for effect sizes, including sample size, age, and gender.

Method

Literature search

A set of 10 searches were performed in PsycInfo and PubMed for articles published after 1991 – the year of the earliest validated RST-based self-report questionnaire, MacAndrew & Steele's BIS scale (MS-BIS; 1991, see Torrubia et al., 2008). Search terms included keywords related to reinforcement sensitivity theory and its corollary measures (e.g., *RST* , "*Reinforcement Sensitivity*", "*Reward Sensitivity*", "*Punishment Sensitivity*", *etc*.) and keywords related to bipolar disorders (e.g., *bipolar, mania, etc*). Abstracts were collected between May and June 2017, then again in February 2019. A final literature search was performed after initial submission but prior to publication, on October 2020. An invitation for published and unpublished manuscripts was also publicized on ResearchGate. The reference sections of narrative literature reviews on the topic were also reviewed for additional potential articles (Alloy et al., 2015, 2016; Bijttebier et al., 2009; Johnson et al., 2012; Klein et al., 2011; Kotov et al., 2010; Nusslock & Alloy, 2017; Urosević et al., 2008; Zald & Treadway, 2017). A search protocol can be found in the Supplemental Materials section of this manuscript. A total of 1,678 references were identified for further screening. References were assembled in Endnote X8.2, and duplicates were eliminated. Abstract screening was performed on the remaining 1,134(see Figure 1 for a flow chart of the screening procedure).

Inclusion/Exclusion Criteria

Studies were included if they could provide a unique estimate of the relationship between bipolar symptomatology and reinforcement sensitivity. These fell in one of two categories. First, studies were included if they reported a correlation between a relevant validated clinical measure (e.g., HPS; Eckblad & Chapman, 1986) and a validated measure of reinforcement sensitivity

(e.g., the BIS/BAS scale; Carver & White, 1994). These effects were derived from student samples (e.g., Giovanelli, Hoerger, Johnson, & Gruber, 2013) and community samples (e.g., Ristić-Ignjatović et al., 2014). Second, studies were included if they reported reinforcement sensitivity levels of participants diagnosed with bipolar disorder and healthy controls, that could then be used to calculate standard mean differences. The original research could be performed in any language, but only manuscripts written in English were included in the meta-analysis.

Raters also excluded studies that had attributes incomparable to other studies. First, because effect sizes were only collected from validated, comparable self-report data, clinical studies were not eligible if they did not include self-report data of reinforcement sensitivity. Thus, for example, studies that only included behavioral measures of reinforcement sensitivity (e.g., Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008) were excluded. Second, we excluded studies that divided participants into groups based on reinforcement sensitivity. Many such divisions were not symmetrical (e.g., high BAS vs moderate BAS; Moriarity et al., 2020; Stange et al., 2013). This division artificially limited the range of effect sizes as compared to other effect sizes derived from unconstrained ranges of reinforcement sensitivity. Alternatively, one study divided participants based on high and low levels of self-reported hypomanic personality (Schonfelder et al., 2017). This study was not included due to such groupings' tendencies to artificially inflate effect sizes (Borenstein et al., 2009; Fisher et al., 2020). Third, to reduce potential confounding effects, studies were rejected if participants were selected based on any criteria extraneous to the meta-analysis (e.g., health anxiety; Brady & Lohr, 2014). Similarly, if the clinical group in a study was selected based on comorbidity beyond that of bipolar disorder, it was excluded from analysis (e.g., bipolar disorder with alcohol abuse; Le Strat & Gorwood, 2008). Fourth, in order to calculate standardized mean differences, participants diagnosed with

bipolar disorder were only included if they were compared to a healthy control group (cf. Kotov et al., 2010). Studies containing only data from a diagnosed group were not included (e.g., Abbasi, Sadeghi, Pirani, & Vatandoust, 2016). Fifth, experiments and treatment studies were only included if data was collected prior to any intervention taking place (e.g., Salavert et al., 2007). The first author (BAK) sorted all studies based on abstracts and reviews of the full text. The third author (KM) independently sorted a randomly selected ten percent of the studies, in order to examine the interrater reliability of sorting decisions. Reliability was high (*r*s > .86) for all stages of the sorting process. Authors of eighteen manuscripts were contacted for further information between February and April 2018, and again in February 2019, with six agreeing to send the unpublished data. Altogether, 54 manuscripts were included.

Coding of Studies

For the current study, publications were first divided based on population (see Table 1): single-sample, self-report correlational studies (Table 2) and diagnosed-healthy comparison studies (Table 3). For single-sample studies, correlations between self-reported (hypo)manic risk measures and BAS/BIS were recorded. For diagnosed-healthy comparison studies, the standard mean differences of reinforcement sensitivity were calculated from the means and standard deviations provided for each of the populations. Demographic variables which are known to be correlated with reinforcement sensitivity (e.g. proportion of female participants; Gray, Hanna, Gillen, & Rushe, 2016; Torrubia et al., 2008), were also recorded. Sample sizes and gender ratio were recorded as meta-data for each publication.

Next, we coded the clinical characteristics of the samples in the diagnosed-healthy comparison studies. Diagnosis was coded as either BP- I, BP-II, or for mixed bipolar disorders (i.e., BP-I and BP-II). Diagnosed participants' clinical states were coded as well (Zaninotto et al.,

2016). Originally, participant mood state (i.e., mania vs depression) was included as a moderator of interest for the meta-analysis. However, the majority of non-euthymic, diagnosed-healthy effects were derived from groups consisting of both mood states (i.e., 7 out of 24) or did not list the mood states of the participants (i.e., 14 out of 49). This large variance in moods within diagnosed groups prevented any meaningful conclusion to be derived from studies where participants were undergoing a current episode. Thus, only participants who were not undergoing a manic or depressive episode (i.e., euthymic) were included in the meta-analysis (see Table 3) while all other diagnosed-healthy comparison studies were excluded. A summary of these excluded studies may be found in the Supplemental Materials (Supplemental Table 2). Previous mood state was considered as a potential moderator for euthymic participants. However, a lack of available data precluded such an analysis, as only one study reported the previous episode experienced by euthymic participants (Davila et al., 2013). Similarly, clinical history of depressive and manic episodes was considered, but only three studies provided adequate data for such an analysis (Sarisoy et al., 2012; Say in et al., 2007; Van der Gucht et al., 2009).

The first author (BAK) coded all 56 studies. The third author (KM) independently coded a subset consisting of 27 studies (48.2%) randomly selected from the pool of coded studies. Interrater reliability was high (r = .96 or above) for all variables. Disagreements in ratings were discussed until a consensus was reached.

Coding Decisions

When studies contained multiple clinical or reinforcement sensitivity measures, several steps were taken to ensure that all collected data would be included and that the assumption of independence of all samples' effect sizes would be preserved. If a study reported multiple correlations from different measures of RST and clinical severity, the correlations were averaged

(see Aldao, Nolen-Hoeksema, & Schweizer, 2010). If groups were compared based on multiple measures of RST, the distributions of each group's measures were merged, creating an aggregated clinical group and an aggregated healthy control group. To achieve this, multiple means were averaged together and their corresponding standard deviations were merged by taking the square root of the pooled variances (Borenstein et al., 2009). When there were multiple clinical groups, but only one healthy control group, separate standard means differences were calculated for each group and the control group was evenly divided by the number of comparisons for which it was used (Borenstein et al., 2009; Kotov et al., 2010). Only one study was found that both answered criteria for inclusion and also reported longitudinal data (Salavert et al., 2007). Thus, only cross-sectional effects were ultimately included in the meta-analysis.

Data Analytic Plan

Effects in the original studies were derived from correlations and standard mean differences. To facilitate comparison across effects, we transformed all effect sizes to standard mean differences using standard formulae (Cooper et al., 2009). We used Hedges' *g* to calculate group differences, due to its greater robustness in the face of sample size variations (Hedges & Olkin, 1984). Effects were coded as such that larger effect sizes would indicate a greater association between BAS/BIS sensitivity and measures of (hypo)manic risk or euthymic bipolar disorders. Effect sizes were evaluated according to the same standards as Cohen's *d* (Cohen, 1988), with absolute sizes below |.49| considered small, between |.50| and |.79| considered medium, and greater than |.80| considered large.

We then summarized the effect sizes using standard meta-analytic procedures found in Borenstein et al. (2009). Summary effect sizes were calculated by taking a weighted average of effects, weighted based on the inverse sample size. In order to generalize findings beyond the

studies included in the present dataset, we used a random-effects model, which calculates standard errors as a function of both sampling error and between-study variance (Schmidt et al., 2009). Analyses were divided based on reinforcement sensitivity (i.e., BAS vs BIS) and data type (i.e., self-report measures of (hypo)manic risk vs euthymic bipolar disorder).

Moderator analyses were performed for each meta-analysis. The sample's size, average age, and gender ratio (i.e., percent of women in the total sample size) were continuous variables. As such, they were assessed using univariate regression, with the moderator entered as the predictor variable and effect size entered as the criterion variable. For the diagnosed-healthy meta-analyses, diagnosis (i.e., BP-I, BP-II, mixed) was a categorical moderator and was therefore assessed using a mixed-model subgroup analysis that used diagnosis as a grouping variable.

Publication bias was assessed by examining the distribution of effect sizes for asymmetry. Asymmetry of effect size distribution may have a number of causes, including real differences between studies or publication bias (Bakker et al., 2012; Peters et al., 2006; Sterne et al., 2000). Effect size asymmetry was assessed in two ways. First, to evaluate the overall presence of asymmetry, we used the Egger's test of the intercept to test for significant asymmetry (Egger et al., 1997; Sterne et al., 2000). In doing so, we were able to quantify the forms of asymmetry often observed informally by generating a funnel plot to map out effect sizes as a function of sample size. Next, we used Duval and Tweedie's (2000) "trim-and-fill" procedure to quantify the extent to which missing studies may have artificially inflated the final estimates, and test the robustness of the meta-analysis's findings. This was done by imputing missing studies to generate a more symmetrical distribution of effects. A new effect size summary was then calculated including the imputed studies. This new effect size summary may

then be interpreted as the furthest extent to which results of the meta-analysis may change when more fully accounting for publication bias (Borenstein et al., 2009). These procedures were performed for all meta-analyses.

Analyses were performed using R version 3.4.0 (R Core Team, 2017). The recommended packages were used (Polanin et al., 2017), including: 'compute.es' version 0.2.4 (Del Re, 2013) to calculate effect sizes; 'meta' version 4.9.2 (Schwarzer, 2007) and 'metafor' version 2.0.0 (Viechtbauer, 2010) to perform the meta-analysis, subgroup analysis and meta-regression.

Results

Description of studies

Studies were partitioned into two databases based on method of clinical assessment. The first database (see Table 2) consisted of correlations between self-report measures of (hypo)manic risk (e.g., HPS; Eckblad & Chapman, 1986) and measures of reinforcement sensitivity. Effects were sampled among nondiagnosed populations such as students (e.g., Pornpattananangkul, et al., 2015) and the general population (e.g., Rózsa et al., 2008). It consisted of 20 articles, published between 1994 and 2020, representing 23 distinct samples and 11,115 participants. Forty-two effect sizes were calculated altogether. Samples were drawn from adult participants (age M = 22.72, SD = 5.49, range = 18.00 – 37.83). Twenty-one samples provided all the information necessary for calculating effect sizes while two samples required access to unpublished data.

The second database consisted of standardized mean differences in reinforcement sensitivity between currently euthymic participants with bipolar disorders and healthy controls. This second database (see Table 3) consisted of 28 diagnosed-healthy comparison articles

published between 1995 and 2020. These articles represented 33 distinct samples and 5,628 participants. Sixty-two effect sizes were calculated altogether. Participants' mean ages spanned a wide range as well (M = 39.1, SD = 6.86, range = 19.7 - 55.3). Thirty-one samples provided adequate amounts of published data to calculate effect sizes. Two samples required access to unpublished data as well.

Meta-Analysis of Self-Report Correlations

Main effects. Hypothesis 1 predicted that BAS would have a positive relationship with measures of (hypo)manic risk. Consistent with this hypothesis, a positive relationship was found, g = .74, 95% CI [.54; .93] (see Figure 2a). Tests for homogeneity of variance found large portions of real variance, $Q(22) = 451.22$, $p < .0001$; $tau^2 = 0.21$; $I^2 = 95.1\%$ [93.7%; 96.2%], which accordingly also led to a wide prediction interval of effect sizes observed in the literature, 95% PI [-.24; 1.71]. On the other hand, no relationship was observed between (hypo)manic risk and BIS sensitivity, g = -.08, 95% CI [-.28, .12] (see Figure 2b). Here too, tests for homogeneity of variance found large portions of real variance, $Q(18) = 323.71$, $p < .0001$; $tau^2 = 0.18$; I^2 = 94.4% [92.6%; 95.8%], which accordingly also led to a wide prediction interval of effect sizes observed in the literature, 95% PI [-1.00; .83]. Thus, in studies on non-diagnosed populations, self-reported measures of risk for (hypo)mania were found to have a medium positive relationship with BAS sensitivity and no relationship with BIS sensitivity.

Moderator Analysis. We examined potential moderators as well. To examine the role that continuous variables (i.e., sample size, age and percent women) may play as moderators, we performed a series of univariate regressions using the continuous variables as predictors and BAS/BIS effect sizes as criterion variables (see Tables 5a and 5b). No continuous variables significantly moderated effect sizes for BAS (ps > .28) or for BIS (ps > .08) effect sizes. Thus,

no moderators were found to meaningfully moderate the relationship between self-report measures of (hypo)manic risk and reinforcement sensitivity.

Diagnosed-Healthy Comparisons

Main effects. Hypothesis 2 predicted that euthymic diagnosed participants would have higher levels of BAS sensitivity than healthy controls. Consistent with this hypothesis, a positive (albeit small) relationship was found, g = .20, 95% CI [.06; .33] (see Figure 3a). Tests for homogeneity of variance found large portions of real variance in the literature, $Q(32) = 121.96$, $p < .0001$; $tau^2 = 0.33$; $I^2 = 73.8\%$ [63.1%; 81.4%]. A wide prediction interval of effect sizes was observed in the literature, 95% PI [-.48; .88].

Hypothesis 3 predicted that diagnosed participants in a euthymic state would have higher levels of BIS sensitivity. Here too findings supported this hypothesis, with a positive relationship observed, g = .64, 95% CI [.47; .81] (see Figure 3b). As with BAS, tests for homogeneity of variance in BIS effect sizes found large portions of real variance in the literature, $Q(28) = 138.41$, $p < .0001$; $tau^2 = 0.16$; $I^2 = 79.8\%$ [71.6%; 85.6%]. This was also reflected in a wide prediction interval of BIS effect sizes, 95% PI [-.19; 1.47].

Thus, effect sizes derived from euthymic diagnosed-healthy comparisons showed a different pattern from self-reported correlations. Correlational studies among nondiagnosed populations showed (hypo)manic risk to have a medium positive relationship with BAS and no relationship with BIS. Euthymic diagnosed-healthy comparison studies, on the other hand, found only a small positive relationship between bipolar disorder and BAS sensitivity, and a medium positive relationship between bipolar disorder and BIS sensitivity.

Moderator Analysis. Moderating variables were explored for diagnosed-healthy comparison studies as well. Hypothesis 4 predicted that disorder would moderate effect sizes. To evaluate this hypothesis, we examined categorical moderators of disorder (i.e., BP-I, BP-II) using subgroup analysis (see Table 4). Contrary to Hypothesis 4, disorder did not moderate effect sizes for BAS $Q(2) = .20$, $p = .91$ or BIS $Q(2) = .86$, $p = .65$. Next, we performed a series of univariate regressions to examine the role that continuous variables (i.e., sample size, age and percent women) as moderators (Tables 5a-b). Age to a very small degree negatively moderated effect sizes for BAS, $b = -.02$, $p = .02$, 95% CI [-.04; -.00], but not for BIS, $b = .01$, $p = .64$, 95% CI [-.02; .03]. No other continuous variable moderated BAS ($ps > .48$) or BIS ($ps > .32$) effect sizes. Thus, no moderators were found to meaningfully moderate the relationship between bipolar disorder and reinforcement sensitivity.

Publication bias analysis

We then examined the data for publication bias. Egger's tests were conducted to examine the possibility of asymmetrical distributions of effects and Duval and Tweedie's trim-and-fill procedures were implemented to quantify the possible impact of such asymmetries. For the self-report correlational studies, the test was significant for BAS effect sizes, $t(21) = -2.15$, $p = .04$, but not for to BIS effect sizes, $t(17) = -.07$, $p = .95$. However, the trim-and-fill procedures did not impute any missing studies for either distribution, leaving the newly estimated effect sizes unchanged (see Figures 2a-b).

For the diagnosed-healthy comparison studies, Egger's test was not significant for BAS, $t(31) = -1.04$, $p = .31$, and was for BIS, $t(27) = 2.41$, $p = .02$. However, as with the correlational studies, no new studies were imputed in either distribution (see Figures 2c-d). Thus, we concluded that there was a possibility of systematic bias in the distribution of BAS effect sizes

for self-report correlational studies and BIS effects sizes in diagnosed-healthy comparison studies, there was little evidence that publication bias impacted the final estimates in the meta-analysis overall.

Discussion

The relationship between reinforcement sensitivity (Corr & McNaughton, 2008; J. A. Gray, 1970, 1987; J. A. Gray & McNaughton, 2000) and the bipolar spectrum has been subjected to an array of basic and applied research (e.g., Farreny et al., 2016; Keough, Wardell, Hendershot, Bagby, & Quilty, 2017; Pizzagalli et al., 2008). Reviews of the topic are narrative and typically highlight the role of BAS dysregulation in mania (e.g., Alloy & Abramson, 2010; Alloy et al., 2015; Gruber, 2011; Johnson et al., 2012; Trew, 2011). However, they do not employ quantitative methods, account adequately for the role of BIS sensitivity, or neutralize the opposing effects of manic versus depressive mood states on reinforcement sensitivity (Bijttebier et al., 2009; Borenstein et al., 2009; Corr et al., 2014). For this reason, we performed a meta-analysis of the literature on the reinforcement sensitivity in bipolar disorder, focusing on self-report measures of risk for (hypo)mania in the general population, and reinforcement sensitivity dysregulation in euthymic bipolar disorders.

First, we examined the relationship between reinforcement sensitivity and self-report measures of risk for (hypo)mania in the general population. A large, positive relationship was found with BAS sensitivity, while no relationship was found with BIS sensitivity. This pattern was in stark contrast to reinforcement sensitivity's relationship with depression (Katz et al., 2020). Self-report measures of depression share a large, positive relationship with BIS sensitivity and a small negative relationship with BAS sensitivity. Thus, the relationship between reinforcement sensitivity and self-reported, nonclinical bipolar severity depends on the valence

of the bipolar-related mood. In the general population, BIS sensitivity only aligns with self-report measures of depression. BAS sensitivity, on the other hand, aligns positively with risk for (hypo)mania to a large extent and negatively with depression to a small extent.

Next, we examined how both systems would be dysregulated among people with diagnosed bipolar disorders, who are at risk for experiencing both manic and depressive episodes. The widespread practice of combining manic and depressive participants in the same bipolar group prevented our ability to separately quantify the effects of manic and depressive state on reinforcement sensitivity. Because the opposing effects of these mood states are likely to depend on the unique and unknown composition of the specific sample, we focused on studies that compared participants with bipolar disorders in a euthymic state to healthy controls. We found that individuals diagnosed with bipolar disorders were more BAS sensitive to a small degree and more BIS sensitive to a medium degree. This was, essentially, a combination of the relationships that reinforcement sensitivity has with self-report measures of risk for (hypo)mania and depression. Effect sizes were not moderated by diagnosis (e.g., BP-I vs. BP-II ;see Izci et al., 2016; cf. Lu et al., 2012).

A Dual-System Theory of Bipolar Disorders

Taken together, the current findings support a dual-system theory of bipolar disorders, where BAS sensitivity is more closely associated with manic episodes while BIS sensitivity is more closely associated with bipolar depressive episodes. The few diagnosed-healthy comparison studies that grouped bipolar participants based on mood state indicate this as well. Participants undergoing a current manic state were found to be more BAS sensitive than healthy controls with no difference in BIS sensitivity (Van der Gucht et al., 2009). Participants undergoing a bipolar depressive episode, on the other hand, were found to be more BIS sensitive

than healthy controls, with no difference in BAS sensitivity (Sasayama et al., 2011; Van der Gucht et al., 2009). This trend holds longitudinally as well (Alloy et al., 2008; Salavert et al., 2007; Zaninotto et al., 2015). Under this dual-system model, the current meta-analysis reveals that euthymic bipolar disorder shows diatheses for both mania and bipolar depression – BAS sensitivity and BIS sensitivity, respectively.

A dual-system theory of bipolar disorders may serve as an extension of BAS sensitivity theories of bipolar disorders (Alloy et al., 2009; Depue & Iacono, 1989; Urosević et al., 2008). These theories have played a critical role in identifying BAS hypersensitivity as a longitudinal risk factor for bipolar disorder (Alloy et al., 2008; Alloy, Urošević, et al., 2012; Walsh et al., 2015). However, based on the relationship between BAS sensitivity and self-reported risk for (hypo)mania, the more precise theory may be that BAS hypersensitivity is a risk factor for mania – a phenomenon unique to bipolar disorders (American Psychiatric Association, 2013).

Indeed, this distinction may also help answer a controversy surrounding the role of BAS sensitivity in bipolar depression (Johnson et al., 2012). Some argue that bipolar disorder is caused by BAS lability, with BAS hypersensitivity leading to mania and BAS hyposensitivity leading to depression (R. A. Depue & Iacono, 1989). Others argue that bipolar disorder is characterized by BAS hypersensitivity across mood states and that bipolar depression would be the result of more acutely felt goal frustration (Nusslock et al., 2007). In general, however, the link between BAS sensitivity and bipolar depression has been tenuous. In some cases, BAS hyposensitivity has been found to correlate with depressive episodes (B. Meyer et al., 1999). More often, however, no direct relationship has been found (e.g. Alloy et al., 2008). It may be that some of these conflicting findings may be explained using a dual-system framework. Although all agree that BAS sensitivity does positively predict mania, it may be that it is BIS

sensitivity is more closely related to depression. If so, future research may be employed to better understand the interplay between the two systems prior to a bipolar episode.

The current findings are also consistent with other approaches that use a combination of positive and negative valence sensitivities to classify affective psychopathology. A meta-analysis of mood disorders and temperament found euthymic bipolar disorder to be hypersensitive in positively-valenced temperaments (e.g., Novelty Seeking) to a small degree, and hypersensitive in the negatively-valenced temperament (i.e., Harm Avoidance) to a large degree (Zaninotto et al., 2016). Euthymic Major Depressive Disorder, on the other hand, was hyposensitive in Novelty Seeking and even more hypersensitive in Harm Avoidance than bipolar disorder. This is one of the reasons that the Hierarchical Taxonomy of Pathology (HiTOP) has classified bipolar disorders as a function of thought disturbance (i.e., BAS hypersensitivity-Impulsivity) and distress (i.e., BIS sensitivity; Kotov et al., 2017).

The dual-system theory also has implications for bipolar disorders' research practices. While depression differs in effect size as participants become more acute, the general pattern of reinforcement sensitivity dysregulation remains the same (Katz et al., 2020). This is not the case when depression is compared to (hypo)manic risk, which shows a strongly different reinforcement sensitivity profile.

These findings raise a question regarding the representativeness of nonclinical, analogue samples based only on self-report measures of risk for (hypo)mania. Indeed, in nonclinical samples, these measures may only be a proxy for BAS hypersensitivity since they do not select for the BIS hypersensitivity that is found in euthymic bipolar disorder. While BAS hypersensitivity is itself a notable risk factor for bipolar disorder, it may only be so in the presence of other individual differences, such as BIS hypersensitivity (Alloy, Urošević, et al.,

2012; Gonen et al., 2014) or thought disturbance (Kotov et al., 2017). Furthermore, (hypo)mania and bipolar depression are dissociable phenomena with separable risk factors (Alloy et al., 2008; Johnson et al., 2011). It has even been argued that bipolar disorders may be best conceptualized as separate, highly comorbid disorders of mania and depression (Cuellar et al., 2005; Schweitzer et al., 2005). As such, measures of BAS hypersensitivity may only select for (hypo)manic risk, but not depressive risk. Studies that utilize only measures of (hypo)manic risk or BAS sensitivity may only be adequate analogue samples for participants undergoing clinical manic episodes – and even so only at the measures' upper ranges (Alloy, Urošević, et al., 2012; T. D. Meyer, 2002; Walsh et al., 2015). However, to assemble a nonclinical sample that represents the multifaceted dysregulation present in bipolar disorders, other clinically relevant measures of individual difference should be incorporated as well (Gomez et al., 2004; Gonen et al., 2014; Power, 2005).

The current findings are relevant to research on clinical populations as well. Reinforcement sensitivity has been found to be quite sensitive to fluctuations in depression and (hypo)mania (Clark et al., 2012; Katz et al., 2020; Schoevers et al., 2020). Thus, in order to examine the underlying reinforcement sensitivities in people with bipolar disorders, it is necessary to carefully consider these effects in the clinical group. The widespread research practice of including both manic and depressive participants in the same group (see Supplementary Table 2), however, prevents such steps from being taken (Tohen et al., 2009). Rather, when taking part in research on RST, participants with bipolar disorders should either be put into separate groups based on their clinical state (e.g., Van der Gucht et al., 2009) or only included after they are euthymic (Davila et al., 2013).

The dual-system theory may also be helpful in signaling potential ways through which unipolar depression and bipolar depression may be differentiated from each other (Stanton et al., 2020). First, people who suffer from bipolar depression are more likely to have diatheses for mania than those who suffer from unipolar depression. As such, they are likely to be less BAS hyposensitive (i.e., relatively more BAS sensitive) than their peers with unipolar depression (Weinstock et al., 2018). Thus, while both types of depression will usually entail anhedonia, differences in BAS hyposensitivity may be found in other ways. Bipolar depression is characterized by greater emotional lability than unipolar depression (P. B. Mitchell et al., 2008). Similarly, people undergoing a bipolar depressive episode are found to have higher resting state connectivity in their reward networks than those suffering from a unipolar episode, despite their similar levels of hyporeactivity to reward consummation (Satterthwaite et al., 2015; Shi et al., 2018). Furthermore, the dual-system theory may be useful in identifying how the shared symptoms in unipolar and bipolar depressions may show different clinical presentations. For example, it has been suggested that racing thoughts, which are present in generalized anxiety and unipolar depression, may be more focused on worry and stress, while they may be more focused on grandiose ideas and disappointment in bipolar depression (Stanton et al., 2019). Similarly, irritability in unipolar depression may present more attitudes of fatigue and upsetness, while in bipolar depression it may also be presented with aspects of acutely felt frustrative nonreward (Eisner et al., 2008; Stanton, 2020).

Future work on the dual-hypothesis theory would particularly benefit from research that utilizes longitudinal, within-subject designs that track both BAS sensitivity, BIS sensitivity and bipolar symptom severity over time (e.g., Alloy, Urošević, et al., 2012; Sperry & Kwapil, 2017). While such studies require additional time and resources, they are also critical for the precise

understanding of the roles that BAS and BIS sensitivities play in the etiology of mania and depression (Bijttebier et al., 2009; Brown & Rosellini, 2011). For example, in one study (B. Meyer et al., 1999), BAS sensitivity prospectively predicted mania, while BIS sensitivity only correlated with depression cross-sectionally. If this finding is replicated, it may imply that the relationship between BAS sensitivity and mania operates differently from that between BIS sensitivity and depression. Because BAS sensitivity prospectively predicts mania, its dysregulation may play an etiological role. If BIS sensitivity only predicts depression cross-sectionally, its dysregulation may only be an epiphenomenon of depression that develops in parallel to it (Klein et al., 2011). Similarly, temporal measurements can measure reinforcement sensitivity's stability among people who suffer from bipolar disorders, beyond their elevated baselines. For example, the current meta-analysis found BIS sensitivity to be elevated among people with euthymic bipolar disorder and the dual-hypothesis theory expects it to be particularly related to shifts in bipolar depression symptomatology (Van der Gucht et al., 2009). However, ecological momentary assessments have revealed that greater instability of BIS sensitivity between measures is associated with both depressive and (hypo)manic symptoms (Sperry & Kwapil, 2020). Ultimately, a further developed theory of RST and bipolar disorders should integrate studies included in the current meta-analysis with longitudinal research. Cross-sectional research offers the opportunity to compare a wide range of individual differences between people with bipolar disorders and healthy controls. Longitudinal research may closely explore within-participant fluctuations, integrating data on the instability of these individual differences in the face of bipolar mood swings.

Ideally, such research will include multimodal forms of assessment. Doing so may circumvent mood-dependent response biases in self-report assessments. Self-report assessments

alone may be biased by the fact that respondents undergoing manic and depressive episodes may be more likely to rate items based on their present mood state, instead of how they behave in general (Clark et al., 2003; Schraedley et al., 2002; Spinhoven et al., 2013; cf. Kasch et al., 2002). Implicit, behavioral, and physiological measures may be useful in circumventing such biases (Bartholomew et al., 2019; Nielson et al., 2020; Satterthwaite et al., 2015). Longitudinal, multimodal, within-participant research may more precisely model the interplay between reinforcement sensitivity and bipolar symptom severity.

Such lines of research may also provide further insight into the malleability of reinforcement sensitivity among those with bipolar disorders. Indeed, evidence of reinforcement sensitivity's instability in bipolar disorders challenges its generally accepted role as a stable trait across situations (Alloy, Urošević, et al., 2012; Corr, 2008; Hamaker et al., 2016; Sperry & Kwapil, 2020). For example, some models explore the common causes which may lead to changes in both temperamental reinforcement sensitivity as well as increases in symptom severity (Garland et al., 2010; Klein et al., 2011; Vittengl et al., 2020). Others may construe reinforcement sensitivity as being influenced by two factors: diathetic personality traits as well as symptom-derived "personality states" (Clark et al., 2003; Naragon-Gainey et al., 2013; Roberts et al., 2017). The dual-system theory adds to this theoretical discussion by predicting that any malleability observed in reinforcement sensitivity would be related to which bipolar mood state is being activated.

Limitations and Future Directions

While assessing the findings from the current meta-analysis, it is worth keeping certain limitations in mind. RST is a biobehavioral model (Corr, 2008; J. A. Gray & McNaughton, 2000) that posits a physiological basis for personality and behavior (J. A. Gray, 1970; J. T. Mitchell et

al., 2007). In the general population, self-report measures of reinforcement sensitivity are related to their corollary reward and punishment neurological subsystems (Torrubia et al., 2008). However, future meta-analyses may more directly estimate reinforcement sensitivity by including biological (e.g., Urosevic, Youngstrom, Collins, Jensen, & Luciana, 2016) and behavioral assessments (e.g., Treadway, Bossaller, Shelton, & Zald, 2012) of reinforcement sensitivity as well.

Additionally, the current systematic review and meta-analyses summarize the overall relationships between BAS sensitivity, BIS sensitivity and the bipolar disorder spectrum. Future studies may go further by examining subsets of each sensitivity. Each reinforcement sensitivity consists of multiple dissociable subtypes of responses (Insel et al., 2010; Zald & Treadway, 2017). While these different subtypes are interrelated in the general population (Lehner et al., 2017), they may differentially predict bipolar symptoms (Gruber & Johnson, 2009). For example, bipolar disorders predict a greater valuation of rewards and a greater willingness to expend effort to attain them. However, they do not predict differences in hedonic response to rewards once attained (Johnson et al., 2012; Nusslock et al., 2012). Future reviews of RST and bipolar disorders will benefit from more refined examinations that will better define which reinforcement processes were operationalized in a given study. These examinations may be particularly aided by the careful selection of behavioral measures of reinforcement sensitivity. Thus, for example, the Effort Expenditure for Rewards Task (i.e., EEfRT task; Treadway et al., 2012) may be utilized to assess willingness to expend effort to attain rewards while mood response to task success may be utilized to assess reward satiation (Farmer et al., 2006; Nielson et al., 2020). These measures may compliment other self-report measures that also compare

different sub-types of reinforcement sensitivity (e.g., BIS/BAS – Drive vs Reward Responsiveness; Carver & White, 1994).

Additionally, all studies included utilized the original framework of RST (J. A. Gray, 1970, 1987). In 2000, the theory was revised (J. A. Gray & McNaughton, 2000). The BAS continued to regulate reward sensitivity while the punishment sensitivity system was renamed the Fight/Flight/Freeze System (FFFS). The revised BIS was theorized to govern goal choices and regulate BAS/FFFS conflicts (Corr, 2008). The vast majority of the bipolar literature, however, still utilizes the formulations in the original RST (Bijttebier et al., 2009). Thus, the current analyses should be understood as reflecting general sensitivities to positively and negatively valenced experiences and stimuli, similar to those noted in the Research Domain Criteria (RDoC; Insel et al., 2010). However, the revised BIS plays a critical role in regulating between reward and punishment sensitivities (Corr, 2008). In light of the role that each of these sensitivities play in manic vs depressive states, future research may find that the revised BIS plays an underappreciated role in predicting the shifts between bipolar mood states.

It is also worth noting that the current meta-analyses are impacted by decisions made within each of their component studies. Commonly excluded comorbidities, such as substance use and neurological damage, are likely under-represented in the samples included in the meta-analysis. Future reviews of the bipolar literature would benefit from attending to the range of common selection criteria utilized, and how they impact findings.

A final limitation of the current meta-analysis lies in the relationship between bipolar diagnosis subtype (i.e., BP-I vs BP-II) and symptom severity. Different diagnostic subtypes were expected to differ as a function of their differing patterns of manic vs depressive impairment (Merikangas et al., 2007). However, while diagnostic subtype was used as a proxy for manic vs.

depressive impairment, it was an indirect one. The current analysis assumed general trends of impairment observed within bipolar diagnoses, instead of assessing the actual impairment incurred by each sample. Currently, very few studies provide information about previous symptom severity in general (e.g.,Sarisoy et al., 2012; Sayin et al., 2007; Van der Gucht et al., 2009) and even fewer about the previous episode experienced (e.g., Davila et al., 2013). Future studies may more directly examine the dual-system theory by comparing reinforcement sensitivity directly to previous levels of manic and depressive severity.

Conclusion

The current paper provides a meta-analysis of the relationship between RST and bipolar disorders. In doing so, it supports a dual-system theory of bipolar disorders, wherein BAS sensitivity positively predicts mania and BIS sensitivity positively predicts bipolar depression. It found support for this theory among two populations. In the general population, self-report measures of risk for (hypo)mania were positively related to BAS sensitivity but not BIS sensitivity. This stands in contrast to self-report measures of depression that are positively related to BIS sensitivity to a large degree, and are negatively related to BAS sensitivity to a small degree (Katz et al., 2020). In studies that compared euthymic bipolar participants to healthy controls, participants with euthymic bipolar disorder were BAS hypersensitive to a small degree and BIS hypersensitive to a medium degree. Thus, they showed diatheses for mania and bipolar depression, respectively. The dual-system theory of bipolar disorder proposed here offers a theoretical framework that brings together positive valence systems and negative valence systems into the same model for bipolar disorders. Practically, it highlights the importance of directly accounting for the contradictory effects inherent in bipolar disorders' opposing mood states when performing clinical research in the future.

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Tables and Figures

Table 1. Summary of databases

	General Population	Diagnosed (euthymic) vs healthy controls	Diagnosed (non-euthymic) vs healthy controls
Included in meta-analysis	Yes	Yes	No
Summary Table	Table 2	Table 3	Supplementary Table 2
Type of effect	Correlation	Standardized mean differences	Standardized mean differences
N studies	22	28	25
N individual samples	23	33	31
N effect sizes	42	62	59
Total N	11,115	5.628	5,154
Mean (SD) n per study	483.26 (906.24)	170.54 (220.39)	166.26 (184.39)
Median [range] n per study	230 [36-4462]	100 [25-1069]	117 [29 – 788]

Table 2. Summary of correlational studies

ID Text	N	% Wom.	Age	RST Scales	Pub Status	*g* BAS	*vg* BAS	*g* BIS	*vg* BIS
Applegate et al., (2009)	516	0.66	21.70	BIS/BAS	Y	0.43	0.01	0.06	0.01
Carver et al. (2009); Study 1	235	0.57	19.50	BIS/BAS	Y	0.57	0.02	-0.32	0.02
Carver et al. (2009); Study 2	394	0.67	19.50	BIS/BAS	Y	0.97	0.01	-0.10	0.01
Dempsey et al., (2017)	127	0.82	24.30	BIS/BAS	Y	0.91	0.03	-0.49	0.03
Dempsey et al., (2020)	168	143	27.41	BIS/BAS	Y	0.46	0.02	-0.67	0.02
Dodd et al., (2011)	175	0.88	19.75	BIS/BAS	Y	0.25	0.02	0.36	0.02
Fulford et al., (2008)	233	0.57	18.75	BIS/BAS	Y	0.53	0.02	-0.32	0.02
Fulford et al., (2015)	214	0.65	18.25	BIS/BAS	Y	0.87	0.02	-0.02	0.02
Giovanelli et al., (2013)	823	0.76	19.00	BIS/BAS-FS	Y	1.04	0.01	NA	NA
Johnson et al., (2006); Study 1	138	0.68	18.00	BIS/BAS	Y	0.75	0.03	-0.18	0.03
Johnson et al., (2006); Study 2	285	0.68	18.00	BIS/BAS	Y	0.71	0.01	-0.28	0.01

Jones et al., (2007); Study 2	230	0.67	22.36	BIS/BAS	Y	0.81	0.02	NA	NA
Jones et al., (2008)	231	0.79	28.52	BIS/BAS-BAS	Y	0.66	0.02	0.29	0.02
Kim et al., (2017)	543	0.52	20.26	BIS/BAS-BAS; Korean	Y	1.32	0.01	NA	NA
Mansell et al., (2008)	191	0.84	20.00	BIS/BAS	Y	0.36	0.02	0.27	0.02
Mason et al. (2012)	49	0.51	21.40	BIS/BAS-BAS	Y	0.61	0.08	NA	NA
Meyer et al. (2005)	59	0.54	19.70	BIS/BAS	Y	1.64	0.09	-0.18	0.07
Pastor et al., (2007); Segarra et al., (2007)	193	0.59	20.10	BIS/BAS; SPSRQ	N	1.05	0.02	-0.35	0.02
Pornpattananangkul et al., (2015)	36	0.58	18.56	BIS/BAS; SPSRQ	N	0.87	0.12	-0.24	0.11
Ristić-Ignjatović et al., (2014)	570	0.53	35.55	TCI-R	Y	0.14	0.01	0.87	0.01
Rózsa et al., (2008)	1132	0.70	27.74	TCI-R	Y	0.14	0.00	0.72	0.00

Shirahama et al., (2018)	111	0.40	26.30	TCI	Y	0.87	0.04	-1.49	0.05
Windle, (1994)	4462	NA	37.83	MS-BIS; MMPI-MAC Scale	Y	1.22	0.00	0.10	0.00

Note. BIS/BAS: Behavioral Inhibition System/Behavioral Activation scale,, BIS/BAS-BAS: BIS/BAS, BAS subscale, MMPI-MAC: Minnesota Multiphasic Personality Inventory's MAC scale, SPSRQ: Sensitivity to Punishment, Sensitivity to Reward Questionnaire, TCI: Temperament and Character Inventory, TCI-R: Revised TCI.

Table 3. Summary of clinical-healthy comparison studies included in meta-analysis

ID_Text	N	Perc Wom	Age	RST Scales	Pub status	*g* BAS	*vg* BAS	*g* BIS	*vg* BIS	Disorder
Afshari et al. (2019)	124	0.62	32.2	BIS/BAS; J-5	Y	0.06	0.03	0.23	0.03	Mixed
Alloy et al. (2009)	389	0.6	19.7	BIS/BAS	Y	0.56	0.01	0.22	0.01	BP-II
Almeida et al. (2011)	137	0.64	38.2	TCI	Y	0.5	0.03	1.88	0.04	BP-I
Blairy et al. (2000)	129	0.62	41.5	TPQ	Y	-0.28	0.04	0.92	0.04	Mixed
Caseras et al. (2013)	27	NA	42.63	BIS/BAS	Y	1.01	0.17	1.56	0.19	BP-I
	25	NA	41.36	BIS/BAS	Y	0.76	0.17	1.26	0.19	BP-II
Chan et al. (2018)	180	0.61	41.27	BIS/BAS-BAS	Y	0.41	0.02	NA	NA	Mixed
Davila et al. (2013)	67	0.6	35.23	TCI	Y	-0.53	0.06	0.55	0.06	BP-I
Engstrom et al. (2004)	125	0.24	55.30	TCI	Y	-0.07	0.03	0.24	0.03	BP-I
	75	0.13	55.30	TCI	Y	0.00	0.06	0.65	0.06	BP-II
Fayyazi Bordbar et al., (2014)	669	0	36.10	TCI	Y	0.08	0.02	0.74	0.02	BP-I

ID_Text	N	Perc Wom	Age	RST Scales	Pub status	*g* BAS	*vg* BAS	*g* BIS	*vg* BIS	Disorder
	639	1	36.10	TCI	Y	-0.04	0.02	0.14	0.02	BP-I
Ford et al. (2015)	62	0.68	30.20	BIS/BAS	Y	0.69	0.07	NA	NA	BP-I
Hayden et al. (2008)	38	0.58	41.70	BIS/BAS	Y	0.13	0.10	0.34	0.10	Mixed
Izci et al. (2016)	77	0.32	34.6	TPQ	Y	0.21	0.06	0.36	0.06	BP-I
	74	0.34	34.6	TCI	Y	-0.02	0.06	0.09	0.06	BP-II
Loftus et al. (2008)	170	0.48	34.60	TCI	Y	0.17	.02	NA	NA	BP-I
Lu et al. (2012)	137	0.61	34.52	TPQ	Y	0.73	0.03	1.30	0.04	BP-I
	177	0.63	33.07	TPQ	Y	0.47	0.03	1.36	0.03	BP-II
Mellick (2019)	60	0.52	37.40	SPSRQ-SR	Y	0.64	0.07	NA	NA	Mixed
Nowakowska et al. (2005)	73	0.63	35.20	TCI	Y	0.72	0.06	1.03	0.07	Mixed
Osher et al. (1996)	1069	0.03	38.70	JTCI	Y	0.14	0.02	0.47	0.02	Mixed
Osher et al. (1999)	50	0.56	42.66	TPQ	Y	0.72	0.08	0.48	0.08	Mixed
Pavlickova et al., (2014)	44	.73	48.41	SPSRQ	Y	0.73	0.09	1.24	0.11	Mixed
Salavert et al. (2007)	77	0.55	36.47	SPSRQ	Y	1.14	0.06	0.34	0.05	BP-I

ID_Text	N	Perc Wom	Age	RST Scales	Pub status	*g* BAS	*vg* BAS	*g* BIS	*vg* BIS	Disorder
Sapir et al. (2013)	100	0.54	43.7	TCI	Y	-0.05	0.04	0.45	0.04	BP-I
Sarisoy et al. (2012)	222	0.71	37.6	TCI	Y	-0.08	0.02	0.42	0.02	Mixed
Sayin et al. (2007)	180	1	39.5	TCI	Y	-0.12	0.02	0.12	0.02	Mixed
Van der Gucht et al. (2009)	57	.56	47.62	BIS/BAS	Y	-0.12	0.09	0.83	0.10	Mixed
Young et al. (1995)	38	0.00	37.00	TPQ	Y	0.22	0.11	0.46	0.11	Mixed
	57	1.00	37.00	TPQ	Y	0.54	0.07	0.61	0.07	Mixed
Zaninotto et al. (2015)	143	0.55	44.20	TCI	N	-0.37	0.03	0.67	0.03	BP-I
	137	0.57	45.07	TCI	N	-0.39	0.03	0.46	0.04	BP-II

Note. BIS/BAS: Behavioral Inhibition System/Behavioral Activation scale,, BIS/BAS-BAS: BIS/BAS, BAS subscale, JTCI: Junior Temperament and Character Inventory, MMPI-MAC: Minnesota Multiphasic Personality Inventory's MAC scale, MS-BIS: MacAndrew & Steele's Behavior Inhibition Scale, SPSRQ: Sensitivity to Punishment, Sensitivity to Reward Questionnaire, SPSRQ: Sensitivity to Punishment, Sensitivity to Reward Questionnaire – Sensitivity to Reward Subscale, TCI: Temperament and Character Inventory, TCI-HA: TCI Harm Avoidance subscale, TCI-R: Revised TCI

Table 4. Analysis summary of reinforcement sensitivity and categorical moderators for diagnosed-healthy comparison studies

	BAS				BIS			
Moderator	*k*	*g*	95% CI	Test of subgroup differences	*k*	*g*	95% CI	Test of subgroup differences
Main Effect	32	.19	[.05; .32]		29	.64	[.47; .81]	
Disorder				$Q(2) = .20$, $p = .90$				$Q(2) = .86$, $p = .65$
Bipolar I	13	.23	[-.01; .47]		11	.72	[.40; 1.04]	
Bipolar II	6	.21	[-.14; .56]		6	.64	[.20; 1.08]	
Mixed	14	.17	[-.02; .35]		12	.55	[.36; .73]	

Table 5a. Random-effects models of continual moderators of reinforcement sensitivity and bipolar disorder among self-report correlational studies

	BAS				BIS			
Moderator	*Beta*	SE	95% CI	R^2	*Beta*	SE	95% CI	R^2
Sample size	.00	.00	[-.00; .00]	.19	.00	.00	[-.00; .00]	.00
Age	-.01	.02	[-.05; .03]	.00	03	.02	[-.01; .06]	.00
Percent women	-.87	.80	[-2.45; .71]	.00	1.93	1.10	[-.23; 4.08]	.00

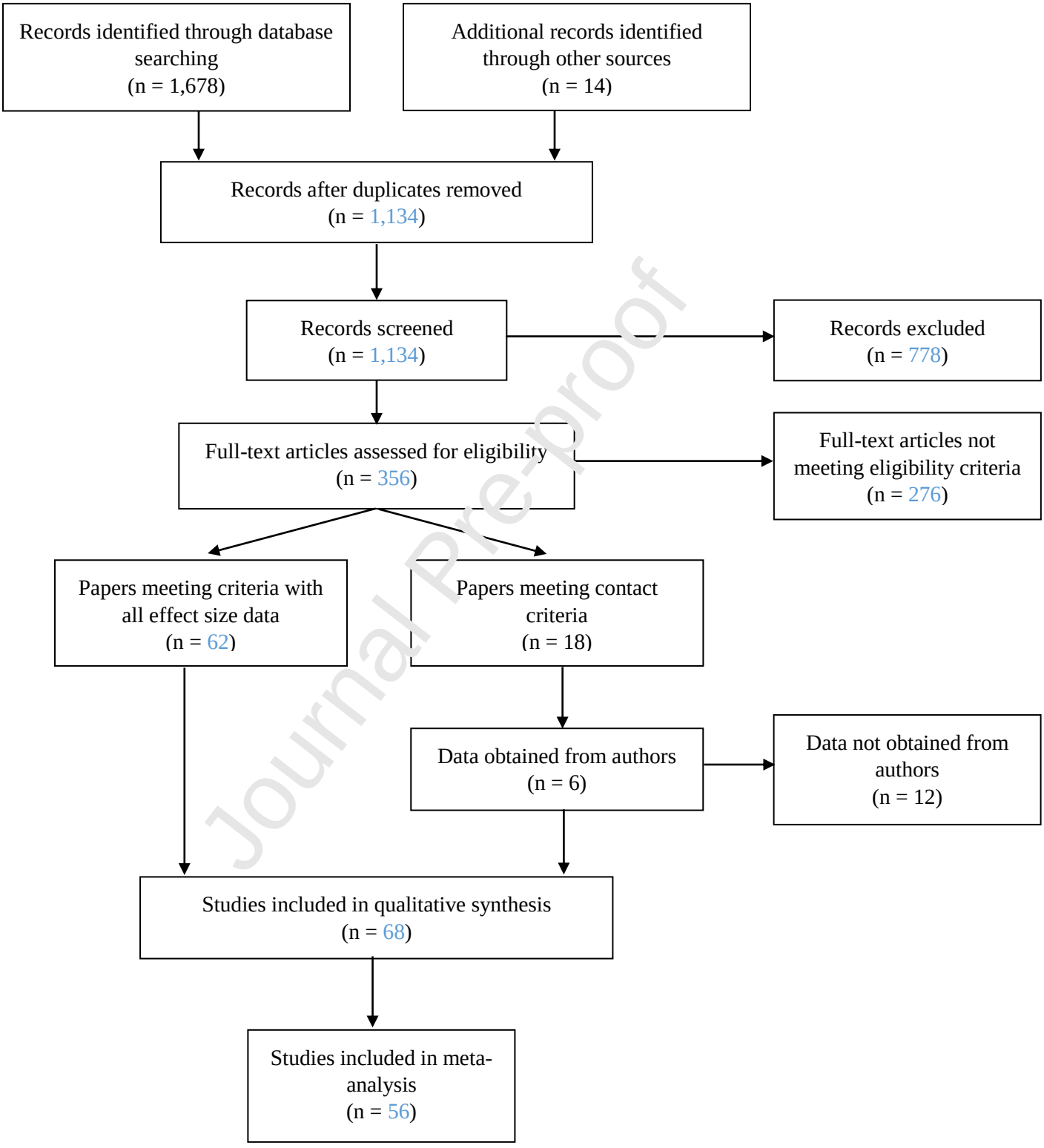
Note. BAS *k* = 21; BIS *k* = 19; Age = mean age of participants; Percent women = Percent of sample that was female

Table 5b. Random-effects models of continual moderators of reinforcement sensitivity and bipolar disorder among diagnosed-healthy comparison studies

	BAS				BIS			
Moderator	*Beta*	SE	95% CI	R^2	*Beta*	SE	95% CI	R^2
Sample size	-.00	.00	[-.00; .00]	.00	-.00	.00	[-.00; .00]	.00
Age	-.02*	.01	[-.04; -.00]	.22	.01	.01	[-.01; .03]	.00
Percent women	.20	.28	[-.35; .74]	.00	.05	.32	[-.58; 69]	.00

Note. * - $p < .05$; BAS *k* = 33; BIS *k* = 29; Age = mean age of participants; Percent women = Percent of sample that was female

Figure 1. Derivation of analysis samples



Figures 2a-b. Forest plots summarizing the relationships between reinforcement sensitivity and bipolar disorder from self-report correlational data

Figure 2a. Forest plot of BAS effect sizes derived from self-report correlational data

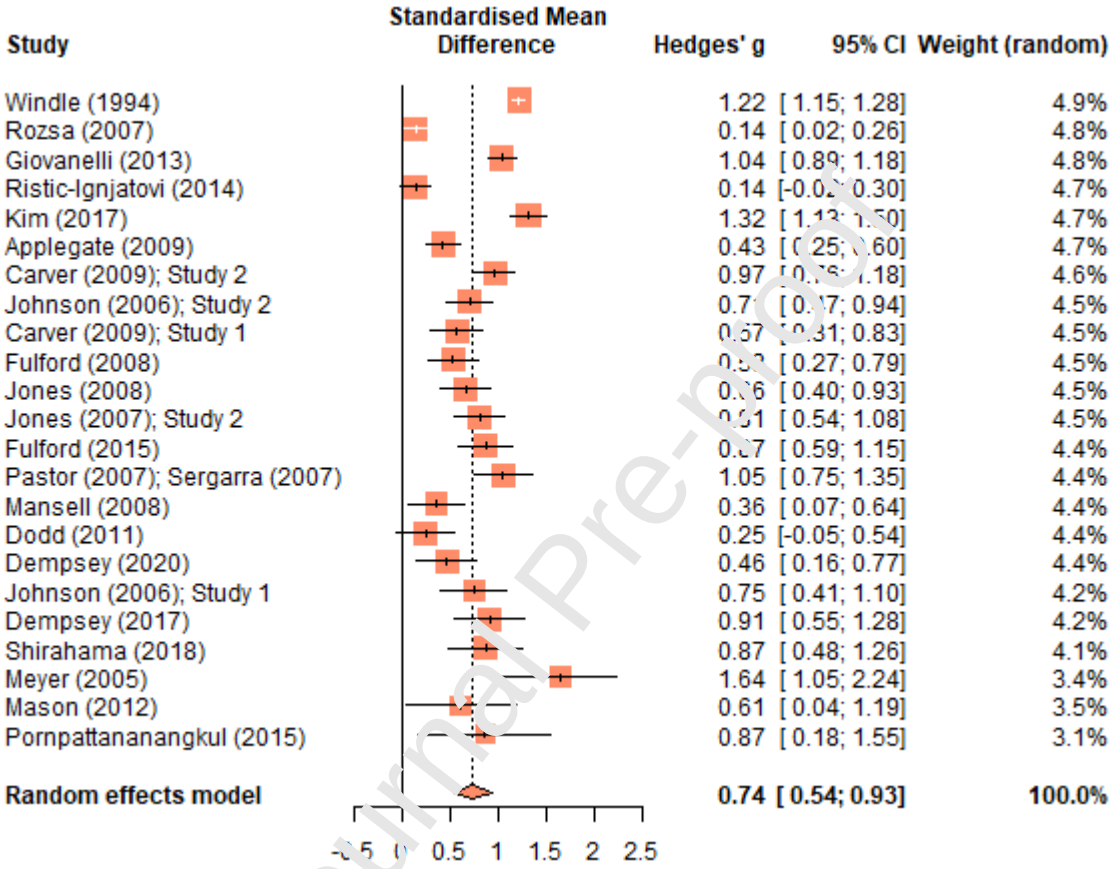
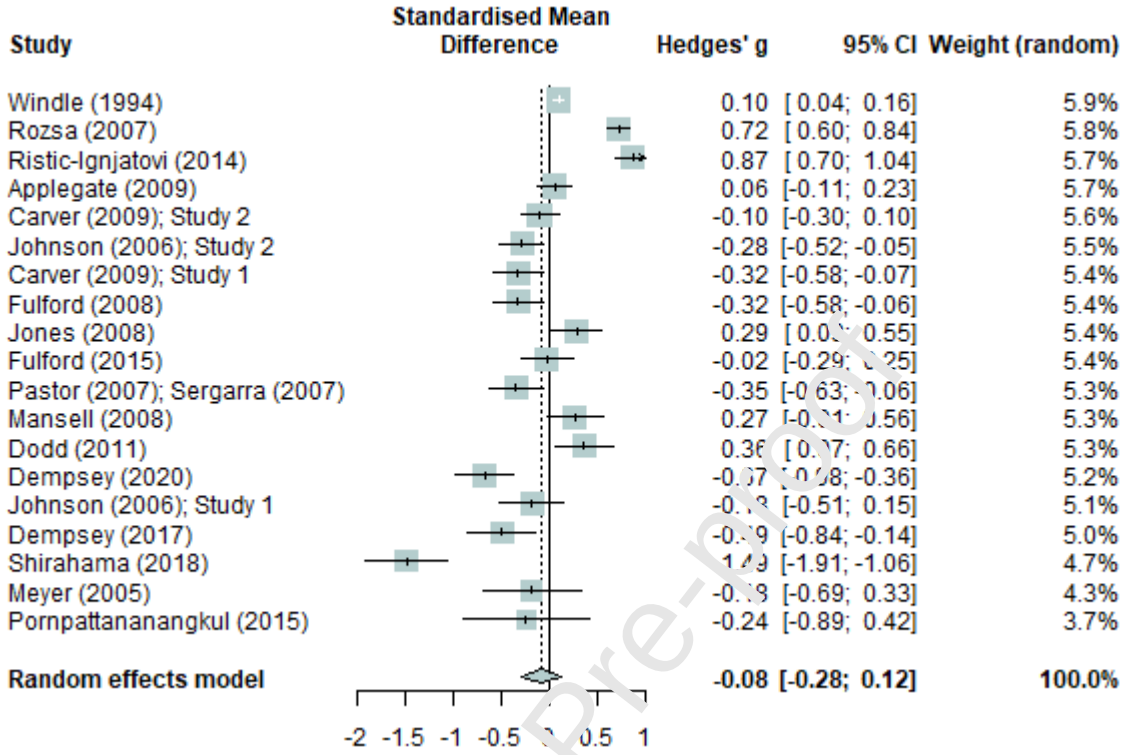


Figure 2b. Forest plot of BIS effect sizes derived from self-report correlational data



Note. Effect sizes were standardized mean difference, calculated using Hedges' g. They are presented graphically (i.e., Standardized Mean Difference*) as well as numerically (i.e.,* Hedges' g*). Positive effects indicate a positive relationship between BAS/BIS sensitivity and self-reported (hypo)manic personality. Studies presented in descending order based on weight assigned in a random effects model, which are calculated as a function of sample size*

Figures 3a-b. Forest plots summarizing the relationships between reinforcement sensitivity and bipolar disorder from diagnosed-healthy data

Figure 3a. Forest plot of BAS effect sizes derived from diagnosed-healthy data

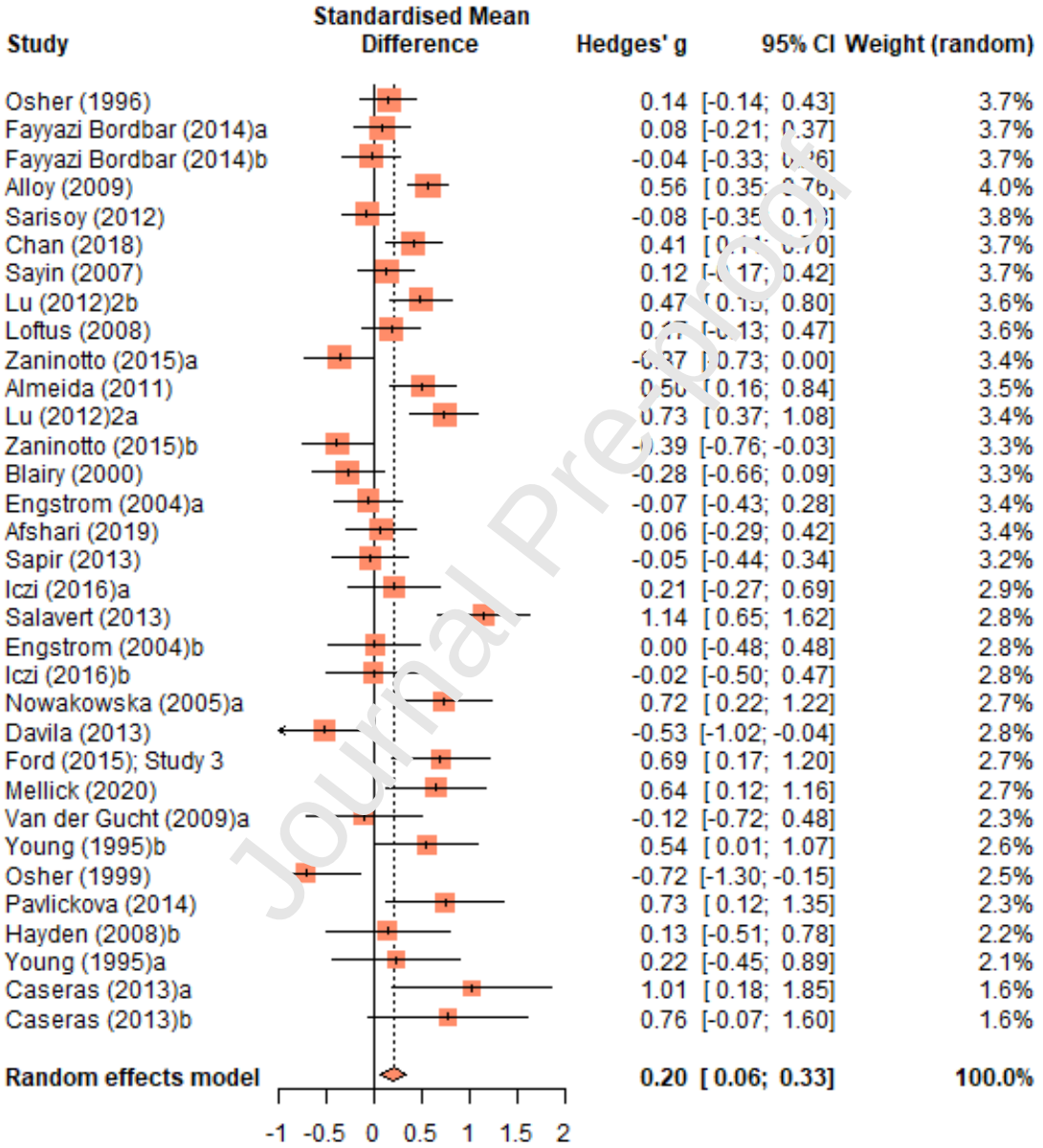
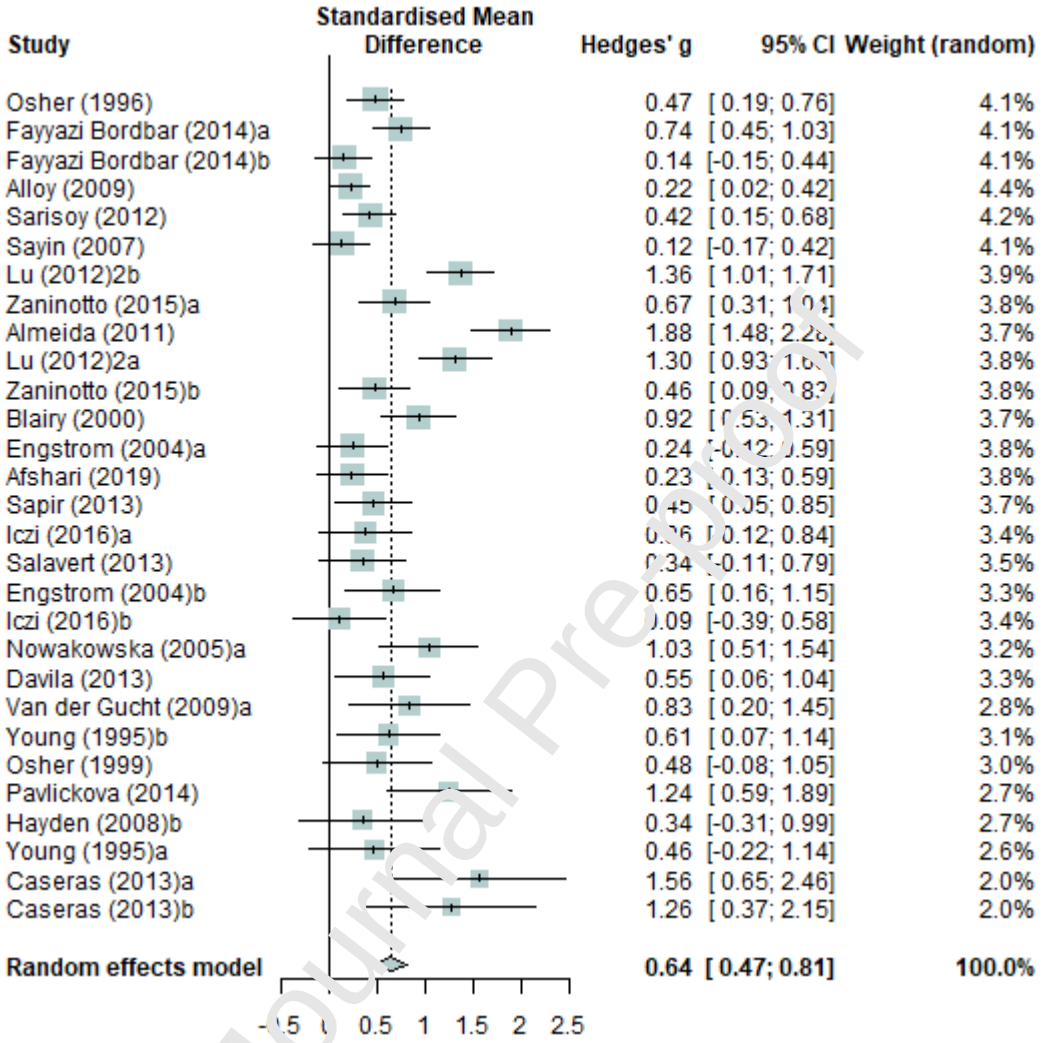


Figure 3b. Forest plot of BIS effect sizes derived from diagnosed-healthy data



Note. Effect sizes were standardized mean difference, calculated using Hedges' g. They are presented graphically (i.e., Standardized Mean Difference*) as well as numerically (i.e.,* Hedges' g*). Positive effects indicate a positive relationship between BAS/BIS sensitivity and euthymic bipolar disorder. Studies presented in descending order based on weight assigned in a random effects model, which are calculated as a function of sample size*

Figures 4a-d. Trim-and-fill funnel plots for the relationships between reinforcement sensitivity and bipolar disorder

Figure 4a. Funnel plot of BAS self-report correlational effect sizes following the trim-and-fill procedure

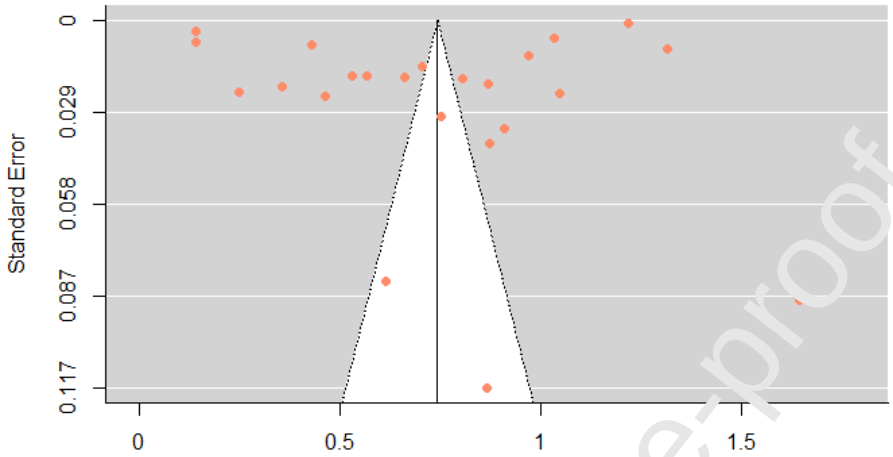


Figure 4b. Funnel plot of BIS self-report correlational effect sizes following the trim-and-fill procedure

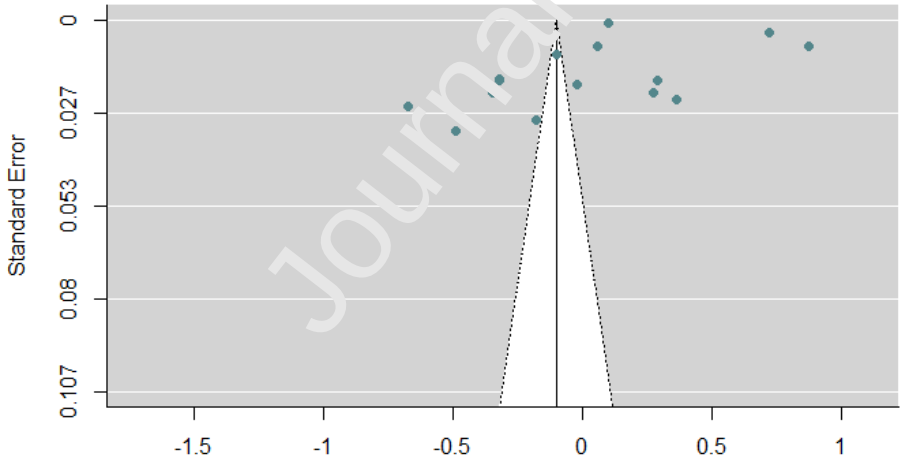


Figure 4c. Funnel plot of BAS diagnosed-healthy comparison effect sizes following the trim-and-fill procedure

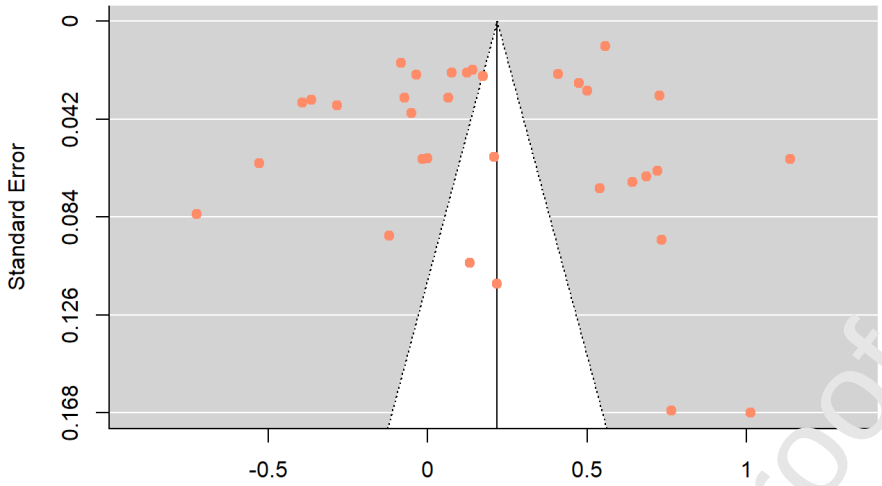
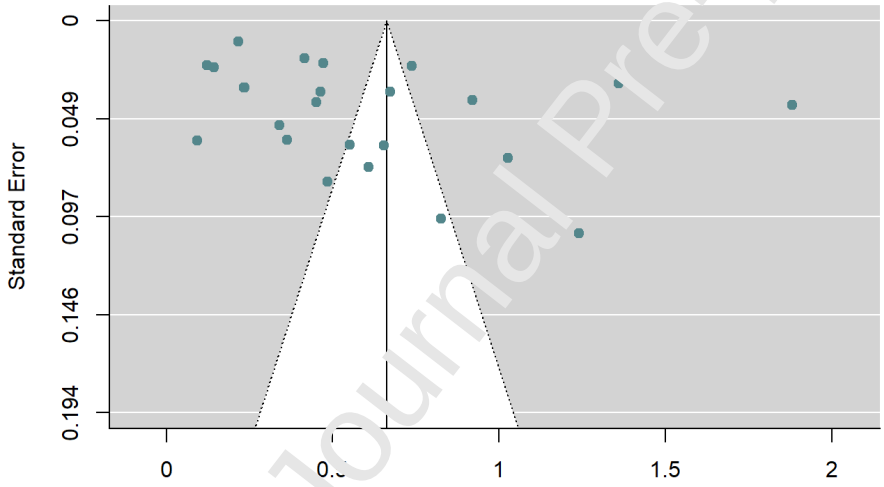


Figure 4d. Funnel plot of BIS diagnosed-healthy comparison effect sizes following the trim-and-fill procedure



Note. Empty circles represent studies imputed by the trim-and-fill procedure.

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Highlights:

- Mania is positively associated with BAS sensitivity
- Conversely, bipolar depression is positively associated with BIS sensitivity
- Both risk factors are present in euthymic bipolar disorder
- BAS sensitivity is strongly associated with self-reported nonclinical (hypo)manic personality
- Findings support a dual-system approach to bipolar disorders