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Spontaneous Eye-Blink Rate as an Index of Reward Responsivity: Validation and Links to Bipolar Disorder

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Abstract

Extensive research supports the role of striatal dopamine in pursuing and responding to reward, and that eye-blink rate is a valid indicator of striatal dopamine. This study tested whether phasic changes in blink rate could provide an index of reward pursuit. This hypothesis was tested in people with bipolar I disorder (BD; a population with aberrations in reward responsivity) and in those without BD. A total of 31 adults with BD and 28 control participants completed a laboratory task involving effort toward monetary reward. Blink rate was recorded using eye tracking at baseline, reward anticipation, and postreward. Those in the BD group completed self-report measures relating to reward and ambition. Results showed that across all participants, blink rates increased from reward anticipation to postreward. In the BD group, reward-relevant measures were strongly correlated with variation in blink rate. These findings provide validation for phasic changes in blink rate as an index of reward response.

Keywords

rewards, psychophysiology, bipolar disorder

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In both humans and other animals, the reward system is a key network of neurobiological pathways that help an organism to identify, pursue, and achieve environmental rewards, and to learn from these rewarded experiences (Haber & Knutson, 2010). Research further shows that the reward system is multifaceted, with differential biological and psychological mechanisms responsible for the hedonic response to a reward, sometimes termed "liking," and the engagement of effort to achieve rewards, broadly termed "wanting," or incentive salience (Berridge & Robinson, 1998; Berridge, Robinson, & Aldridge, 2009).

Regarding this second process, extensive research in animal and human studies supports a key role for mesolimbic dopamine (DA) in guiding pursuit of rewards (Berridge, 2007; Berridge et al., 2009; Salamone, Correa, Farrar, Nunes, & Pardo, 2009). Though studies clearly show a role for DA in reward anticipation (cf. Knutson, Fong, Adams, Varner, & Hommer, 2001; Schott et al., 2008), animal (Salamone et al., 2009) and human research (Treadway et al., 2012) has identified that individual differences in dopaminergic activity in the striatum are particularly correlated with willingness to expend effort for reward. In keeping with the idea that DA supports motivation to pursue rewards, greater activation in the nucleus accumbens (a DA-rich area of the striatum) while anticipating effort for reward has been shown to predict the degree of effort an individual will expend on reward (Kroemer et al., 2014). Transdiagnostic studies increasingly show evidence for the importance of differences in willingness to expend effort for reward across different forms of psychopathology (Salamone, Koychev, Correa, & McGuire, 2014; Whitton, Treadway, & Pizzagalli, 2015). Hence, our focus is on willingness to expend effort toward reward. In the present study, we aimed to test whether an indicator of striatal DA, spontaneous eye-blink rate, is an effective marker of effort for reward.

Aim 1: Phasic Blink Rate as an Index of Reward Response

The role of DA in reward has been well documented in neuroimaging research. In human studies, much of what is known about DA transmission stems from PET imaging

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studies (e.g., Davis et al., 2003; Drevets et al., 2001; Volkow, Fowler, & Wang, 1999; Zald et al., 2004; see Haber & Knutson, 2010, for review). Ligand and metabolic PET imaging studies provide a wealth of information on neurotransmitter action, but are limited by several practical factors such as high cost and exposure to radioactive isotopes. Given this, there is a need to consider other ways to approximate striatal DA levels, and spontaneous eye-blink rate has been used as one such measure (Karson, 1983).

Several decades of research have validated eye-blink rate as a reliable proxy for dopaminergic functioning. In an important validational study, Taylor and colleagues (1999) found that blink rate in monkeys correlated strongly with DA concentration in the ventromedial caudate nucleus. This relationship between eye-blink rate and DA is supported by studies of clinical populations known to be affected by altered dopaminergic functioning, such as increased eye-blink rate among people with schizophrenia (Chen, Lam, Chen, & Nguyen, 1996; Freed et al., 1981; Karson, 1983; Mackert, Flechtner, Woyth, & Frick et al., 1991; Mackert, Woyth, Flechtner, & Volz, 1990) and decreased blink rates among those with Parkinson's disease (Deuschl & Goddemeier, 1998; Karson, 1983; Karson, LeWitt, Calne, & Wyatt, 1982) and among cocaine users (Colzato, van den Wildenberg, & Hommel, 2008). Blink rate has also been found to be associated with a genetic polymorphism relevant to DA transmission, the DRD4 genotype (Dreisbach et al., 2005). More recently, tonic eye-blink rate has been shown to correlate with personality traits (Barbato, della Monica, Costanzo, & de Padova, 2012; Colzato, Slagter, van den Wildenberg, & Hommel, 2009) as well as cognitive flexibility in humans (Akbari Chermahini & Hommel, 2010, 2012; Colzato, van den Wildenberg, van Wouwe, Pannebakker, & Hommel, 2009; Dreisbach et al., 2005; Müller et al., 2007; Tharp & Pickering, 2011).

Although tonic blink rate has helped to classify specific populations characterized by altered dopaminergic functioning and predicted behavioral performance, strong evidence from studies that manipulate DA suggest that phasic changes in midbrain DA are particularly relevant for mobilizing effort toward reward (Salamone et al., 2009). Beyond evidence that tonic DA is correlated with eye-blink rates, several studies have tested how phasic changes in DA relate to eye-blink rates. Across multiple studies of humans and nonhuman primates, increases in eye-blink rate have generally been documented after administration of a DA agonist (Blin, Masson, Azulay, Fondarai, & Serratrice, 1990; Elsworth et al., 1991; Jutkiewicz & Bergman, 2004; Kleven & Koek, 1996; though see van der Post, de Waal, de Kam, Cohen, & van Gerven, 2004, for a nonreplication). In addition to pharmacological evidence, Akbari Chermahini and Hommel (2012) studied phasic changes in blink rate as corresponding with a behavioral task. Specifically, they found that eye-blink rates increased significantly after a positive mood induction (but not a negative mood induction), particularly for those participants with low tonic dopamine levels. Thus, changes in eye-blink rate may be a viable measure of individual fluctuations in DA. Further evidence regarding positive stimuli and eye-blink rate shows that variation in tonic blink rate interacts with the valence of pictures (positive or neutral) to predict participants' reported self-agency on a laboratory task (Aarts et al., 2012). This finding, combined with those of Akbari Chermahini and Hommel (2012), suggests that responses to positive stimuli and positive mood inductions each may relate to eye-blink rate.

In sum, an abundance of evidence supports using eye-blink rate as a sensitive indicator of striatal DA function, and more important, as an index of phasic shifts in DA levels. Given the large literature suggesting that phasic shifts in striatal DA are central in mobilizing effort for the pursuit of anticipated rewards, that individual differences in striatal DA are associated with degree of effort for reward (Treadway et al., 2012), and that activation of the nucleus accumbens is associated with anticipating effort for reward (Kroemer et al., 2014), it is surprising that studies to date have not used blink rate to study the reward anticipation processes more directly. That is the goal of this study. We hypothesized that eye-blink rate should increase during anticipation of reward. The first goal of this study was to test whether changes in eye-blink rate correspond with a specific component of the reward process: preparing to expend effort toward reward.

Aim 2: Blink Rate and Reward in Psychopathology

As numerous studies have supported alterations in eye-blink rate in clinical populations characterized by dopaminergic dysregulation, we also tested an extension of this hypothesis in a clinical sample: adults with bipolar disorder. Converging evidence suggests a central role for DA dysfunction in bipolar disorder, in that those with the disorder show evidence of a possible hypersensitization of DA receptors (Cousins, Butts, & Young, 2009). Neuroimaging studies as well suggest heightened striatal activation during reward anticipation in bipolar disorder (Caseras, Lawrence, Murphy, Wise, & Phillips, 2013; Nusslock et al., 2012; Nusslock, Young, & Damme, 2014; though see Abler, Greenhouse, Ongur, Walter, & Heckers, 2008; Chase et al., 2013), and striatal activation during reward anticipation is correlated with self-report measures of reward responsivity in people with bipolar disorder (Caseras et al., 2013). Thus, although some evidence suggests differences in anticipating reward in bipolar

disorder, it is unknown if these differences would also manifest in differences in anticipating effort for reward.

More specifically, we studied the link between blink rate and reward in this population because of well-documented dysregulation in the reward system in people with bipolar disorder (Johnson, Edge, Holmes, & Carver, 2012). People with bipolar disorder also describe themselves on self-report measures as more sensitive to reward (Johnson, Edge, et al., 2012; B. Meyer, Johnson, & Winters, 2001). Specifically, those with the disorder or at risk for the disorder have been shown to plan for pursuing more ambitious goals (Johnson & Carver, 2006; Johnson, Carver, & Gotlib, 2012; Johnson, Eisner, & Carver, 2009), to sustain greater engagement during pursuit of difficult goals (Harmon-Jones et al., 2008), to be less likely to reduce effort toward goals after attaining their goals (Fulford, Johnson, Llabre, & Carver, 2010), and to demonstrate greater increases in confidence after success on self-report and laboratory-based measures (Eisner, Johnson, & Carver, 2008; Johnson & Jones, 2009; T. D. Meyer, Baron, Baur, & Jordan, 2010; G. S. Stern & Berrenberg, 1979). Some people with bipolar disorder also endorse experiencing mania after achieving reward (Edge et al., 2013), a finding that has also been substantiated by longitudinal research with life event interviews (Johnson et al., 2000; Johnson et al., 2008).

Based on these studies, we predicted that people with bipolar disorder would show evidence of a potentiated blink response before and after engaging in the pursuit of reward. Given previous evidence that self-reported sensitivity to reward correlates with striatal activation during reward anticipation (Caseras et al., 2013), as well as research showing elevations in ambition, reward sensitivity, and confidence in bipolar disorder (Johnson, Edge, et al., 2012), we also hypothesized that eye-blink rate during a reward task would correspond with self-reported parameters of ambition, reward-triggered mania, and confidence.

Despite significant evidence implicating reward dysregulation and altered DA functioning, very little research has considered eye-blink rate in people with bipolar disorder, and no research to date has explored the potential link between eye-blink rate and reward in this population. In a small sample, Depue and colleagues (1990) found that people with a seasonal affective course of bipolar II disorder showed elevated tonic blink rates compared with healthy control participants, but not as compared with persons with unipolar depression with a seasonal course. To our knowledge, no research to date has considered blink rate in bipolar I disorder, nor have studies considered phasic changes in eye blink in those with bipolar disorder, or how eye-blink rate relates to measures relevant to reward function within a bipolar sample.

Hypotheses

The primary goals of this study were to investigate whether eye-blink rate increased as a function of preparing to pursue a reward and upon receiving reward; to investigate if people with bipolar disorder show elevations in blink rate during reward anticipation and reward receipt, relative to controls; and to test whether blink rate is related to validated measures of goal striving and reward responsivity. To investigate these hypotheses, we measured blink rate in healthy adults with no history of a mood disorder, and in adults with remitted bipolar I disorder. Blink rate was tested during a baseline condition, and at two phases (preparing to pursue a reward and after receiving reward) of a previously validated reward engagement paradigm (Harmon-Jones et al., 2008). Participants with bipolar disorder also completed self-report measures of reward sensitivity, confidence, and ambition.

Method

All study procedures were approved by the university Institutional Review Board. Participants provided consent before study procedures, and all participants were financially compensated for their time. All data were collected as part of a larger study also described elsewhere (Edge, Lwi, & Johnson, in press; Ng & Johnson, 2013).

Participants

Participants were recruited in the San Francisco Bay Area using online advertisements, and for the bipolar group, additional participants were recruited via advertising with local support groups and treatment centers. Effort was made to recruit demographically comparable control participants who were comparable on age, employment status, and education history through advertising in unemployment centers and through targeted ads in online media. Potential participants were screened initially by phone to ensure eligibility. Only participants who were fluent in the English language and between the age of 18 and 60 were invited to participate. Exclusion criteria included history of severe head trauma, vision problems that would interfere with eye tracking (e.g., glaucoma, cataracts), central nervous system illness (e.g., Alzheimer's disease), or learning disabilities that would interfere with understanding consent and study procedures.

Potential participants were invited to the university to complete the Structured Clinical Interview for *DSM-IV* (SCID; First, Spitzer, Gibbon, & Williams, 1997; described in more detail later). Participants in the bipolar disorder group (n = 32) were included if they met criteria for a

lifetime history of bipolar I disorder; those in the control group (n = 31) were included only if they did not meet criteria for a lifetime mood disorder (bipolar disorder, major depressive disorder, dysthymic disorder, or cyclothymic disorder). In both participant groups, those who met criteria for a primary psychotic disorder or a current substance use disorder (abuse or dependence) were excluded. Participants reporting regular cannabis use were also excluded regardless of whether they met criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association [APA], 1994) for a substance use disorder, given evidence for significantly altered blink rates in heavy cannabis users (Kowal, Colzato, & Hommel, 2011).

Measures

SCID. The SCID (First et al., 1997) is a well-validated semistructured clinical interview that evaluates for the presence of *DSM-IV* (APA, 1994) Axis I disorders. Interviews were conducted by trained clinical psychology graduate students; interviewers achieved strong interrater reliability based on a random sample of audiotaped interviews: for current and lifetime manic episodes and lifetime major depressive episodes, intraclass correlation coefficients (ICCs) ranged from .88 to .89, for current major depressive episode ratings, the ICC was .99.

Modified Hamilton Rating Scale for Depression (MHRSD). The MHRSD (Miller, Bishop, Norman, & Maddever, 1985) is a clinician-administered interview designed to assess severity of current depression symptoms. The semistructured interview has achieved good reliability and validity in previous studies (Miller et al., 1985) and has been validated for use in bipolar I disorder (Johnson et al., 2008). MHRSD scores range from 0 to 52, with scores below 7 indicating remission and those above 17 indicating the presence of a depressive episode. Interviews were conducted by trained graduate students, who achieved strong interrater reliability on the basis of randomly selected interviews (ICC > .99).

Young Mania Rating Scale (YMRS). The YMRS (Young, Biggs, Ziegler, & Meyer, 1978) is an 11-item interview designed to assess the severity of current symptoms of mania. This scale shows good reliability and consistency with other mania ratings (Young et al., 1978). As with the other clinical scales, ratings were conducted by trained graduate students. Randomly selected tapes of interviews suggested strong interrater reliability (ICC > .99).

Mood state and confidence rating. Participants completed six items regarding their current mood state and arousal using a five-item Likert-type scale (1 = *very slightly or not at all* to 5 = *extremely*) for positive emotion (enthusiasm, confidence), negative emotions (sad, nervous, frustrated), as well as how tired they currently felt.

Medication coding. For participants in the bipolar group, medication information and adherence was assessed using the Somatotherapy Index (Bauer et al., 1997). Dosages were adjusted for adherence. Medications were converted to standard equivalent dosages for mood stabilizers, antiseizure medications, lamotragine, antidepressants (imipramine equivalents), atypical antipsychotic medication (risperidone equivalents), and benzodiazepines (diazepam equivalents). Participants who were not taking a medication were coded as 0.

Reward Responses Inventory (RRI). The RRI (Edge et al., 2013) is a 21-item self-report measure designed to evaluate responses to reward in people with bipolar disorder. The RRI contains two subscales: Reward-Triggered Mania, in which participants rate the extent to which they have experienced a manic episode following a rewarding or goal-pursuit-related event, and Reward Avoidance, in which participants rate the degree to which they limit or avoid rewarding activities to prevent mania. Responses are rated on a 4-point scale ranging from 1 (*very false for me*) to 4 (*very true for me*). Only participants in the bipolar group completed this scale, as it is specific to experiences of mania. Prior research using this scale in bipolar I disorder shows good internal consistency for each subscale, and previous validational work shows that many individuals with bipolar I disorder endorse items relating to reward-triggered mania (Edge et al., 2013). In the present study, internal consistency was good for both subscales (Reward-Triggered Mania α = .87, Reward Avoidance α = .87).

Willingly Approached Set of Statistically Unlikely Pursuits (WASSUP). The WASSUP (Johnson & Carver, 2006) is a self-report measure of ambitious goal setting. On this scale, participants read a series of extreme goals and rate the degree to which they expect this goal to occur for them, ranging from 1 (*no chance of occurring*) to 5 (*definitely will occur*). For the present study, participants completed only two of the factor-analytically supported subscales: Popular Fame (measuring extreme ambitions for fame, e.g., "You will appear regularly on TV") and Finances (extreme ambitions for wealth, e.g., "You will have 20 million dollars or more"), as these two subscales have been found to be elevated in bipolar I disorder (Johnson et al., 2009) and to predict symptoms of mania (Johnson, Carver, et al., 2012) and onset of bipolar spectrum disorders (Alloy et al., 2012). These WASSUP subscales have demonstrated good internal

consistency and reliability with other mania-relevant measures (Johnson & Carver, 2006; Johnson, Carver, et al., 2012; Johnson et al., 2009). In the present study, internal consistency was moderate for Financial Success ($\alpha = .60$) and for Popular Fame ($\alpha = .74$).[1]

Procedure

After the phone screening, potential participants were invited to the laboratory to complete a diagnostic interview (SCID). Those who met criteria were invited to participate in the experimental session. Self-report questionnaires (WASSUP and RRI) were also completed at this time. Before the experimental session, participants in the bipolar group also completed mood interviews (MHRSD and YMRS) over the phone with a trained interviewer. Those whose mood rating scores fell below 7 on the YMRS or below 10 on the MHRSD were scheduled to complete the experimental session. Participants whose symptoms exceeded the cutoff range on either the MHRSD or the YMRS were followed monthly with phone interviews until they reached remission and then given the opportunity to complete the experimental session.

To minimize confounds in blink rate, participants were asked to refrain from nicotine and caffeine use during the 12 hr leading up to the experimental session, and not to wear contact lenses for the session (e.g., to wear glasses). All sessions took place between 10 a.m. and 5 p.m., as eye-blink rates have been shown to increase in the evening (Barbato et al., 2000). All procedures took place in a windowless room with constant overhead lighting; temperature and humidity were also monitored for consistency throughout all recording sessions (Doughty, 2001).

Participants completed a 5-min baseline eye-blink recording, in which they sat in front of a fixation cross displayed in the center of the eye-tracking computer and were instructed not to look away from the screen. Eye-blink rate was recorded continuously during these 5 min, and blink rate per minute was calculated by dividing the total number of blinks by five. After the baseline, participants completed the mood and confidence rating and then began the anagrams reward task.

Anagrams reward task. The reward task was adapted from a previously validated reward paradigm used in a study of effort toward reward in bipolar disorder (Harmon-Jones et al., 2008). In the version of this paradigm used in the present study, participants completed a computerized reward task in which they were given 5 min to solve as many anagrams as possible, for the chance to win 50 cents per correctly solved anagram (incorrect responses did not result in any money won, but were not penalized). Before the task, participants read instructions on-screen that were also provided verbally by an experimenter and then given the chance to practice solving anagrams to ensure they understood the goals of the task.

For each trial, a scrambled word appeared at the center of the screen, and participants used a keyboard to type their solution under the scrambled word. Trials advanced after each participant either entered a solution word or pressed the space bar to move on without providing a response. Immediately before each trial, participants received a cue on-screen that stated whether the next trial was easy, medium, or difficult; all trials were randomized so that easy, medium, and hard trials were interspersed throughout the task. Participants were not informed of their accuracy on each individual trial, and did not receive feedback about their total winnings until the end of the 5-min task. After 5 min had elapsed, participants saw a screen that showed their actual monetary winnings on the task.

To enhance reward anticipation and to encourage participants to mobilize effort for the task at hand, the anagrams task was preceded by a "countdown" phase lasting 1 min. During this minute, participants saw the phrase "Get Ready!" displayed onscreen, adjacent to a digital countdown display counting down the seconds remaining until the task began (60 to 1). To further enhance anticipation, participants heard a clip of upbeat music during the count-down minute ("Vamos a Bailar," recorded by the Gipsy Kings; this recording has previously been used in the context of positive affect inductions in the laboratory; cf. Edge et al., 2013). The "countdown" phase occurred only once, immediately before the start of the 5-min anagrams task. While participants viewed their winnings on-screen after the task, the same music was played again for 60 s, to enhance the positive effects of winning money on the task.

Eye-blink rate was recorded during the 60-s "countdown" phase immediately before the task (reward anticipation), as well as during the 60-s "reward" phase immediately after the task, when participants saw their winnings displayed onscreen (postreward). Eye-blink rate was not calculated during the anagram task due to the potential confounding nature of reading words (cf. Doughty, 2001) and sustained cognitive effort (cf. Caplan, Guthrie, & Komo, 1996; J. A. Stern, Walrath, & Goldstein, 1984) during the task itself. Therefore, dependent variables of interest were limited to the eye-blink rate during reward anticipation (the count down) and postreward (the feedback screen).

Apparatus and data reduction. Eye-blink rate was captured using a Tobii T-120 infrared eye-tracker (Tobii Technologies, Dandyred, Sweden), synchronized with a secondary computer used to display stimuli. The anagrams task and baseline phase were programmed with E-Prime Professional, Version 2.0, linked with the eye-tracker using

Table 1. Sample Characteristics: Demographic Variables and Self-Report Measures

Demographic or mood variable	BP I *M* (*SD*) or % (*n* = 31)	Control *M* (*SD*) or % (*n* = 28)	Test statistic (*t* or χ^2)
Age	38.16 (11.13)	34.11 (13.51)	$t(57) = 1.26$, $p = .21$
Gender (% female)	51.6	42.9	$\chi^2(1) = 0.45$, $p = .50$
Race (% minority race)	19.4	30.8	$\chi^2(1) = 0.99$, $p = .32$
Years of education	15.26 (1.59)	15.07 (2.21)	$t(48.61) = 0.37$, $p = .71$
% employed	41.9	50	$\chi^2(1) = 0.39$, $p = .54$
MHRSD	2.42 (2.86)	—	
YMRS	1.19 (1.55)	—	
WASSUP–Popular Fame	10.52 (3.67)	—	
WASSUP–Financial Success	7.22 (3.04)	—	
RRI–Reward Avoidance	16.41 (6.53)	—	
RRI–Reward-Triggered Mania	27.95 (7.29)	—	

Note: *n* = 29 for RRI. BP I = bipolar I disorder; MHRSD = Modified Hamilton Rating Scale for Depression; RRI = Reward Responses Inventory; WASSUP = Willingly Approached Set of Statistically Unlikely Pursuits; YMRS = Young Mania Rating Scale.

E-Prime Extensions for Tobii (Psychology Software Tools, Pittsburgh, PA). Eye tracking was recorded at 120 Hz, providing one sample per 8.3 ms. Stimuli were displayed on a 17-inch computer monitor with 1,280 × 1,024 screen resolution. A nine-point calibration was conducted before the baseline recording and again before the reward task. Based on previously established infrared eye tracking norms, eye blinks were coded as continuous periods of time of at least 100 ms and < 500 ms in which the coordinates and pupil diameter for both left and right eyes were not recorded (cf. Aarts et al., 2012; den Daas, Häfner, & de Wit, 2013; Smilek, Carriere, & Cheyne, 2010).

Results

Analyses were conducted with SPSS version 22.0 (IBM, Chicago, IL). Four participants (3 control, 1 bipolar) were excluded from data analyses because of eye-tracking equipment failure during the anagrams reward task (3 participants) or eye injuries not disclosed during screening (1 participant). Baseline data were also not available for 3 BD participants. As this was the result of equipment or experimenter error, the baseline data were imputed, resulting in a final sample of 31 in the bipolar group and 28 in the control group. Within the bipolar group, three MHRSD and two YMRS scores were missing, and these data were imputed (using linear regression) as well. As would be expected, analyses were parallel with and without the imputed scores. Before analyzing eye-blink rates, distributions of blink rates were analyzed for normality. Observed outliers, defined as blink rate values greater than 2.5 standard deviations from the sample mean, were Winsorized to the next highest nonoutlying value for each task phase (baseline: 2 participants, reward anticipation and postreward phases: 1 participant each), amounting to less than 2.5% of all blink measurements. Blink rate estimates throughout the baseline and reward task phases were comparable to previously established norms (Doughty, 2001).

As shown in Table 1, diagnostic groups were well matched and did not differ on age, gender, employment status, race, or years of education. Bipolar and control groups did not differ on self-reported enthusiasm, confidence, or fatigue (all *p*s > .06); however, those in the bipolar disorder group reported experiencing significantly more frustration, $t(45.38) = 2.21$, $p = .03$, and sadness, $t(32.96) = 2.44$, $p = .02$. Of participants in the bipolar group, 84% reported taking at least one psychotropic medication, the most common of which were atypical antipsychotic medication (13/31), lithium (11/31), and lamotrigine (7/31).

Before testing hypotheses, bivariate Pearson correlations were used to consider potential confounds influencing eye-blink rates. Across the sample as a whole (*n* = 59), mood and arousal variables (enthusiasm, frustration, sadness, and tiredness) were not significantly correlated with baseline or task-related blink rate, *r*s < .22, *p*s > .09. Correlations with confidence are presented in tests of hypotheses later. Because bipolar and control groups differed on two negative emotion variables (frustration and sadness), these variables were also compared with eye-blink rates in the bipolar group alone; frustration and sadness were not significantly correlated with eye-blink at any time point (*r*s < .17, *p*s > .20). Within the bipolar group (*n* = 31), medication dosages were unrelated to eye-blink rate for any medication class at baseline (all *r*s < .18, *p*s > .33) or during reward anticipation or reward receipt (all *r*s < .31, *p*s > .09). Current mood symptoms in the bipolar group were also unrelated to baseline or reward-task blink rates (MHRSD: *r*s < .04, *p*s > .83; YMRS: *r*s < .10, *p*s > .59). Given the possibility that blink rate would shift with perceived task difficulty,

Pearson correlations were used to examine the relationship between blink rate at each task phase and accuracy on the anagrams task. Accuracy was not significantly correlated with baseline blink rate (r = .05, p = .69), reward anticipation blink rate (r = .11, p = .41), or reward receipt blink rate (r = .10, p = .46). Furthermore, there was no evidence that variability in the difficulty of anagrams was related to blink rate: Correlational analyses between eye-blink rate at each time point and accuracy within each difficulty level showed no association between performance on easy anagrams and blink rates (rs < .11, ps > .42), nor with medium-difficulty (rs < .13, ps > .32) or hard anagrams (rs < .15, ps > .26).

Behavioral data

In the sample as a whole, participants correctly solved more than half of the anagram trials (56.64%, SD = 20.58). A 3 (trial difficulty: easy, medium, or hard) by 2 (group: bipolar or control) ANOVA with task accuracy as the dependent variable showed a large main effect of trial difficulty, $F(2, 112) = 134.18$, $p < .001$, $\eta_p^2 = .71$. Planned contrasts showed that participants were significantly more accurate on easy trials (89.09%, SD = 22.62) than medium trials (56.56%, SD = 32.29), $F(1, 56) = 57.27$, $p < .001$, and significantly more accurate on medium trials than on hard trials (26.48%, SD = 23.44), $F(1, 56) = 69.2$, $p < .001$. There was no main effect of group, $F(1, 56) = 0.11$, $p = .74$, $\eta_p^2 = .002$, nor evidence of a Group × Difficulty interaction, $F(2, 112) = 0.40$, $p = .67$, $\eta_p^2 = .007$.

Overall, participants won an average of $4.65 ($SD$ = $2.68) and completed 15.36 trials (SD = 4.13). In parallel to the task accuracy findings, bipolar and control groups did not differ on overall money won, $t(57) = -1.55$, $p = .13$, nor on number of completed trials (regardless of success), $t(57) = -1.87$, $p = .07$. Bipolar and control groups were therefore matched on behavioral performance of the reward task.

Eye-blink rate

To assess change in eye-blink rate as a function of reward and diagnostic category, a 3 (task phase: baseline, reward anticipation, and reward receipt) by 2 (group: bipolar or control) ANOVA was conducted, with spontaneous eye-blink rate (blinks per minute) as the dependent variable. Figure 1 shows the results for eye-blink rate across these time points. This analysis yielded a significant main effect of time (task phase), $F(2, 114) = 6.88$, $p < .01$, $\eta_p^2 = .11$. Planned contrasts showed that eye-blink rate marginally increased from the baseline phase to the reward anticipation phase, $F(1, 57) = 3.15$, $p = .08$, $\eta_p^2 = .05$, and then significantly increased from the reward anticipation phase to the reward receipt phase, $F(1, 57) = 4.35$, $p = .04$, $\eta_p^2 = .07$. There was no significant main effect of diagnostic group, $F(1, 57) = 0.25$, $p = .62$, $\eta_p^2 = .004$, nor evidence of a significant Task Phase × Diagnostic Group interaction, $F(2, 114) = 0.20$, $p = .82$, $\eta_p^2 = .003$.[2]

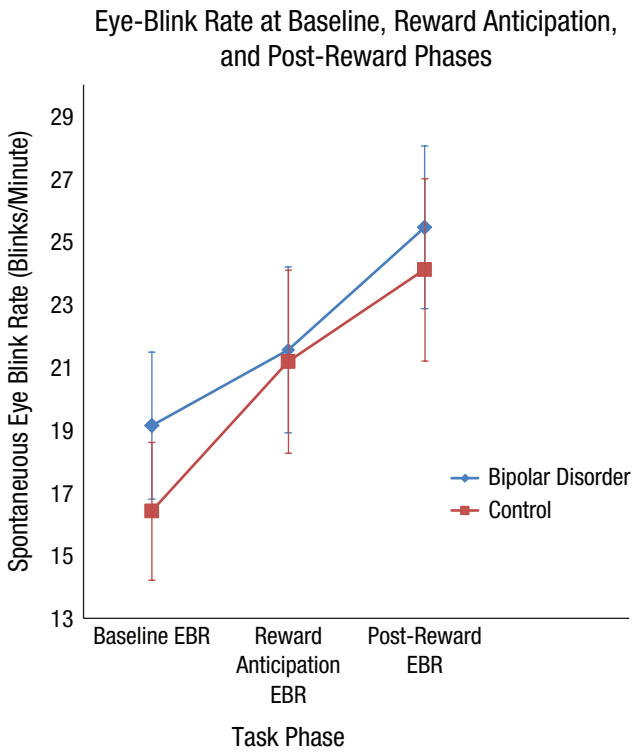

Fig. 1. Eye-blink rate at baseline, reward anticipation, and postreward phases. Error bars indicate 1 standard error of the mean. EBR = spontaneous eye-blink rate.

Correlations of blink rate with measures of reward, ambition, and confidence

Blink rate during reward anticipation and reward receipt were compared against self-report measures of reward, confidence, and goal setting, using partial correlations controlling for baseline blink rate. As shown in Table 2, blink rate during the reward anticipation phase was significantly correlated with ambitious goal setting (WASSUP Popular Fame subscale) and confidence ratings in those with bipolar disorder, whereas blink rate during reward receipt was correlated with higher scores on the reward-triggered mania scale of the RRI. In contrast, confidence ratings were not significantly correlated with either reward anticipation (partial r = .18, p = .37) or postreward blink rate (partial r = .25, p = .22) in the control group, although the strength of the correlations between blink rate and confidence did not significantly differ between bipolar and control groups (Fisher's Z test; reward anticipation p = .36; postreward p = .68).

Table 2. Partial Correlations of Confidence and Reward Measures With Eye-Blink Rate, Controlling for Baseline Eye-Blink Rate

	Eye-blink task phase	
Measure	Reward anticipation eye-blink rate	Postreward eye-blink rate
WASSUP–Popular Fame	.43*	.24
WASSUP–Financial Success	.11	.04
RRI–Reward-Triggered Mania	.11	.38*
RRI–Reward Avoidance	.18	.12
Pretask confidence rating	.41*	.14

Note: $n = 29$ for RRI; $n = 31$ for WASSUP and confidence. RRI = Reward Responses Inventory; WASSUP = Willingly Approached Set of Statistically Unlikely Pursuits.
*$p < .05$.

Discussion

Eye-blink rate is a validated, though indirect, measure of striatal dopamine. The present study contributes one of the first investigations of repeated measurement of eye-blink rates on a behavioral task, and the first to evaluate changes in eye-blink rate as a function of striving toward reward. We tested whether preparing to expend effort for reward and receiving a reward would be associated with increases in eye-blink rate in both healthy adults and adults with bipolar disorder. Eye-blink rate across both groups of participants marginally but nonsignificantly increased while preparing to expend effort on a difficult, rewarding task; blink rate further and significantly increased upon receipt of reward. These findings suggest that eye-blink rate may provide a psychophysiological marker of response to receiving reward. Although no group differences between those with and without bipolar disorder emerged, measures of confidence, ambitious goal setting, and reward-triggered mania were strongly correlated with blink responses in people with bipolar disorder, suggesting a potential role for eye-blink rate to index individual differences in reward sensitivity.

Neuroimaging studies show consistent evidence for heightened activity in the striatum during reward anticipation (Haber & Knutson, 2010; Knutson et al., 2001), and mounting evidence shows the importance of mesolimbic dopamine for effort toward reward (Salamone et al., 2009). Though speculative, the trend toward elevated eye-blink rate during the reward anticipation phase in the present study is consistent with these findings.

It is less clear why participants showed additional elevations in eye-blink rates (both compared with baseline and to the prereward phase) immediately after receiving reward. One possibility is that the elevated blink rate postreward may reflect a residual signal of prior effort toward reward. Evidence suggests that among people with and without bipolar disorder, many do not reduce effort after achieving a goal (Fulford et al., 2010). Thus, the sustained increase in blink rate after goal attainment may reflect continued striving. Another possibility is that participants experienced the reward as unexpected. Striatal activation is associated with receiving unanticipated rewards (Haber & Knutson, 2010; Schultz, 1998), and although participants were informed that they would have 5 min to work on the reward task to win as much money as possible, their actual winnings were not displayed during the task and they did not receive feedback along the way. Thus, the sudden appearance of monetary reward feedback after 5 min may have served to function as an unexpected reward, and thus could index a phasic dopamine response.

It will be important for future studies to validate this method of testing effort toward reward. In particular, measurement of eye blink during the actual expenditure of effort toward reward was not explored in the present study, so future research is needed to test eye-blink responses during goal-striving behavior. This next step of measurement is particularly important in validating a behavioral index of dopaminergic responses to reward, given research suggesting that striatal dopamine is tightly linked to the actual expenditure of effort toward reward (Berridge, 2007; Salamone et al., 2009). The present findings suggest that receiving a reward and to a lesser extent preparing to expend effort toward reward are each tied to increased blink rate—essentially, two time periods that bookend the reward pursuit process. We eagerly await future applications of this paradigm that will fill in these bookends.

Also, we cannot rule out the possibility that the observed increase in eye-blink rate was also influenced by other cognitive or biological influences, rather than reward processing. It is possible that other components involved in solving anagrams, such as verbal fluency or cognitive flexibility, also contributed to the increase in eye-blink rate. Given that performance on the anagrams task was unrelated to eye-blink rate, it seems unlikely cognitive effort alone was responsible for this increase in blinking. Similarly, it is possible that blink rate was influenced by music during the measurement periods before and after the reward task. However, this too seems unlikely to explain the observed increase in blink rate, as other studies have found no differences in eye-blink rate measured with and without music (cf. Lichtenberg et al., 2008). Finally, although eye-blink rate was unrelated to medication dosages and other confounds (such as caffeine and nicotine use) were controlled to the best of the experimenters' abilities, it is possible that other biological mechanisms influencing ocular or dopaminergic systems could have contributed to the increase in eye-blink rate or might have differed by group.

The hypothesis that bipolar disorder would be linked to a larger increase in blink rate on a reward task was not confirmed. This is somewhat surprising, as many studies have documented evidence for increased reward sensitivity in people with bipolar disorder (Johnson, Edge, et al., 2012). Given some previous evidence showing enhanced striatal activation during passive reward anticipation in bipolar disorder (Nusslock et al., 2012), it is possible that group differences in blink rate would emerge during a passive reward anticipation paradigm, rather than anticipating reward in the context of effort. Furthermore, although the task used in the present study was designed to maximize ability to test blink rates before and after reward, this design precluded the ability to test group differences in responses to reward on individual trials. In a previous study using a similar anagrams paradigm, Harmon-Jones and colleagues (2008) found evidence for increased preparatory effort for difficult trials in bipolar disorder, suggesting that future studies of blink rate and reward could benefit from studying changes in blink rate before and after individual trials. This is a goal for future studies.

The present findings also showed that baseline eye-blink rate did not differ in people with and without bipolar disorder, in contrast to early findings in this population (Depue et al., 1990). Depue and colleagues' (1990) early findings of elevated blink rate in bipolar disorder were observed in individuals with bipolar II disorder, a subtype that has been found to show a different neural reward profile than bipolar I disorder (Caseras et al., 2013). It is possible that the difference in subtypes contributed to this divergent finding. Bipolar disorder is a highly heterogeneous disorder, and gaining specificity in identifying specific facets of reward that are disrupted, as well as individual differences in response to reward is needed.

Consistent with the importance of individual differences, measures of confidence, extreme ambition, and reward-triggered mania were strongly linked to eye-blink response to the reward task in bipolar disorder. Given our finding that the strength of blink rate-confidence correlations did not differ between bipolar and control groups, it seems possible that the observed links between individual difference measures and eye-blink rate are indicative of general individual differences rather than a disorder-specific mechanism. However, given the strong correlations between blink rate and individual differences on the two bipolar-specific measures, more research is needed in this domain to understand where psychopathology-specific differences may emerge. These findings are compatible with research showing links between individual differences in reward responsivity and neural response to reward (Hahn et al., 2009; Linke et al., 2010; Simon et al., 2010; Tomer et al., 2014), including recent findings within a bipolar sample (Caseras et al., 2013).

It is important that we observed a dissociation between the effects of ambition and confidence (relating to reward anticipation blink rate) and reward-triggered mania (relating to postreward blink rate). That is, the questionnaires showed expected temporal patterns in their links with pre- and postgoal blink rates. Across multiple studies, heightened ambition has been documented among those diagnosed with bipolar disorder (Johnson, Carver, et al., 2012; Johnson et al., 2009) and has been consistently found to be present before onset among those at risk for the disorder (Alloy et al., 2012; Carver & Johnson, 2009; Fulford, Johnson, & Carver, 2008; Gruber & Johnson, 2009; Johnson & Carver, 2006; Johnson & Jones, 2009). Heightened ambition also predicts a more severe course of mania (Johnson, Carver, et al., 2012) and the onset of bipolar spectrum disorder (Alloy et al., 2012). To date, this literature has rested entirely on self-report measures. These findings are novel in providing a window into a potential biological mechanism, in that blink rate may capture one aspect of biological sensitivity to goal striving in bipolar disorder.

The finding that higher blink rates when receiving a modest monetary reward significantly correlated with more frequent instances of experiencing mania after a rewarding life event also seems highly relevant. Several studies have suggested that life events involving reward can trigger mania (Johnson et al., 2000; Johnson et al., 2008), and recent research suggests that those with bipolar disorder show considerable variability in whether they have observed this process in their own course of symptoms (Edge et al., 2013). Findings in this study suggest that persons who reported reward-triggered mania demonstrated a stronger physiological response to the reward task, raising the possibility that eye-blink rate in response to reward could potentially be relevant for predicting the course of mania. Longitudinal studies are needed to test this possibility.

On the whole, the current findings suggest a new approach to measuring reward sensitivity for basic research, and for understanding how this sensitivity might differ among those with psychopathology. Increasingly, researchers have emphasized the need to incorporate neuroscience-informed methods to inform diagnosis and treatment of psychological disorders (Craske, 2014; Holmes, Craske, & Graybiel, 2014; Siegle, 2011; Siegle, Ghinassi, & Thase, 2007), though one observed challenge is the cost and difficulty involved in using neuroimaging to guide this process (Nusslock et al., 2014). Given the comparably low cost of eye-blink rate, future studies could explore the utility of this methodology as a putative index of individual differences in reward response.

The present study has important limitations. Previous literature has often tested eye-blink rate over time periods lasting 3 to 5 min (Doughty, 2001), so it is possible that the 60-s measurement periods before and after the reward task may be less reliable than a longer measurement period. However, good reliability has been observed for 1-min blink rate measurement periods (Deuschl & Goddemeier, 1998). Another limitation is the relatively small sample size, which may have reduced the ability to test between-group differences in eye-blink rate; regarding statistical power, though, we would note that between group effect sizes were extremely small. Finally, it is unclear the extent to which between-groups differences in blink rate were influenced by medication usage in the bipolar group: Although group differences remained nonsignificant when controlling for medication dosage, correlational analyses suggest that some degree of variability in blink rate is associated with medication dosage.

In sum, this study provides initial evidence that phasic changes in eye-blink rate are tied to receiving reward, and marginally related to preparing to expend effort toward reward. As spontaneous eye-blink rate is a validated index of dopaminergic activity in the striatum, and given the importance of striatal dopamine in effort toward reward, it is possible that increases in striatal dopamine are driving the observed blink response during the reward task in the present study. Clearly, more research is needed to test this hypothesis, such as PET imaging and animal paradigms of reward response and eye-blink rate. The correlational findings showing links between self-reported confidence and reward response in bipolar disorder indicate a potential window into measuring individual differences in reward responsivity in psychopathology. It is hoped that future research continues to investigate both of these early findings.

Author Contributions

A. D. Peckham and S. L. Johnson jointly developed the study concept and design. A. D. Peckham conducted statistical analyses under the guidance of S. L. Johnson and wrote the first draft of the manuscript. S. L. Johnson provided critical revisions.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Notes

1. Alpha for the Financial Success scale was .77 if one item was excluded; with this item excluded, however, effect sizes for tests of hypotheses were comparable. Results here present effects with the item included, to be consistent with previous research.
2. A separate repeated-measures ANOVA was also conducted including medication dosages for each of the classes of medication described entered simultaneously as covariates. As in the original tests of hypotheses, this analysis revealed a significant main effect of time, $F(2, 102) = 4.38$, $p = .02$, $\eta_p^2 = .08$. Parallel to the initial analyses, there was no significant main effect of diagnostic group, $F(1, 51) = 0.06$, $p = .81$, $\eta_p^2 = .001$, nor evidence of a significant Task Phase × Diagnostic Group interaction, $F(2, 102) = 0.008$, $p = .992$, $\eta_p^2 < .001$. There were no significant main effects of medication classes (Fs < 2.54, ps < .12), nor interactions with medication and time (Fs < 1.81, ps < .17).

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