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The (B)link Between Amotivation and Dopamine in Psychosis: What Phasic Eye Blink Rate Reveals

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THE (B)LINK BETWEEN AMOTIVATION AND DOPAMINE IN PSYCHOSIS: WHAT PHASIC EYE BLINK RATE REVEALS

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LIST OF TERMS AND ABBREVIATIONS

Construct	Variable Description
Paradigm	Name given to the entire series of steps from the start of the pre-task questions to all measurements of eye blink rate and through completion of the post-task questions
Task	Name given to the 3-minute paradigm phase when the participant is pressing buttons to inflate and pop balloons; participants perform the task twice.
Task Phase	Name given to each epoch wherein eye blink rate is measured; i.e., baseline, task anticipation, task, reward anticipation, reward receipt, and post-reward rest
Cycle	Name given to the set of five task phases from task anticipation through post-reward rest. All participants complete 2 cycles through these task phases.
Eye blink rate (EBR)	Measured in blinks per minute, at each task phase
Baseline EBR	Blinks per minute during the 3-minute, pre-task, resting-state task phase wherein participants view a static screen with a fixation cross and instructions to look forward and relax
Task Anticipation EBR	Blinks per minute during the task phase immediately preceding the button-pressing task phase; screen displays a countdown until the button-pressing task begins on the subsequent slide
Reward Anticipation EBR	Blinks per minute during the task phase immediately following the button-pressing task and immediately preceding the screen revealing feedback of their behavioral performance and monetary winnings; screen displays instruction that the program is calculating their feedback and a countdown displays seconds remaining until feedback is revealed
Reward Receipt EBR	Blinks per minute during Reward Receipt task phase; static screen displays balloons popped and money earned during the preceding 3-minute button-pressing task phase
Post-Reward Rest EBR	Blinks per minute during task phase immediately following the Reward Receipt Phase; participants view a static screen with a fixation cross and instructions to look forward and relax
Self-Reported Amotivation	Sum of items from the Motivation and Pleasure Scale (MAPS) Self-Report - Effort/Motivation subscale

Clinician-Rated Amotivation	Sum of items from the Brief Negative Symptoms Scale (BNSS) - Avolition subscale
State Positive Affect (PA)	Average self-reported ratings of pre-task confidence, energy, and enthusiasm
State Negative Affect (NA)	Average self-reported ratings of pre-task frustration, anxiety, tiredness, and sadness
Behavioral Effort	Average number of balloons popped, averaged across Cycles
Anticipated Behavioral Performance	Anticipated number of balloons participants estimate they will pop after sampling two trials of the task (and before attempting the full task)
Anticipated Monetary Reward	Amount of bonus cash participants estimate they will win before attempting the full task ($0.00-$5.00).
Schizophrenia Spectrum Disorders (SSDs)	Term for the collective set of psychiatric diagnoses where psychotic symptoms (i.e., hallucinations and delusions) are a primary feature; e.g., schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, major depressive disorder with psychotic features, unspecified psychotic disorder.

ABSTRACT

Motivation deficits (i.e., avolition or amotivation) are a cardinal feature of schizophrenia spectrum disorders (SSDs) and are linked to worse functional outcomes. Accumulating evidence implicates underactive dopamine responses in reward areas of the brain (e.g., striatum) in the etiology of amotivation. Phasic dopamine firing in the striatum purportedly has a role in increasing the perceived value of a potential reward that, in effect, helps "push" the organism toward initiating and persisting in the action to pursue rewards. Previous research has suggested that eye blink rate (EBR) may be a reliable and valid index of striatal dopamine. Amotivation (clinician-rated and self-reported) and phasic changes in EBR on an effort-based reward task were assessed in 28 stable outpatients with an SSD. Overall, the paradigm detected robust changes in blink rate across task phases; however, the pattern of changes was not in the direction hypothesized. Moderation analyses were used to examine the influence of various factors (pre-task state affect, expectations, and behavioral performance) on the relationships between baseline and reward task phases (i.e., reward anticipation and reward receipt). Results revealed that greater behavioral effort was associated with lower EBR during Reward Receipt. Higher anticipated monetary reward was associated with lower EBR during Reward Anticipation and Reward Receipt. Positive affect and self-reported amotivation moderated the relationship between Reward Anticipation EBR and Reward Receipt EBR, such that *lower* positive affect and *higher* amotivation *weakened* the relationship between those conditions. Changes in blink rate appeared better accounted for by literature supporting the inverse relationship between blink rate and task engagement. Implications for understanding the relationship between EBR and amotivation are discussed.

INTRODUCTION

Amotivation (also known as apathy or avolition) – lacking the drive to engage and/or persist in goal-directed behavior – is a cardinal feature of schizophrenia spectrum disorders (SSDs), is inadequately responsive to pharmacological treatments, is linked to worse functional outcomes, and its underlying mechanisms are poorly understood (Calabrese et al., 2014; Hanson, Healey, Wolf, & Kohler, 2010; Kirkpatrick, Fenton, Carpenter, & Marder, 2006). Amotivation has important clinical implications, as it has been linked to worse treatment engagement and compliance, poorer maintenance of goals, reduced treatment attendance, longer delays in treatment seeking, and more relapses in SSDs and other psychiatric populations (e.g., major depressive disorder and substance use disorder; Altamura, Bassetti, Sassella, Salvadori, & Mundo, 2001; Malla, et al., 2002; Ryan & Deci, 2008; Ryan, Plant, & O'Malley, 1995; Tattan & Creed, 2001).

Within SSD populations, amotivation plays a critical role in predicting real-world functioning, both cross-sectionally and longitudinally as well as across illness course from first-episode (Evensen et al., 2012; Faerden et al., 2009, 2010) through chronic phases of illness (Foussias et al., 2011; Foussias & Remington, 2010; Konstantakopoulos et al., 2011). Some studies have found that amotivation severity accounts for over 70% of the variance in functional outcomes (Foussias et al., 2011; Konstantakopoulos et al., 2011). Not surprisingly then, amotivation accounts for significant variance in functional outcomes above and beyond the contribution of positive (i.e., hallucinations and delusions), depressive, and cognitive symptoms (Evensen et al., 2012; Ho, Nopoulos, Flaum, Arndt, & Andreasen, 1998; Milev, Ho, Arndt, & Andreasen, 2005; Rabinowitz et al., 2012). These findings highlight the critical importance of better understanding the mechanisms that underlie this deleterious symptom. The next sections

summarize the behavioral and neurobiological findings related to amotivation in individuals with SSD, the link between dopamine and eye blink rate, existing gaps in the literature, and the rationale for the present study.

Behavioral Findings in Schizophrenia Spectrum Disorders Relevant to Motivated Behavior

A substantial body of research suggests that individuals with SSD underestimate the value of rewards, overestimate the cost of effort, and have difficulty integrating cost/benefit information to guide learning and future behavior. Interestingly, individuals with SSD report in-the-moment levels of enjoyment and arousal to pleasant stimuli comparable to nonpsychiatric control participants (Cohen & Minor, 2010; Llerena, Strauss, & Cohen, 2012); however, they report less enjoyment or pleasure than non-psychiatric control participants when rating non-current activities – i.e., when asked about an upcoming pleasant activity or reward, when asked how they "generally" feel about these activities, or when asked to retrospectively recall how much they enjoyed a positive experience (e.g., Gard, Kring, Gard, Horan, & Green, 2007; Horan, Blanchard, Clark, & Green, 2008; Strauss & Gold, 2012). Such results suggest that individuals with SSDs have difficulty binding reward or incentive value information with specific behavioral activities when reporting on non-current experiences; consequently, such individuals appear to underestimate how valuable or rewarding future activities will be.

This undervaluing of rewards appears coupled with giving undue weight to the costs of both physical and cognitive effort, which has been demonstrated both in the lab and in daily life. For instance, when given the choice between high-effort/high-reward [HE/HR] and low-effort/low-reward [LE/LR] options (e.g., 100 button presses for $3.00-$7.00 versus 10 button presses for $1), individuals with SSD choose the HE/HR option less often, particularly in situations where it would seem to be most "worth the effort" to select the HE/HR option. In other

words, the greater the reward-to-cost ratio (i.e., when the HE/HR choice is closer to the maximum reward for the same amount of physical effort cost) or when the likelihood of reward receipt is more certain (e.g., closer to 100% chance than 25% chance), the *fewer* HE/HR choices they make (Barch, Treadway, & Schoen, 2014; Fervaha et al., 2013; Gold et al., 2013; Treadway, Peterman, Zald, & Park, 2015). Furthermore, compared to non-psychiatric controls, individuals with SSD are less and less willing to engage in behaviors as the cognitive effort required increases (i.e., steeper cognitive effort discounting; Culbreth, Westbrook, & Barch, 2016; Hartmann et al., 2015) and value rewards less strongly as the wait-time to receiving the reward increases (steeper temporal delay discounting; Heerey, Matveeva, & Gold, 2011). These deficits on lab tasks appear to translate to real world settings. In an ecological momentary assessment study, compared to non-psychiatric controls, the SSD group set fewer and less effortful goals as well as demonstrated greater inaccuracy in estimating the difficulty of future goals in daily life (Gard et al., 2014). Taken together, individuals with SSD appear to overestimate the weight of (physical, cognitive, and time) costs, underestimate reward value, and non-optimally integrate cost-benefit information; understandably, such deficits undermine initiation and persistence of goal-directed behavior.

The Role of Dopamine in Motivated Behavior

In both humans and other animals, dopamine-rich areas in the reward pathways of the brain (especially the ventral striatum) play an integral role in guiding pursuit of rewards (Berridge & Kringelbach, 2008; Salamone, 2009). Leading theories suggest that *phasic dopamine* – i.e., transient, stimulus-induced bursts of dopamine – in the striatum enhances the cue-triggered "motivational value" or "incentive salience" of a potential stimulus (Berridge, 2007; Treadway & Zald, 2011); put simply, more dopamine firing in response to a cue or

stimulus triggers a stronger "wanting" or "push" to pursue that stimulus or goal. In animal models where dopamine is blocked or reduced in the ventral striatum, rodents demonstrate a pattern similar to that of individuals with SSD; they make fewer high-effort/high-reward choices (compared to low-effort/low-reward choices) despite intact "liking" of the rewards (i.e., intact food preferences; Berridge, 1996; Salamone, Correa, Farrar, & Mingote, 2007; Salamone et al., 1991). By contrast, rodents show increased preference for the harder, but larger rewards when given drugs that increase dopamine in the striatum (e.g., amphetamine; Wyvell & Berridge, 2000; Salamone et al., 2007).

As the behavioral data in the previous section would suggest, individuals with SSD show intact neural responses to receiving rewards (i.e., intact "in-the-moment" "liking"; Dowd & Barch, 2012; Mann, Footer, Chung, Driscoll, & Barch, 2013), yet show reduced activation in the ventral striatum to reward-predicting cues during reward anticipation – that is, just prior to reward receipt (i.e., impaired "wanting"; Juckel et al., 2006; Kirsch, Ronshausen, Mier, & Gallhofer, 2007; Schlagenhauf et al., 2008; Subramaniam et al., 2015; Waltz et al., 2009). Importantly, decreased activation within the ventral striatum during reward anticipation has been associated with anhedonia/avolition in individuals with SSD (Dowd & Barch, 2012), in healthy individuals with higher physical anhedonia (Dowd & Barch, 2012), and in individuals with major depressive disorder (particularly those with elevated anhedonia; Forbes et al., 2009; Smoski et al., 2009). Taken together, evidence indicating an inadequate neural "push" from the reward pathways required to pursue rewards and goals observed in many individuals with SSD (i.e., amotivation) is consistent with the behavioral data demonstrating that individuals with SSD set fewer and less effortful goals and with the self-report data demonstrating that individuals with SSD rate future activities as being less enjoyable and less "worth the effort."

Eye Blink Rate as an Index of Striatal Dopamine

Cumulating evidence across both animal and human studies suggests eye blink rate (EBR) is a reliable, valid, and noninvasive proxy for striatal dopamine levels (e.g., Karson, 1983; Taylor et al., 1999). Pharmacological studies have shown that EBR is selectively, independently, and rapidly increased in a dose-dependent fashion by dopamine (e.g., D_1 and D_2 receptor) agonists (i.e., dopamine enhancers) and reversed by dopamine antagonists (i.e., dopamine blockers; Blin, Masson, Azulay, Fondarai, & Serratrice, 1990; Elsworth et al. 1991; Jutkiewicz & Bergman, 2004; Kleven & Koek, 1996; Lawrence & Redmond, 1991; but see van der Post, de Waal, de Kam, Cohen, & van Gerven, 2004).

Moreover, studies examining *spontaneous* (i.e., baseline or resting-state) EBR have shown predictable relationships in clinical populations with known dopamine dysfunction. For instance, populations known to have deficient resting-state dopamine levels have shown lower spontaneous EBR compared to healthy control participants. Specifically, chronic cannabis or cocaine users, who show reduced functioning of dopamine (D2) receptors, have lower spontaneous EBRs (Colzato, van den Wildenberg, & Hommel, 2008; Kowal, Colzato, & Hommel, 2011). In addition, individuals with Parkinson's disease, a disease known to deplete dopamine receptors in the nigrostriatum (i.e., part of the striatum) have lower spontaneous EBRs (Deuschel & Goddemeier, 1998; Karson, 1983; Karson, LeWitt, Calne, & Qyatt, 1982). Individuals with early Parkinson's disease also demonstrate mild increases in EBR when treated with dopamine replacement therapy (e.g., L-DOPA; Karson, 1983).

By contrast, individuals with SSD, who are thought to have elevated resting-state striatal dopamine, have elevated spontaneous EBR (Chen, Lam, Chen, & Nguyen, 1996; Freed et al., 1980; Karson, 1983; Karson, Dykman, & Paige, 1990; Mackert, Fletchner, Woyth, & Frick,

1991; Mackert, Woyth, Flechtner, & Volz, 1990; Stevens, 1978; for null findings, see Mueser, Dysken, Sussman, Lyons, & Davis, 1984; for decreased spontaneous EBR, see Mackintosh, Kumar, & Kitamura, 1983). In addition, some treatment studies illustrated decreases in EBR following antipsychotic pharmacotherapy (Karson, Freed, Kleinman, Bigelow, & Wyatt, 1981; Kleinman et al., 1984; Macket et al., 1990). Mackert and colleagues (1990) also found antipsychotic treatment effects such that greater decreases in spontaneous EBR from pre-to-post treatment were associated with greater decreases in anxiety, hostility, and unusual thought content (as rated by the Brief Psychiatric Rating Scale [BPRS]). Interestingly, there was no association of change in spontaneous EBR with changes in negative symptom items (e.g., blunted affect, emotional withdrawal, self-neglect, psychomotor retardation); however, this may be attributable either to the insensitivity of the BPRS to detect such changes since it does not include an avolition or anhedonia item or to the insensitivity of antipsychotics to producing changes in negative symptoms. In sum, spontaneous EBR levels appear lower in populations with diminished resting-state striatal dopamine and appear higher in populations thought to have elevated resting-state striatal dopamine.

One theory that accounts for the apparent paradox (reduced versus excessive striatal dopamine) in SSD comes from Grace (1991) who posited that low tonic (i.e., resting-state) levels of dopamine within the frontal cortex lead to consequent increases in mesolimbic (e.g., striatal) dopamine; this imbalance leads to homeostatic compensations that dysregulate phasic dopamine release. Dysregulated phasic release in combination with excessive tonic levels of dopamine would appear to produce a relatively blunted phasic (i.e., relatively smaller or less intense) response to stimuli that elicit phasic dopamine firing (i.e., reward anticipation, willingness to exert effort for reward; Heinz & Schlagenhauf, 2010). The relatively blunted phasic increase,

thereby, produces a relatively smaller "push" to pursue desired rewards and, consequently, undermines motivated behavior.

Although spontaneous EBR has been used in numerous studies, relatively few studies have examined task-induced (i.e., phasic) EBR. Several studies in humans and nonhuman primates have demonstrated acute increases in EBR immediately following administration of dopamine-increasing drugs (i.e., dopamine agonists) in a dose-dependent manner (i.e., higher change in blink rate with higher dose; e.g., Blin et al., 1990; Elsworth et al., 1991; Jutkiewicz & Bergman, 2004). Moreover, two studies known to this author demonstrated task-induced changes in EBR. One mood induction study in healthy individuals found that EBR increased significantly after a positive, but not negative, mood induction, particularly in those with lower resting-state EBR (Akbari Chermahini & Hommel, 2012). In a study germane to the present project, researchers utilized a laboratory task requiring effort to obtain monetary reward to examine task-related EBR changes in healthy controls and individuals with bipolar I disorder not in a current mood episode. Both groups showed increased EBR from the baseline phase to the task anticipation and reward receipt phases of the paradigm (Peckham & Johnson, 2015). In the bipolar group, elevated EBR was associated with increased positive affect (i.e., confidence), ambitious goal setting, and reward-triggered mania (Peckham & Johnson, 2015), which is consistent with theories of elevated striatal dopamine and elevated reward responsivity in individuals with bipolar disorder (Johnson, Carver, & Gotlib, 2012; Johnson, Eisner, & Carver, 2009). Such results are in line with evidence that phasic changes in striatal dopamine are particularly relevant for mobilizing effort toward reward (Salamone, 2009). Taken together, evidence suggests phasic EBR may be a viable measure of reward sensitivity in both healthy and clinical populations.

Summary and Purpose

Accumulating evidence suggests that individuals with SSDs have abnormal dopamine functioning in reward-related areas (e.g., striatum), which has been associated with higher negative symptoms (including amotivation). Given that striatal, phasic dopamine firing is purported to increase the motivational value of a stimulus, such a deficit (phasic dopamine underactivity) would understandably undermine individuals' "wanting" to engage in rewarding activities. This may at least partly explain why individuals with more severe amotivation do not appear to feel the drive to engage in high-effort goal-directed activities, even ones they rate as being highly enjoyable.

Research has largely supported the relationship between EBR and striatal dopamine levels, with emerging evidence suggesting it is sensitive to resting-state as well as phasic (e.g., task-related) changes in dopamine. Therefore, this method may be a particularly useful and noninvasive method for examining reward sensitivity in individuals with SSDs. To my knowledge, the current study is the first to examine phasic changes in EBR in an SSD population as well as the first to examine individual differences in negative symptoms related to phasic EBR.

Aims

1. Establish whether EBR is sensitive to changes in task phase on a novel, effort-based reward task;
2. Determine the extent to which behavioral indices of motivation (i.e., behavioral effort) and baseline predictors (i.e., pre-task state affect, expectations) influence change in EBR across baseline, reward anticipation, and reward receipt task phases;
3. Examine whether and how negative symptoms influence EBR

METHODS

Participants

Participants were clinically stable outpatients who met criteria for a schizophrenia spectrum disorder (SSD; e.g., schizophrenia, schizoaffective disorder, mood disorder with psychotic features, delusional disorder, unspecified psychotic disorder) as per the Fifth Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*; American Psychiatric Association [APA], 2013). Recruitment occurred through two different sites (Louisiana State University and VA Connecticut Healthcare System) and via several sources: referrals from healthcare professionals (nurses, psychiatrists, case managers, group home managers), self-referral via "word-of-mouth" or in response to study flyers placed in treatment clinics, and based on names provided from one collaborator's data repository (Joanna Fiszdon, Ph.D.) wherein participants had consented to being contacted for future studies. Exclusion criteria included the following: a) changes to their psychotropic medications within the past two weeks, b) discharge from an inpatient psychiatric facility within the past 30 days; c) current eye conditions (e.g., glaucoma, cataracts) or any current illness or condition that interferes with visual sensitivity (e.g., cold, flu, migraine); d) neurological insult or head trauma requiring overnight hospitalization; e) age over 65 years; f) current *DSM-5* severe substance use disorder; g) current, regular (i.e., daily) cannabis use regardless of *DSM-5* diagnosis. Substance use exclusion criteria were based on evidence of significantly altered blink rates in heavy cannabis users (defined as weekly consumption of at least 4 joints, for the past 2 years as per, Kowal, Colzato, & Hommel, 2011). All diagnoses were made using information obtained from a structured clinical interview (SCID-5; First, Williams, Karg, & Spitzer, 2015) and available medical records. Interviews were conducted by doctoral students trained to criterion (ICC > .75) under the supervision of an

experienced clinician and licensed psychologist (Drs. Alex Cohen or Joanna Fiszdon). Participants were compensated for completion of the study. Informed consent was obtained for all participants in line with procedures approved by the appropriate Institutional Review Boards (see Appendices A and B).

Measures

Clinician-rated psychiatric symptoms. Psychiatric symptoms were measured using the expanded Brief Psychiatric Rating Scale (BPRS; Kopelowicz, Ventura, Liberman, & Mintz, 2005; Ventura et al., 1993). The BPRS is a 24-item scale that assesses a broad range of psychiatric symptoms including depression, anxiety, hallucinations, delusions, and unusual behavior. Each symptom is rated 1 (not present) to 7 (extremely severe). Negative symptoms were measured using the Brief Negative Symptoms Scale (BNSS; Kirkpatrick et al., 2011). The BNSS is a 13-item semi-structured interview instrument designed to measure five distinct negative symptoms that load onto two separate factors – diminished emotional experience (anhedonia, asociality, and avolition) and diminished expression (blunted affect and alogia). Items are rated from 0 (normal) to 6 (extremely severe). The two avolition/amotivation items were summed for use as the clinician-rated amotivation variable in the present study.

Self-reported negative symptoms. The Motivation and Pleasure Scale – Self-Report (MAP-SR; Llerena et al., 2013; see Appendix C) was used to assess self-reported deficits in motivation and pleasure (which correspond to avolition and anhedonia symptoms, respectively). The MAPS-SR is a 15-item scale that has been validated in SSD samples with good internal and convergent validity; it was developed from and validated with a clinician-related version of this scale called the Clinical Assessment Interview for Negative Symptoms (CAINS; Kring, Gur, Blanchard, Horan, & Reise, 2013). The MAPS-SR has good discriminant validity separating it

from positive symptoms as well as from anxiety/depression symptoms (Llerena et al., 2013). Items assess consummatory and anticipatory pleasure related to social (3 items) and recreational/work (3 items) domains, feelings and motivations to be around close others (i.e., family, romantic partners, and friends) (3 items), and motivation/effort to engage in activities (6 items). Items are rated regarding participants' experiences in the past week from 0 (none) to 4 (extremely or very true). The six motivation/effort items were summed for use as the self-reported amotivation variable in the present study.

Estimated premorbid intelligence. The Wechsler Reading Achievement Test – 4th Edition (WRAT-4) - Word Reading Subtest (Wilkinson & Robertson, 2006) is a norm-referenced test of the ability to decode letters and words that is frequently used as an estimate of intelligence.

Pre- and post-task questionnaire. Pre- and post-task questionnaire (see Appendices D and E, respectively) items utilized a seven-point Likert scale from 1 (very slightly or not at all) to 7 (extremely) where participants rated their current/state positive affect (enthusiastic, confident., energetic) and state negative affect (sad, nervous, frustrated, tired) as well as perceived task difficulty and motivation to do well. To assess task expectations, participants were also asked to estimate how many balloons they anticipated popping (i.e., anticipated behavioral performance) and how much money they anticipated winning (i.e., anticipated monetary reward).

Demographic and other information. Along with demographic data (e.g., age, race), participants provided information about their current nicotine use (e.g., age at first cigarette, use in the past week, and time since last cigarette), current caffeine use (e.g., drinks per day, time since last caffeinated beverage), and sleep amount/quality.

Reward Task

The computer-based reward task was adapted from a paradigm used in a similar study of healthy control and bipolar I disorder participants (Peckham & Johnson, 2015). In the present version of the paradigm (see schematic in Figure 1), there were six task phases: 1) Baseline, 2) Task Anticipation, 3) Task, 4) Reward Anticipation, 5) Reward Receipt, and 6) Post-Reward Rest. Phases two through six were repeated twice (i.e., two cycles). Before the Baseline phase, participants completed the pre-task questionnaire. Next, during the three-minute initial Baseline phase, participants were seated at a computer with a fixation cross displayed at the center of the computer and asked to remain in a relaxed state without looking away from the screen or falling asleep, in accordance with procedures in other studies (e.g., Chan et al., 2010; Chen et al., 1996; Peckham & Johnson, 2015). After the Baseline phase, participants were provided task instructions and completed two sample trials to practice inflating and popping a balloon presented on the screen. To inflate and pop each balloon, participants pressed repeatedly the "1" button on the keyboard. It took 20 button presses to pop one balloon. Participants were told that each balloon popped during the task phase was worth a bonus 10 cents, that their highest score from either of the two cycles would be used for their bonus cash, and that the maximum bonus is $5 for popping 50 balloons.

After participants completed the sample trials and reported understanding the task, participants estimated their anticipated balloons popped and anticipated monetary reward and then proceeded to phase two of the task. During the one-minute Task Anticipation phase, participants saw the phrase "Get Ready!" displayed onscreen, with a digital countdown displaying the seconds remaining until the task began (60 to 0). This phase was meant to increase performance anticipation and encourage participants to mobilize effort toward the task (as per

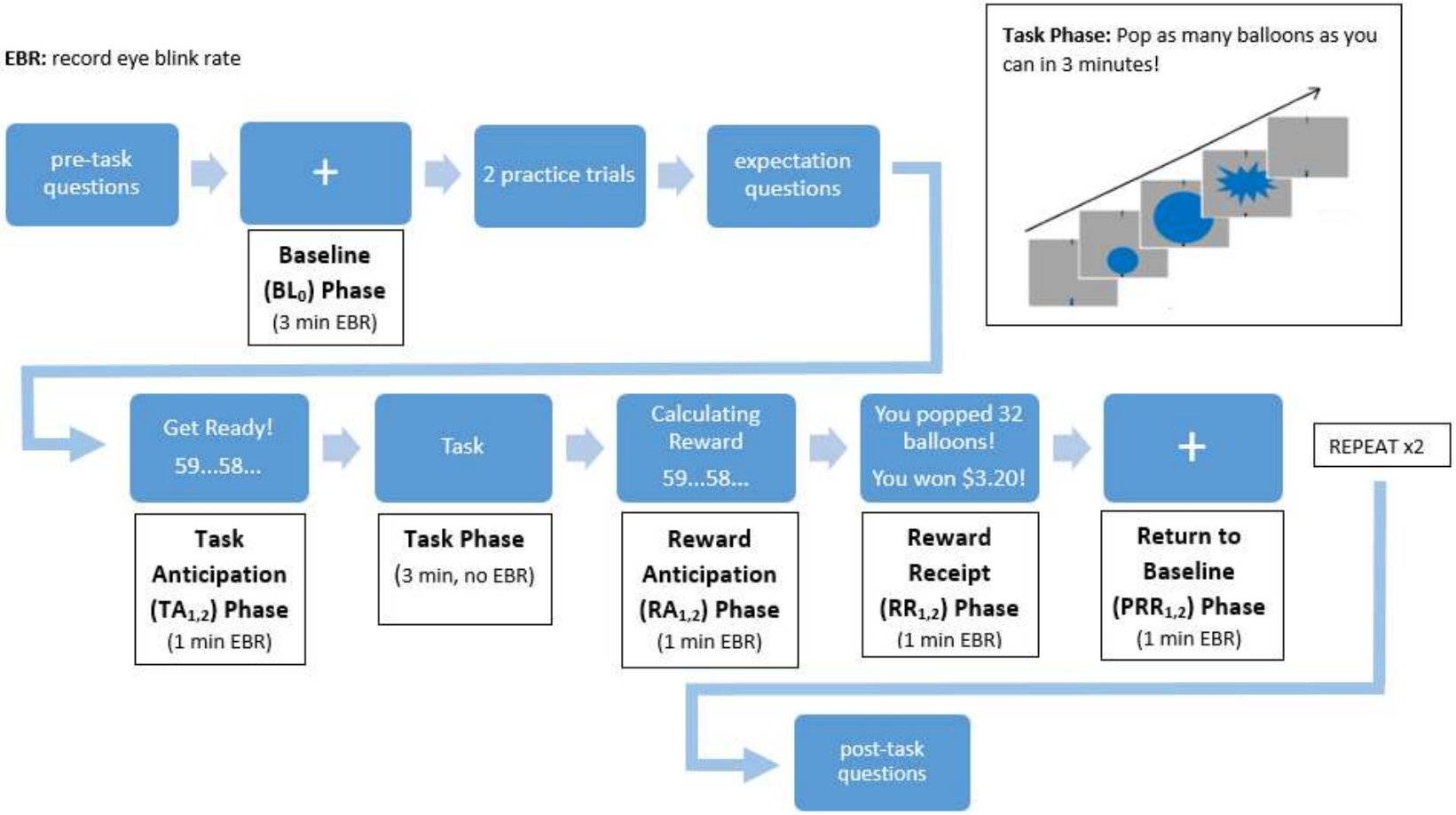

Figure 1. Schematic of Paradigm.

Peckham & Johnson, 2015). Next, during the three-minute Task phase, participants popped as many balloons as they could before time ran out. Importantly, participants were not provided feedback about their total winnings until after the Task phase and Reward Anticipation phase. Once time was up on the task, the paradigm advanced to the Reward Anticipation phase. During the Reward Anticipation phase, the screen displayed text saying, "Calculating Reward!," with a digital countdown displaying time remaining until the total winnings were revealed; the digital countdown was meant to enhance a feeling of anticipation. Participants were told that during the Reward Anticipation phase the program was calculating how much they had won. Next, during the one-minute Reward Receipt phase, participants were shown a static screen displaying accurate feedback reflecting the number of balloons they popped and their calculated monetary winnings. After the Reward Receipt phase, there was a one-minute Post-Reward phase wherein participants were asked to look at the computer screen and relax. Participants cycled twice through phases two to six (i.e., task anticipation, balloon popping task, reward anticipation, reward receipt, and post-reward rest).

Immediately following the second cycle, participants completed the post-task questionnaire. Although participants were told at the start of the task that the highest of their two balloon popping scores would be used for their bonus cash, all participants were told that their effort was appreciated and were awarded the full $5 regardless of their actual performance. The perception of monetary incentive was required in order to measure the construct of interest – reward-based performance; the full amount was provided to all participants to avoid the potential for coercion or unfairness that may be perceived for paying participants different amounts based on their actual performance while completing the task. Based on our pilot testing with healthy controls, no one was able to pop more than 50 balloons in three minutes; thus, it was considered

highly improbable that anyone would pop more than 50 balloons in the three minutes during the experiment itself. Consistent with this, the highest scored obtained was 41; thus, the actual payment was not less than they otherwise would have received. In addition, during pilot testing of 5 healthy, nonsmoking controls, the data suggested that blink rate differed across task phases and cycles; thus, EBR appeared sensitive to differences in task phase and was deemed suitable to administer to the patient sample. The paradigm was completed after at least one other interview (e.g., SCID background information) so that participants had a chance to acclimate to the experimenter and testing environment before completing the paradigm. The paradigm—including Baseline phase, all task phases, and pre- and post-task questionnaire—was programmed with E-Prime Professional, Version 2.0.

Eye Blink Rate

EBR was recorded during each of the six reward paradigm phases (mentioned above) using a digital video camcorder placed on a tripod beside the task computer and positioned to record each participant's face.[1] Participants were told that the videotaping was to see how participants responded to the task; they were not told that their eyes or blink rate were of interest.

Three blink-counting raters were trained to criterion on two gold standard videos; training was continued until raters were discrepant by no more than 2 blinks on any 10-second epoch in any task phase in the gold standard samples. Raters remained blinded to clinical symptom ratings

[1] To enhance reliability of blink counting, blue and green screens and low frequency auditory tones (130 Hz and 146 Hz) embedded in the E-Prime program to signal task phase onset and offset times for the rater when viewing the videos offline. The auditory tones were intentionally selected for being unlikely to induce a startle response. The auditory and visual markers were the same for each condition. A mirror was positioned behind the participant's head so that both the computer screen and the participant's face were included in the frame. The video recorder was set to high resolution with a sampling rate of 60 frames per second to ensure no blinks were missed by the software.

(as per Chan et al., 2010; Kojima et al., 2002). A subsample of 25% of participants' videos were randomly selected to be rated by two raters to determine inter-rater reliability; agreement was excellent (ICC = .946-.989). A subset of participants (n = 7) had EOG electrodes on their faces to examine convergent validity between EOG and manual blink counting as part of a separate study; for those participants, electrodes were placed bilaterally at mastoids (reference), the outer canthi of both eyes (horizontal EOG) and above and below the right orbit (vertical EOG). EBR data from this subset was compared to the subset without EOG electrodes to assess whether the EOG electrodes impacted EBR.

Minimizing EBR confounds. Based on findings that EBR is relatively stable within individuals between 10AM and 5PM (Barbato et al., 2000), data were collected during this time frame. As sleep deprivation increases blink rate (e.g., Barbato et al., 2007; De Padova, Barbato, Conte, & Ficca, 2009), time of day, hours slept in the prior night, and subjective sense of tiredness were recorded, and statistically controlled as necessary. Although EBR was recorded during the task phase (i.e., while participants were inflating and popping balloons), these data were not included in the present analyses due to potential confounds attributable to task demands that add noise to the signal attributable to the striatal dopamine response. For example, evidence suggests that eye blinks get synchronized with manual behavior during motor tasks such as finger tapping (Cong, Sharikadze, Staude, Deubel, & Wolf, 2010).

Due to some evidence that EBR is influenced by acute caffeine and nicotine use, these variables were measured via self-report and statistically controlled as necessary (Kadoya, Domino, & Matsuoka, 1994). Individuals with SSD have an extremely high prevalence of smoking, with some estimates as high as 88% (Hughes, Hatsukami, Mitchell, & Dahlgren, 1986). In addition, over half of individuals with schizophrenia meet criteria for a tobacco use

disorder and smoke cigarettes regularly (APA, 2013). Due to such high co-morbidity rates, it was neither feasible nor rational to exclude smokers in the present study. Of note, in the one study that looked at blink rate in relation to nicotine levels in non-psychiatric controls, the authors found only a small effect-size correlation (r = .265) between increase in EBR and increase in plasma nicotine from pre- to post-cigarette use in daily smokers who had been abstinent from nicotine for at least 10-12 hours (Kadoya et al., 1994). In addition, although some prior EBR studies have required that participants remain abstinent from smoking in the 10-12 hours prior to participation (e.g., Peckham & Johnson, 2015), smokers were not asked to abstain from smoking prior to participating in the present experiment due to evidence that nicotine withdrawal induces anhedonic states. Several studies indicate that nicotine withdrawal attenuates incentive value for non-nicotine reinforcers (including monetary reward) and diminishes interest in pleasant events (Besheer & Bevins 2003; Chaudhri et al. 2006; Dawkins, Powell, West, Powell, & Pickering, 2006; Donny et al. 2003; Geier, Sweitzer, Denlinger, Sparacino, & Donny, 2014; Powell, Pickering, Dawkins, West, & Powell, 2004; Weaver et al., 2012). Therefore, the relationship between EBR and cigarette use was examined and statistically controlled when necessary (as below). Given unclear evidence on the impact of IQ on blink rate, their relationship was examined statistically. Given mixed evidence that age impacts blink rate (Sun et al., 1997 but not in Bentivoglio et al., 1997), age was examined statistically.

Statistical Analyses

Examination of skew and kurtosis as well as box plots with 95% confidence intervals were used to identify outliers on EBR task phase, symptom, and demographic variables. Data were checked for violations of normality, skewness ($Z \geq 3.0$), and kurtosis ($Z \geq 3.0$), and statistical corrections, transformations, or non-parametric tests were employed, as appropriate.

The relationships between demographic and other confounding (e.g., caffeine, nicotine) variables and EBR were assessed using Pearson's *r* correlations (e.g., age, years of education, WRAT-4 Word Reading IQ estimate, cigarettes per day, time since last cigarette, time since last caffeinated beverage), *t*-tests (e.g., gender), and repeated-measures ANOVAs (e.g., gender, smoking status), where appropriate. When a confounding variable was associated with EBR, ANCOVAs were used to examine its influence across conditions. Covariates were not significant unless otherwise stated. Significant results were further explored via Tukey's LSD test for post hoc pairwise comparisons. For repeated-measures ANOVAs, where violations of sphericity were present (i.e., Mauchly's test of sphericity was significant), Greenhouse-Geisser corrections were reported. Cohen, Cohen, West, and Aiken's (2003) recommendations for *d* (.20, .50, and .80), *r* (.10, .30, and .50), and partial eta squared (.02, .09, and .25) were used to interpret effect-size magnitude (small, medium, and large, respectively).

Moderation analyses were used to examine the influence of each variable of interest (e.g., state affect, expectations, behavioral effort, negative symptoms) on the relationship between the key task phases of interest (Baseline EBR, Reward Anticipation EBR, and Reward Receipt EBR). Each moderator was entered into three separate models (see Figure 2 for schematic) to examine whether the moderator variable (M) influenced the relationship between: 1) Baseline EBR (X) predicting Reward Anticipation EBR (Y), 2) Baseline EBR (X) predicting Reward Receipt EBR (Y), and 3) Reward Anticipation EBR (X) predicting Reward Receipt EBR (Y). First, all X and M variables were each centered at their grand mean and then XM interaction terms were computed. Second, separate hierarchical regressions with each centered X and M variable entered in step 1 (to examine unconditional [i.e., main] effects) and the XM interaction term entered in step 2 (to examine moderation effects). Moderation was considered present if the

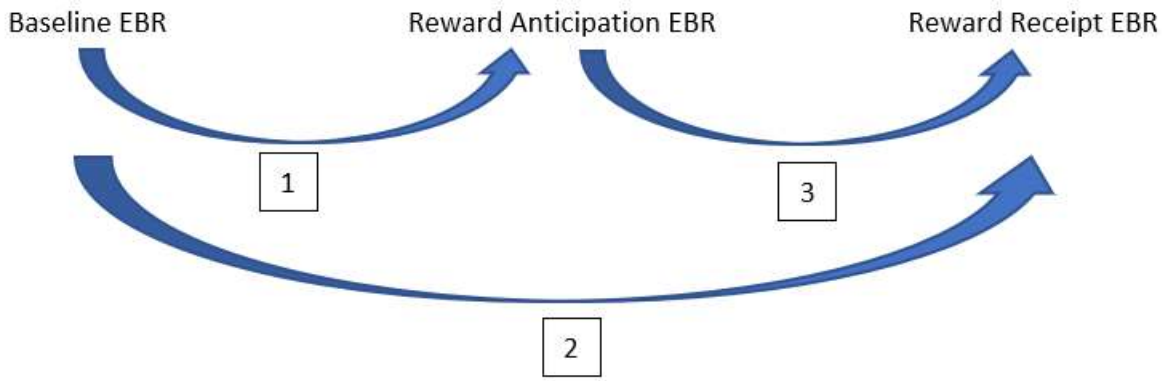

Figure 2. Depiction of three models being tested for each moderator in Aims 2 and 3.

addition of the interaction term (XM) significantly improved the model (i.e., significant R^2 change with a significant interaction term). If moderation was significant, the interaction was examined in two ways (per recommendations by Field, 2018) using Hayes's (2018) PROCESS macro version 3: first, data were graphed using -1 SD, mean, and +1SD values of the M and X variable to visualize the relationship; second, the Johnson-Neyman method (Bauer & Curran, 2005) was used to identify the values of the moderator at which the relationship between X and M changed significance. All tests used statistical significance set at $\alpha < .05$ (two-tailed) and were analyzed using IBM SPSS Statistics 24. For all analyses mentioned above, trend-level significances are indicated though not interpreted; while trend-level relationships are likely less reliable than significant effects, they may be useful as exploratory analyses for future studies.

Specified aims and hypotheses.

Aim one**: **Establish whether eye blink rate is sensitive to changes in task phase on the effort-based reward paradigm.

Hypothesis 1.1. It was hypothesized that blink rate would vary with task phase as tested via a repeated-measures ANOVA (2 cycles: Cycle 1, Cycle 2; 4 task phases: Task Anticipation,

Reward Anticipation, Reward Receipt, Post-Reward Rest) with EBR as the dependent variable; i.e., it was hypothesized that there would be a main effect of task phase.

Hypothesis 1.2. Reward Anticipation EBR and Reward Receipt EBR were hypothesized to be significantly higher than Baseline EBR, as tested via a priori planned *t*-tests.

Aim two: Determine the extent to which behavioral indices of motivation (i.e., behavioral effort) and baseline predictors (i.e., mood/arousal, expectations) influence change in eye blink rate across key task phases. Behavioral effort (number of balloons popped), pre-task positive and negative affect (state PA, state NA), and task expectations (anticipated behavioral performance and anticipated monetary reward) were examined for their main effects and moderation effects on blink rate in three models of interest (as described above; also see Figure 2): 1) Baseline EBR (X) predicting Reward Anticipation EBR (Y), 2) Baseline EBR (X) predicting Reward Receipt EBR (Y), and 3) Reward Anticipation EBR (X) predicting Reward Receipt EBR (Y). These variables were hypothesized to influence blink rate; more specific predictions would have been premature. Results were used to inform interpretation of the relationship with negative symptoms in Aim Three.

Aim three: Determine the extent to which negative symptoms (clinician-rated and self-reported amotivation) influence change in eye blink rate across key task phases. Negative symptoms were examined for their main effects and moderation effects on blink rate in the same three models of interest (as described above; also see Figure 2): 1) Baseline EBR (X) predicting Reward Anticipation EBR (Y), 2) Baseline EBR (X) predicting Reward Receipt EBR (Y), and 3) Reward Anticipation EBR (X) predicting Reward Receipt EBR (Y). It was hypothesized that higher amotivation (i.e., lower motivation) would weaken the relationship between the Reward Anticipation and Reward Receipt task phases. In other words, it was hypothesized that elevated

amotivation (both clinician-rated and self-reported) would moderate the relationship between reward anticipation EBR and reward receipt EBR (in model 3), such that higher amotivation (i.e., lower motivation) would be associated with a shallower slope between task phases.

Power analyses. G*Power 3.1.5 (Faul, Erdfelder, Lang, & Buchner, 2009) was used to compute the minimum number of participants to be recruited for the present study required to detect the expected correlations and regressions with power (1 – β) of .80, two-tailed tests, and α = .05. Given that no study to date has examined phasic changes in EBR in individuals with SSD, the closest comparison study was that of Peckham and Johnson (2015). Using a 3 (task phase: baseline, task anticipation, reward receipt) x 2 (group: bipolar I, control) ANOVA, the authors found a medium-to-large main effect of EBR over time (partial-eta squared [η_p^2] = .11). Such an effect requires a minimum sample size of 13. The authors also found medium-to-large effects in their partial correlations between change in EBR and their psychological variable of interest. Regarding the regression equations, estimating for a medium effect size (R^2 = .13) with power = .80, alpha = .05 with two predictors (1 in each step of the regression) would require N = 55 participants. Thus, in order to adequately power the planned analyses, a minimum of 55 individuals with SSD were intended to be recruited. Despite active recruitment efforts in two different states, we were only able to test a total of 36 participants.

RESULTS

Preliminary Analyses

Examining outliers, normality, and exclusions. A total of 36 participants were tested. Two were removed for having no lifetime psychotic symptoms (both were diagnosed with major depressive disorder without psychotic features). Three were excluded because they were missing data for at least one blink rate condition due to technology malfunction (e.g., video camcorder ran out of battery or recording space). Upon examination of blink rate box plots, two participants were outliers and subsequently excluded; one had previously undisclosed glaucoma (an exclusion criterion) and the other had delusions that an outside force was altering his visual acuity (as well as some symptoms consistent with possible untreated glaucoma). Next, given some data supporting an association between age and EBR, age was correlated with blink rate conditions. In conditions with significant correlations, a scatterplot revealed a significant outlier whose age was 75. Taken together with the fact that the next closest participant's age was 65, this participant was removed from further analyses. After final exclusions, 28 participants were included in the primary analyses. Of these 28, 15 were diagnosed with schizophrenia, 9 with schizoaffective disorder (6 with depressive type, 3 with bipolar type), 2 with bipolar disorder with psychotic features, 1 with major depressive disorder with psychotic features, and 1 with unspecified psychotic disorder. Of these 28, 54% (15) were experiencing current psychotic symptoms, defined as experiencing hallucinations or delusions in the past 2 weeks. Three had a lifetime severe substance use disorder. Four were Veterans.

For sample characteristics see Tables 1 and 2. Regarding smoking status, 57% (n = 16) were current smokers, 25% (n = 7) were former smokers, and 18% (n = 5) never smoked. Current smokers smoked an average ± SD of 13.13 ± 6.21 cigarettes per day. On average, participants

slept 7.5 ± 2.90 hours the night prior to testing and drank an average of 2.13 ± 1.68 caffeinated beverages per day.

Eye blink rate. ICC between raters was excellent (ICC = .95; 95% confidence interval = .27-.99). To examine the stability of the blink rate across minutes, each minute of the 3-minute pre-task Baseline phase was compared. ICC was excellent (.915); Chronbach's alpha was .916. Correlations (e.g., minute 1v2, 1v3, 2v3) ranged from .72-.93, suggesting that resting-state EBR is relatively stable over short periods of time. Participants as a group had an average resting-state (i.e., baseline) EBR of 22.06 (SD = 16.27), which is consistent with other studies in SSD samples (e.g., Chen, Lam, Chen, & Nguyen, 1996; Mackert et al., 1991).

Table 1. Sample Characteristics

Characteristic	Mean (SD)
Age	48.92 (10.27)
Age at First Treatment	24.23 (8.60)
Premorbid IQ	85.11 (14.55)
Number of Hospitalizations	7.74 (12.30)
	% (N)
Gender (% male)	57% (16)
Ethnicity	
African American	61% (17)
Caucasian	32% (9)
Education	
At least some college	32% (9)
High school diploma	43% (12)
< High School diploma	21% (6)
Marital Status	
Never Married	68% (19)
Divorced or Separated	29% (8)

Confounding variables. Before testing hypotheses, bivariate Pearson correlations (or Spearman's rho when one variable had significant skew or kurtosis [$Z \geq 3.0$]) and ANOVAs

were used to consider potential confounds influencing blink rates. Age, IQ (WRAT Word Reading *T*-score), age of illness onset, and age at first treatment were not significantly correlated with EBR at any task phase (*ps* > .20). Number of caffeinated beverages per day and time since last caffeinated beverage were not correlated with EBR at any task phase (*p*s > .10). Among current smokers (n =16), more cigarettes per day had a trend-level association with higher blink rate during Post-Reward Rest, $r = .45$, $p = .08$, and older age at first cigarette had a trend-level association with higher blink rate during pre-task Baseline, $r = .43$, $p = .10$. Gender (Male, Female), Smoking Status (Current Smoker, Non-Current Smoker), EOG Electrodes (Present, Absent) were each examined in a 2 (Group) x 2 (Cycle: Time 1, Time 2) x 4 (Task Phase: Task Anticipation, Reward Anticipation, Reward Receipt, and Post-Reward Rest) ANOVA to

Table 2. Clinician- and Self-Rated Symptom Measures

Symptoms (range)	**Mean (SD)**
BPRS Total (24-168)	45.35 (13.50)
BPRS Positive Symptoms (7-49)	16.11 (8.24)
BPRS Depression/Anxiety Symptoms (4-28)	6.37 (3.40)
BPRS Negative Symptoms (3-21)	6.23 (3.05)
BPRS Agitation/Mania Symptoms (6-42)	8.96 (3.41)
BNSS Total (0-78)	23.15 (14.62)
BNSS Experiential Symptoms (0-42)	14.67 (8.58)
- BNSS Avolition (0-12)	4.48 (2.78)
BNSS Expressive Symptoms (0-30)	6.85 (7.27)
MAPS Total (0-60)	37.89 (11.56)
MAPS Effort/Motivation (0-24)	14.37 (6.79)
MAPS Social Pleasure (0-12)	8.19 (3.74)
MAPS Recreation/Work Pleasure (0-12)	8.41 (3.74)
MAPS Feelings/Motivations Toward Close Relationships (0-12)	6.93 (3.41)

Note. Indents indicate when a measure is a subscale of the superordinate scale. BPRS = Brief Psychiatric Rating Scale. BNSS = Brief Negative Symptoms Scale. MAPS = Motivation and Pleasure Scale – Self-Report.

examine their influence on blink rate. No variable had a significant main effect or interaction (*ps* > .10). *T*-tests comparing groups on pre-task baseline blink rate were also nonsignificant (*ps* > .10).

Behavioral performance and expectations. Participants as a group, popped an average ± SD of 27.71 ± 1.30 balloons at Cycle 1 and 28.92 ± 1.21 balloons at Cycle 2; relatedly, the average amount of bonus money earned was $2.71 ± $0.15 and $2.89 ± $0.12, respectively. Participants took an average of 5.14 ± 2.68 seconds at Cycle 1 and 4.92 ± 2.36 at Cycle 2 to pop each balloon. Taken together, there did not appear to be a fatigue effect, as performance was not significantly different between Cycles 1 and 2. Given that striatal dopamine responses are purportedly increased in response to unexpected rewards and given research suggesting that individuals with SSD underestimate their performance, actual performance was compared with anticipated performance. Collapsing across Cycles (see Table 3 below), participants significantly underestimated how many balloons they would pop (d = -.91, large effect), yet grossly overestimated the amount of bonus cash they would earn (d = .57 medium effect). Moreover, the disconnect between anticipated money and anticipated balloons popped suggested that participants were not correctly computing their anticipated winnings based on their prediction of their anticipated performance, despite being told they would win 10 bonus cents per balloon popped. Consistent with this disconnect, there was no significant correlation between anticipated money and anticipated balloons, $r(27) = .19$, $p = .33$. Expectations were subsequently examined for their relationship with blink rate (see Aim Two).

Table 3. *T*-tests Examining Discrepancies Between Anticipated and Actual Performance

	Anticipated Mean (SD)	Actual Mean (SD)	*t*	*d*
Money	$3.86 ($1.68)	$2.83 ($0.65)	2.95**	.57
Balloons	16.27 (13.91)	28.32 (6.46)	-4.83***	-.91

*$p < .05$. **$p < .01$. *** $p<.005$.

Aim One: Establish Whether Eye Blink Rate Is Sensitive to Changes in Task Phase on the Effort-Based Reward Paradigm

To assess how blink rate varies across task phases and repetitions, a 2 Cycle (Cycle 1, Cycle 2) x 4 Task Phase (Task Anticipation, Reward Anticipation, Reward Receipt, Post-Reward Rest) ANOVA was employed. As hypothesized, there was a large, main effect of task phase, $F(1.90, 51.19) = 11.79$, $p <.001$, $\eta_p^2 = .30$; the pattern was such that blink rate tended to increase across task phases with blink rate lowest during the Task Anticipation phases and highest at the Post-Reward Rest phases (see Figure 3, below). In addition, there was a medium-to-large main effect of cycle, $F(1.00, 27.00) = 10.70$, $p < .003$, $\eta_p^2 = .28$, such that blink rate was significantly higher during Cycle 2. The Cycle x Task Phase interaction was not statistically significant, $F(3.00, 81.00) = 0.60$, $p = .61$, $\eta_p^2 = .02$, suggesting that the EBR pattern across task phases was similar across cycles.

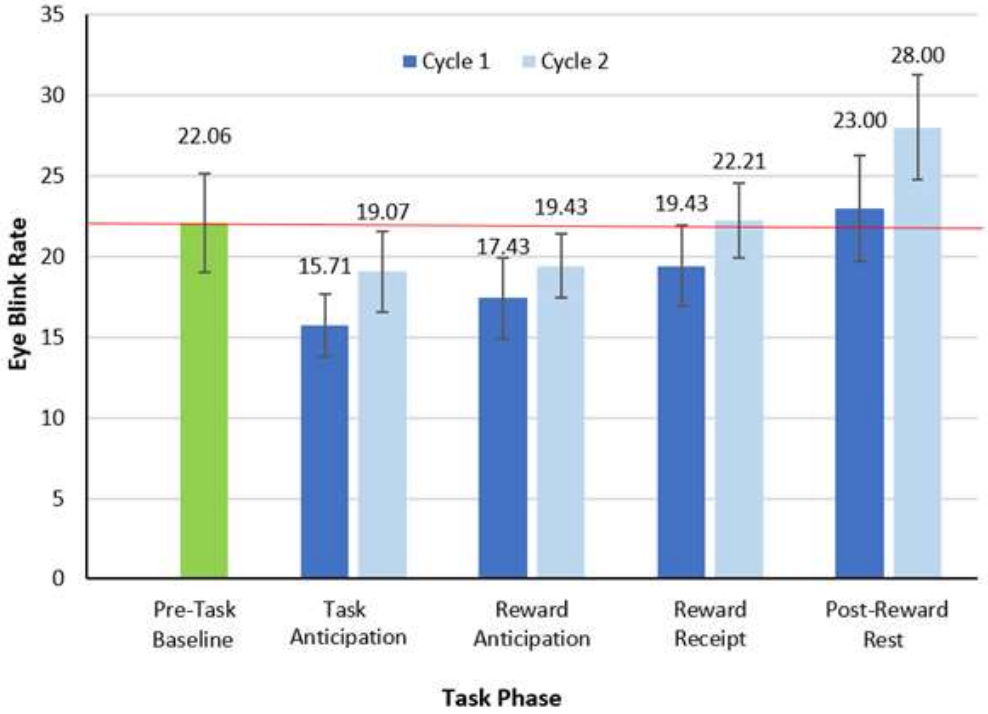

Figure 3. Mean eye blink rate during each task phase, separated by cycle. The error bars represent the standard error of the mean. The red line indicates blink rate during pre-task baseline for ease of comparison with each subsequent task phase.

Given that Pre-Task Baseline is a commonly used reference point in most experimental studies, the data were next examined in a 5 Task Phase ANOVA (Baseline EBR, Task Anticipation EBR, Reward Anticipation EBR, Reward Receipt EBR, Post-Reward Rest EBR). Since there was no Cycle x Task Phase interaction, data were collapsed across cycle (although results were similar when analyses were run separately for each cycle). As expected, there was a significant main effect of task phase, $F(2.30,61.96) = 6.14$, $p = .002$, $\eta_p^2 = .19$. There were significant quadratic and linear trends, $F(1,27) = 8.50$, $p = .007$, $\eta_p^2 = .24$ and $F(1,27) = 6.65$, $p = .016$, $\eta_p^2 = .20$, respectively, indicating a U-shaped pattern such that blink rate *decreased* from Baseline EBR to Task Anticipation EBR and subsequently *increased* from Task Anticipation EBR through Post-Reward Rest EBR (see Figure 4).

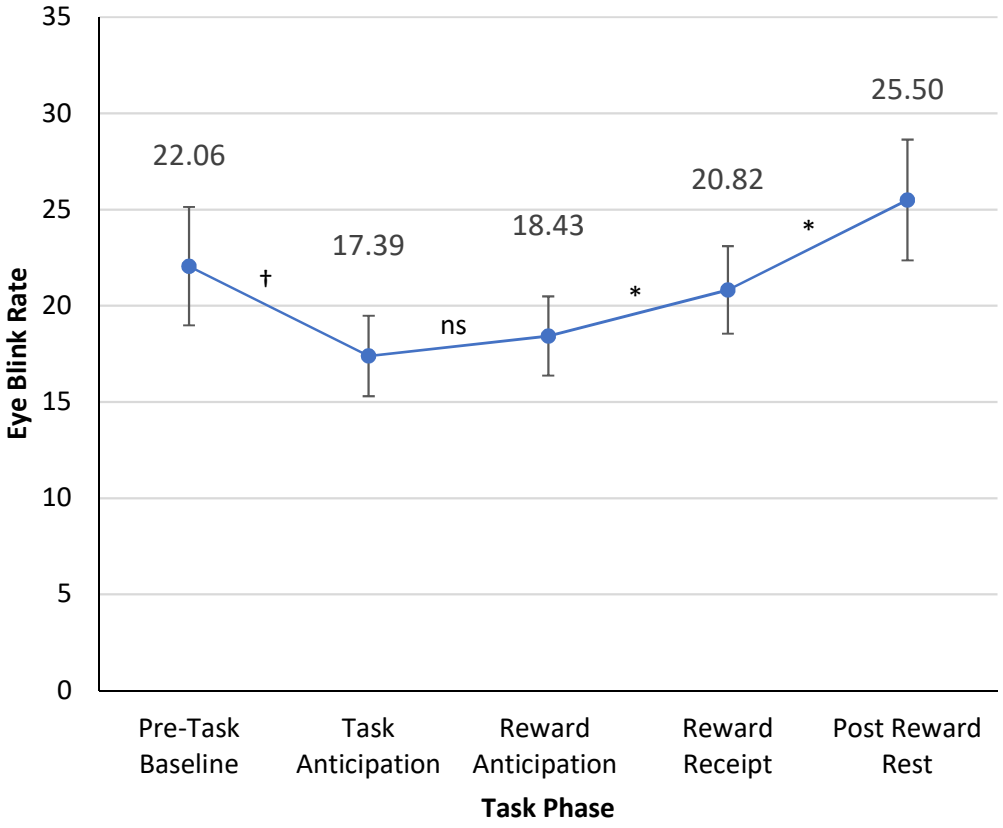

Figure 4. Mean eye blink rate for task phases collapsed across cycle. Error bars represent standard error of the mean. Significant differences between neighboring task phases are indicated. ns = not significant. † $p < .10$. * $p < .05$.

Counter to a priori hypotheses, Baseline EBR was not significantly different from Reward Anticipation EBR, $t(27) = 1.64$, $p = .11$, $d = .31$, or Reward Receipt EBR, $t(27) = 0.54$, p .60, d = .10. As shown in Figure 4, post hoc repeated contrasts (i.e., comparing neighboring task phases) revealed that Baseline EBR trended toward being higher than Task Anticipation EBR, $t(27) = 1.91$, $p = .07$, $d = .36$, Reward Receipt EBR was significantly higher than Reward Anticipation EBR, $t(27) = 2.32$, $p = .03$, $d = .44$, and Post-Reward Rest EBR was significantly higher than Reward Receipt EBR, $t(27) = 2.53$, $p = .02$, $d = .48$. In sum, blink rate is sensitive to changes in task phase; however, rather than increasing linearly from Baseline through Post-

Reward Rest as hypothesized, there was a quadratic shape to the data with an initial decrease from Baseline to Task Anticipation before subsequent increases across remaining task phases. Moreover, Reward Anticipation and Reward Receipt EBRs were not significantly higher than Baseline EBR; if anything, they appeared slightly lower than Baseline EBR although not statistically significantly different.

Aim Two: Determine the Extent to Which Behavioral Indices of Motivation (i.e., Behavioral Effort) and Baseline Predictors (i.e., State Affect, Expectations) Influence Change in Eye Blink Rate Among Key Task Phases

Means, standard deviations, and intercorrelations between moderator, predictor, and outcome variables are shown in Table 4. Baseline EBR had medium-to-large, positive correlations with Reward Anticipation EBR and Reward Receipt EBR; in line with this finding, for all moderator variables examined below (in Aims Two and Three), in all models containing Baseline EBR as an independent variable (i.e., models 1 and 2), Baseline EBR had significant, positive, unconditional, main effects on Reward Anticipation EBR and Reward Receipt EBR. In other words, higher Baseline EBR was associated with higher EBR in all other conditions. State Positive Affect showed a small-to-moderate inverse correlation with each task phase.

Table 4. Intercorrelations, Mean, and Standard Deviations for Each Variable

	1	2	3	4	5	6	7	8	9	10
1. Baseline EBR	-									
2. Reward Anticipation EBR	.70***	-								
3. Reward Receipt EBR	.66***	.89***	-							
4. State Positive Affect	-.46*	-.41*	-.39*	-						
5. State Negative Affect	.06	-.10	-.07	-.34†	-					
6. Behavioral Effort	.21	-.01	-.14	-.00	.03	-				
7. Anticipated Performance	-.05	-.12	-.03	.27	-.38*	.34	-			
8. Anticipated Monetary Reward	-.14	-.52**	-.41*	.06	.22	.02	.19	-		
9. Clinician-Rated Amotivation	.13	.09	.12	-.05	.10	-.27	-.59***	-.19	-	
10. Self-Reported Amotivation[a]	-.30	-.36†	-.29	.48*	.01	-.30	-.21	.48*	-.02	-
Mean	22.06	18.43	20.82	5.63	2.66	28.32	16.27	3.86	4.48	14.37
SD	16.27	10.91	12.05	1.26	1.32	6.46	13.91	1.68	2.78	6.79

Note. EBR = eye blink rate. [a] Higher scores reflect higher motivation; lower scores reflect higher amotivation.
† $p < .10$. *$p < .05$. **$p < .01$. ***$p < .005$.

Surprisingly, clinician-rated amotivation was not correlated with self-reported amotivation, r = .02, p > .50, suggesting these instruments may be measuring independent constructs. In support of this notion, self-reported and clinician-rated amotivation were independently associated with different baseline predictors. Self-reported amotivation (more severe symptoms) was inversely associated with state positive affect and anticipated monetary rewards. By contrast, clinician-rated amotivation (more severe symptoms) was inversely associated with anticipated behavioral performance, and anticipated behavioral performance was associated with state negative affect.

2.1. Does behavioral effort (number of balloons popped) influence the relationship of eye blink rate among key task phases? In model 1 (predicting Reward Anticipation EBR from Baseline EBR), behavioral effort had a trend-level moderation effect (Table 5a). The Johnson-Neyman method revealed that, as behavioral effort increased, the strength of the relationship between Baseline EBR and Reward Anticipation EBR decreased (i.e., a suppressing effect of the moderator; Figure 5); more specifically, the association between Baseline EBR and Reward Anticipation EBR was significant for approximately 82% of the sample (i.e., those who popped 35 or fewer balloons) and was not significant for those who popped over 35 balloons. This might suggest that exerting more behavioral effort created further deviations from baseline (in terms of blink rate) and perhaps signals the engagement of an additional process during Reward Anticipation. In model 2 (predicting Reward Receipt EBR from Baseline EBR), there was an unconditional, main effect of behavioral effort such that higher behavioral effort resulted in lower Reward Receipt EBR (Table 5b; Figure 6) independent of Baseline EBR; this effect was the opposite direction expected and suggests an inverse relationship between blink rate and behavioral effort. Model 3 did not reveal significant main or moderation effects of behavioral effort. In sum, behavioral effort does influence the relationship between task phases: increased

behavioral effort was associated with a trend-level weakening of the relationship between Baseline EBR and Reward Anticipation EBR as well as a significant decrease in Reward Receipt EBR.

Table 5. Hierarchical Models Examining Influence of Behavioral Effort (Number of Balloons Popped) on Eye Blink Rate (EBR)

a. Predicting Reward Anticipation EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.51	13.02***				
Baseline EBR			0.49	0.10	.73	5.10***
Behavioral Effort			-0.27	0.24	-.16	-1.13
Step 2	.05	3.03†				
Interaction			-0.03	0.02	-.25	-1.74†
b. Predicting Reward Receipt EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.52	13.56***				
Baseline EBR			0.54	0.11	.73	5.11***
Behavioral Effort			-0.54	0.26	-.29	-2.06*
Step 2	.01	0.54				
Interaction			-0.02	0.02	-.11	-0.73
c. Predicting Reward Receipt EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.81	54.28***				
Reward Anticipation EBR			0.98	0.10	.89	10.30***
Behavioral Effort			-0.24	0.16	-.13	-1.52
Step 2	.01	1.48				
Interaction			-0.03	0.02	-.11	-1.22

†$p < .10$. *$p < .05$. **$p < .01$. ***$p < .005$.

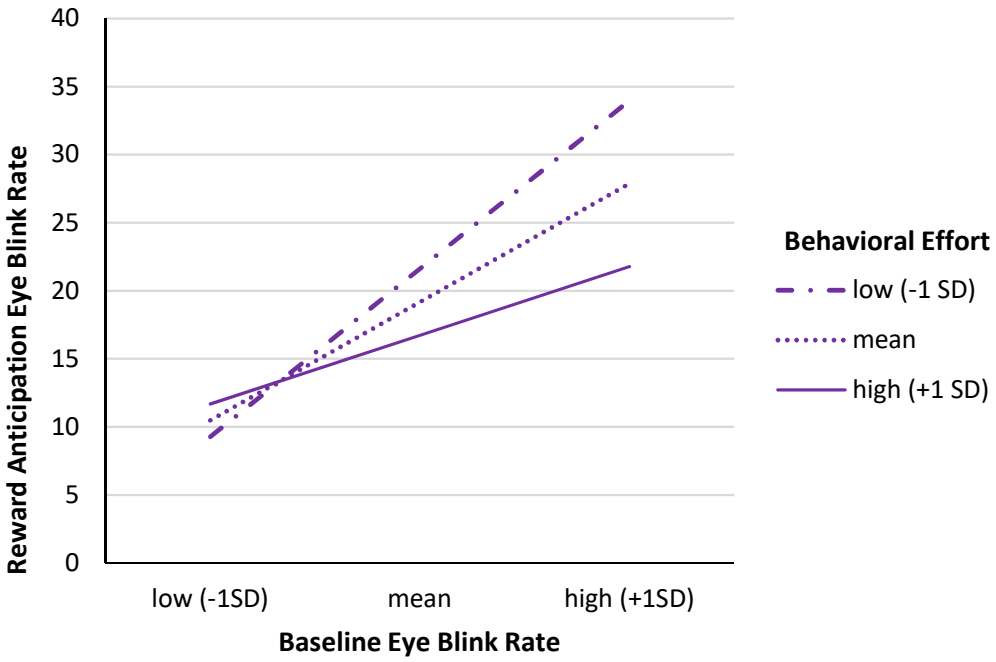

Figure 5. Plot demonstrating moderation of Behavioral Effort (number of balloons popped) on the relationship between Baseline and Reward Anticipation eye blink rates.

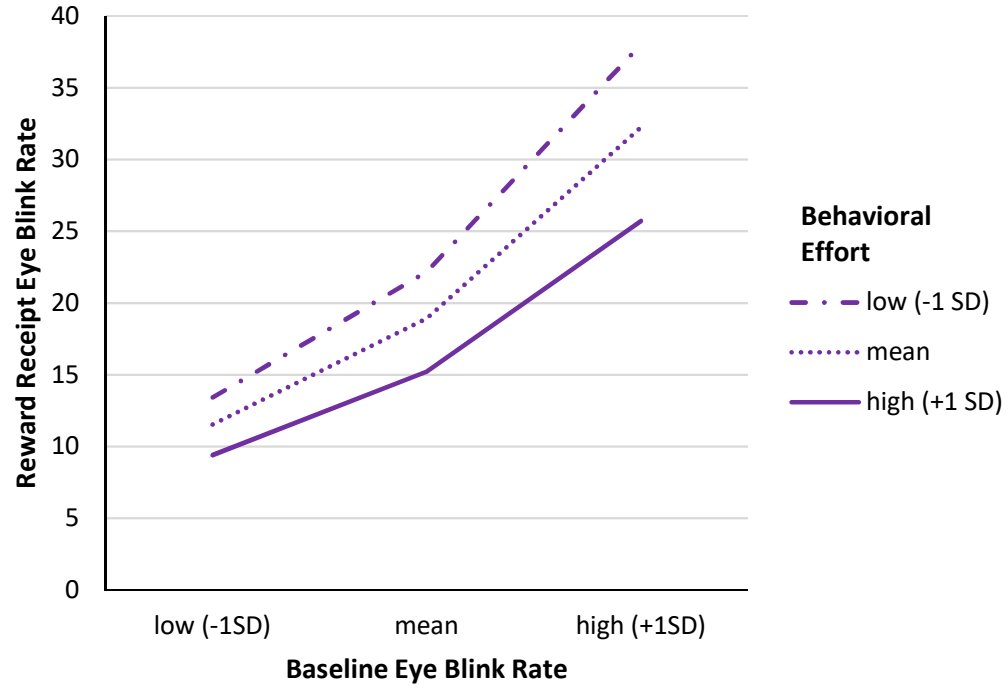

Figure 6. Plot demonstrating main effect of behavioral effort (number of balloons popped) on the relationship between Baseline and Reward Receipt eye blink rates.

2.2 Does state affect (positive or negative) influence the relationship of eye blink rate among key task phases? For State Positive Affect (PA), neither models 1 nor 2 revealed main or moderation effects (Table 6). For model 3, State PA moderated the relationship between Reward Anticipation EBR and Reward Receipt EBR (see Table 6c). The Johnson-Neyman method revealed that, as state PA increases, the strength of the relationship between Reward Anticipation EBR and Reward Receipt EBR increases (i.e., strengthening effect; see Figure 7); the relationship was significant at all values of the moderator. For State Negative Affect (NA), there were no main effects, βs = -.02 – (-.15), *p*s > .30, or moderation effects, ΔR^2s = .00 - .02, *ps* > .30, in any of the three models (Table not shown). Overall, state affect does influence the relationship of blink rate among task phases for State PA but not for State NA; for state PA, higher State PA strengthened the relationship between Reward Anticipation and Reward Receipt (model 3).

Table 6. Hierarchical Models Examining Influence of Pre-Task State Positive Affect on Eye Blink Rate (EBR)

a. Predicting Reward Anticipation EBR						
	ΔR^2	*ΔF*	*b*	*Std. Error*	Beta	*t*
Step 1	.50	12.26***				
Baseline EBR			0.43	0.11	.64	4.02***
State Positive Affect			-0.98	1.38	-.11	-0.71
Step 2	.02	0.83				
Interaction			-0.07	0.07	-.14	-0.91
b. Predicting Reward Receipt EBR						
	ΔR^2	*ΔF*	*b*	*Std. Error*	Beta	*t*
Step 1	.45	10.14***				
Baseline EBR			0.46	0.12	.61	3.67***
State Positive Affect			-0.99	1.60	-.10	-0.62
Step 2	.01	0.40				
Interaction			0.05	0.08	.10	0.63

(table cont'd)

(table cont'd)

c. Predicting Reward Receipt EBR

	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.80	48.82***				
Reward Anticipation EBR			0.97	0.11	.88	8.90***
State Positive Affect			-0.25	0.95	-.03	-0.26
Step 2	.85	9.29**				
Interaction			0.20	0.07	.28	3.05**

*$p < .05$. **$p < .01$. ***$p < .005$.

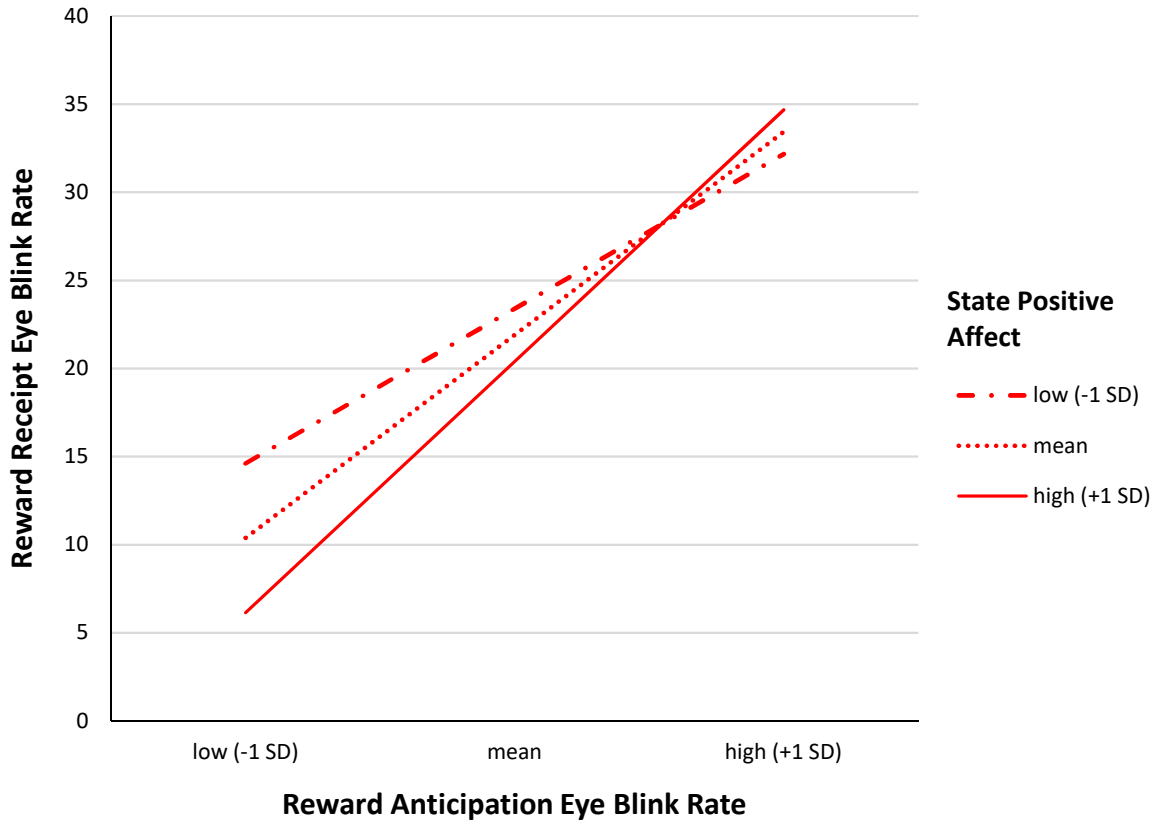

Figure 7. Plot demonstrating moderation of state positive affect on the relationship between Reward Anticipation and Reward Receipt eye blink rates.

2.3. Do expectations (anticipated behavioral performance, anticipated monetary reward) influence the relationship of EBR among key task phases? Anticipated behavioral performance (Anticipated Number of Balloons Popped) did not have main effects, βs = -.08 –

.08, *p*s > .15, or moderation effects, ΔR^2s = .00 - .03, *ps* > .15, in predicting blink rate for any of the models (Table not shown). By contrast, Anticipated Monetary Reward had significant unconditional, main effects for models 1 and 2, in predicting Reward Anticipation EBR and Reward Receipt EBR, respectively (Table 7; Figures 8 and 9). There were no moderation effects. Specifically, *higher* Anticipated Monetary Reward was associated with *lower* Reward Anticipation EBR and *lower* Reward Receipt EBR. Importantly, Anticipated Monetary Reward was not correlated with Baseline EBR (as shown in Table 4 above), suggesting the effect was specific to reward phases of the task. These findings may suggest that lower blink rate may be an index of task engagement in that those who expected higher rewards paid closer attention to the screen, thereby blinking less, during reward phases of the task. Overall, expectations regarding anticipated monetary reward, but not anticipated behavioral performance, influenced the relationship of blink rate among task phases; anticipated monetary reward was inversely related with blink rate during both reward anticipation and reward receipt.

Table 7. Hierarchical Models Examining Influence of Anticipated Monetary Reward on Eye Blink Rate (EBR)

a. Predicting Reward Anticipation EBR						
	ΔR²	*ΔF*	*b*	*Std. Error*	Beta	*t*
Step 1	.71	29.98***				
Baseline EBR			0.45	0.07	.67	6.12***
Anticipated Monetary Reward			-2.78	0.72	-.43	-3.86***
Step 2	.00	0.00				
Interaction			0.00	0.04	0.00	0.04
b. Predicting Reward Receipt EBR						
	ΔR²	*ΔF*	*b*	*Std. Error*	Beta	*t*
Step 1	.61	18.58***				
Baseline EBR			0.49	0.09	.67	5.16***
Anticipated Monetary Reward			-2.31	0.92	-.32	-2.50*

(table cont'd)

(table cont'd)

Step 2	.00	0.09				
Interaction			0.02	0.05	.04	0.31

c. Predicting Reward Receipt EBR

	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.79	45.98***				
Reward Anticipation EBR			1.01	0.12	.92	8.49***
Anticipated Monetary Reward			0.45	0.77	.06	0.58
Step 2	.00	0.01				
Interaction			0.01	0.07	.01	0.08

*$p < .05$. **$p < .01$. ***$p < .005$.

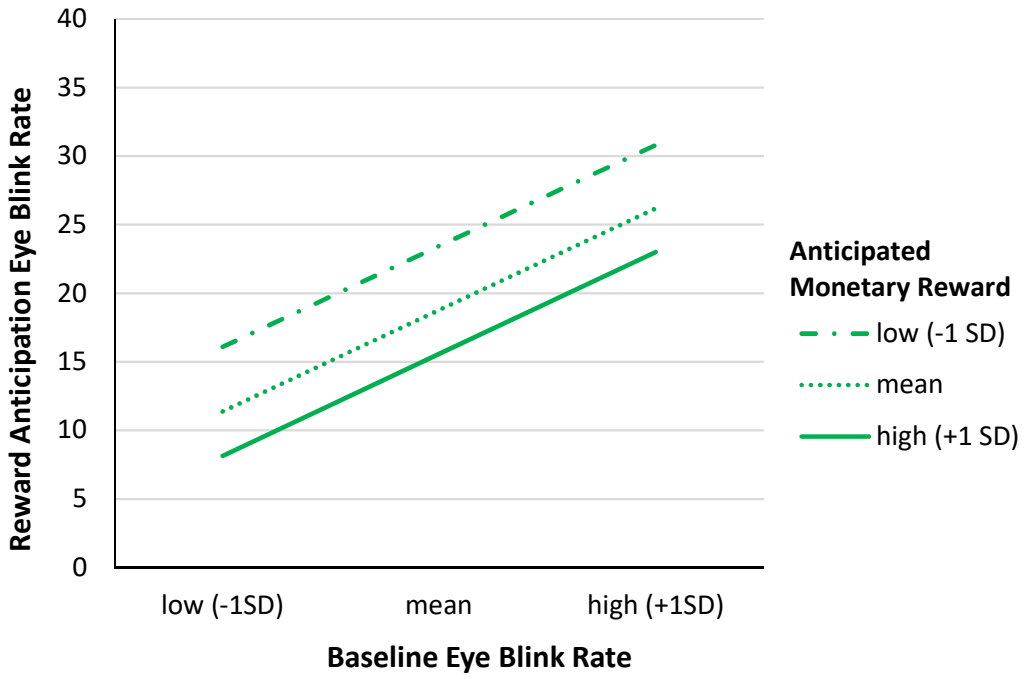

Figure 8. Plot demonstrating the main effect of anticipated monetary reward on Reward Anticipation eye blink rate.

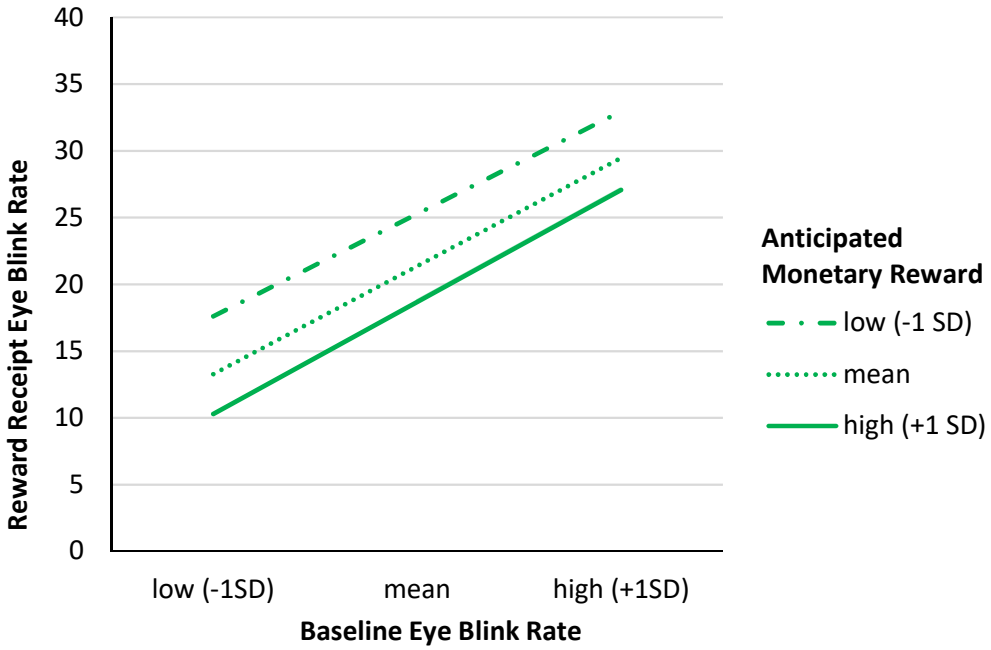

Figure 9. Plot demonstrating the main effect of anticipated monetary reward on Reward Receipt eye blink rate.

Aim Three: What Is the Relationship Between Eye Blink Rate and Amotivation?

Clinician-rated amotivation (i.e., BNSS Avolition) did not have significant main or moderation effects for any of the models (see Table 8, *ps* > .10). For self-reported amotivation (i.e., MAPS Motivation/Effort), there were no main or moderation effects for models 1 or 2. Importantly, as hypothesized, self-reported amotivation did moderate the relationship between reward anticipation EBR and reward receipt EBR (Table 9c), such that *lower* self-reported motivation (i.e., higher amotivation symptoms) *decreased* the relationship between reward anticipation EBR and reward receipt EBR (weakening effect; see Figure 10). The Johnson-Neyman values indicated that participants at or above a value of -13.8152 below the mean (i.e., raw scores greater than 0; 96% of the sample) had a significant relationship between X and Y, with the relationship getting weaker at lower levels of self-reported motivation (recall that lower scores mean higher motivation); the relationship with the moderator was not significant when the

moderator value most closely approximated normal levels of motivation. In sum, while clinician-rated amotivation had no significant effects on blink rate, increased self-reported amotivation weakened the relationship between Reward Anticipation EBR and Reward Receipt EBR as hypothesized.

Table 8. Hierarchical Models Examining Influence of Clinician-Rated Amotivation (BNSS Avolition) on Eye Blink Rate (EBR)

a. Predicting Reward Anticipation EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.48	11.21***				
Baseline EBR			0.47	0.10	.70	4.70***
Clinician-Rated Amotivation			-0.02	0.59	.00	-0.03
Step 2	.49	0.09				
Interaction			0.01	0.04	.05	0.30
b. Predicting Reward Receipt EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.44	9.39***				
Baseline EBR			0.49	0.11	.66	4.26***
Clinician-Rated Amotivation			0.17	0.68	.04	0.25
Step 2	.02	0.81				
Interaction			0.04	0.05	.14	0.90
c. Predicting Reward Receipt EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.80	47.17***				
Reward Anticipation EBR			0.98	0.10	.89	9.62***
Clinician-Rated Amotivation			0.21	0.41	.05	0.51
Step 2	.80	0.01				
Interaction			0.04	0.30	.10	1.06

*$p < .05$. **$p < .01$. ***$p < .005$.

Table 9. Hierarchical Models Examining Influence of Self-Reported Amotivation (MAPS-SR Effort/Motivation Subscale) on Eye Blink Rate (EBR)

a. Predicting Reward Anticipation EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.49	11.69***				
Baseline EBR			0.43	0.10	.63	4.15***
Self-Reported Amotivation			-0.27	0.24	-.17	-1.12
Step 2	.00	0.02				
Interaction			-0.00	0.02	-.02	-0.13
b. Predicting Reward Receipt EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.44	9.36***				
Baseline EBR			0.47	0.12	.63	3.90***
Self-Reported Amotivation			-0.17	0.29	-.10	-0.61
Step 2	.01	0.59				
Interaction			0.01	0.02	.13	0.77
c. Predicting Reward Receipt EBR						
	ΔR^2	ΔF	*b*	*Std. Error*	Beta	*t*
Step 1	.79	46.48***				
Reward Anticipation EBR			1.01	0.11	.91	9.14***
Self-Reported Amotivation			0.07	0.18	.04	0.42
Step 2	.05	6.50*				
Interaction			0.04	0.02	.22	2.55*

Note. For self-reported amotivation, lower scores mean less motivation.
*$p < .05$. **$p < .01$. ***$p < .005$.

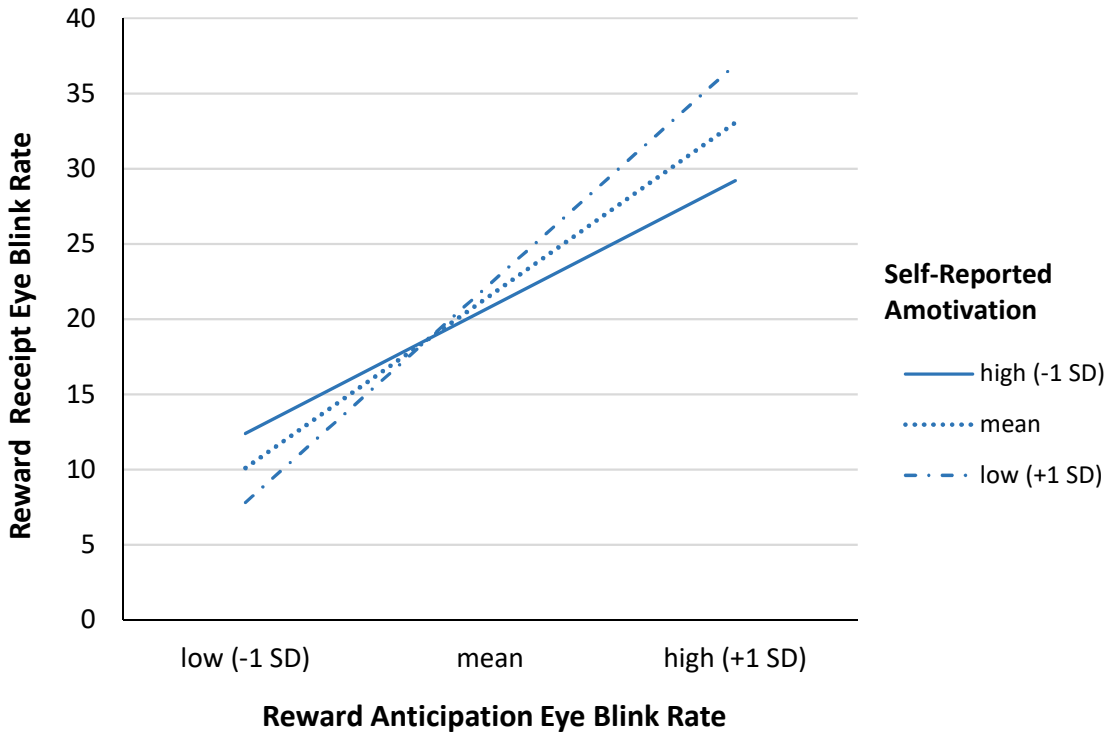

Figure 10. Plot demonstrating moderation of self-reported amotivation (MAPS Effort/ Motivation) on the relationship between Reward Anticipation and Reward Receipt eye blink rates.

DISCUSSION

The present study had three chief aims: First, assess whether a novel effort-based reward paradigm was sensitive enough to detect task phase differences in eye blink rate (EBR). Second, determine the extent to which behavioral indices of motivation (i.e., behavioral effort) and baseline predictors (i.e., state affect, expectations) influence change in EBR between baseline, reward anticipation, and reward receipt conditions. Finally, determine the extent to which negative symptoms (clinician-rated and self-reported amotivation) influence change in eye blink rate across the same key task phases in individuals diagnosed with an SSD. The over-arching goal of the study was to improve understanding of the mechanisms underlying negative symptoms, particularly amotivation, in individuals with SSDs.

Regarding the first aim, as hypothesized, the paradigm detected robust differences in blink rate across task phases. In general, blink rate followed a U-shaped pattern such that blink rate decreased from pre-task (i.e., resting-state) Baseline to Task Anticipation and then increased gradually from Task Anticipation to Reward Anticipation to Reward Receipt and to Post-Reward Rest phases of the task; the pattern repeated from Cycle 1 to Cycle 2. Importantly, differences in EBR did not appear to reflect mere time on task because there was a small effect-sized decrease in EBR (albeit not statistically significant) from the last phase of Cycle 1 (Post-Reward Rest 1) to the task phase immediately following it as the start of Cycle 2 (i.e., Task Anticipation 2). The U-shaped pattern demonstrated in the present study stands in contrast to findings reported by Peckham and Johnson (2015) whose results demonstrated a linear increase from pre-task Baseline to Reward Receipt in non-psychiatric controls and individuals with bipolar I disorder. Previous results were interpreted to suggest a linear positive relationship between EBR and striatal dopamine (i.e., more blinking is associated with stronger dopamine response).

In the present study, Reward Anticipation EBR was significantly lower than Reward Receipt EBR; this was not surprising given previous studies suggesting a linear positive relationship between EBR and striatal dopamine, as previous studies have suggested (e.g., Elsworth et al., 1991; Mackert et al., 1991; Peckham & Johnson, 2015). However, counter to hypotheses, Baseline EBR was not significantly lower than Reward Anticipation EBR or Reward Receipt EBR; if anything, results were in the opposite direction expected, with relative (though statistically non-significant) decreases in blink rate from baseline to reward phases of the task. The U-shaped pattern of changes across task phases found in the present study and the relationships between higher state affect and expectations with lower blink rate (detailed below) cast doubt on this straightforward explanation of a linear, positive relationship between EBR and striatal dopamine.

What Is Eye Blink Rate a Measure of?

Having established that the paradigm detects consistent differences in blink rate across task phases (internal consistency), the construct validity of phasic EBR was examined next. It was hypothesized that behavioral effort, state affect, and task expectations would have an enhancing effect on blink rate during reward phases of the task, given evidence that striatal dopamine fires in a dose-dependent fashion during reward anticipation and reward receipt (e.g., Elsworth et al., 1991; Taylor et al., 1999) and given research illustrating an increase in EBR following a positive, but not negative, mood induction procedure (Akbari Chermahini & Hommel, 2012).

When predicting Reward Anticipation EBR from Baseline EBR (model 1), analyses revealed a trend-level moderation effect for behavioral effort such that increased behavioral effort weakened the relationship between Baseline EBR and Reward Anticipation EBR. That

Reward Anticipation EBR becomes increasingly tied to behavioral performance with increased behavioral effort suggests that a novel cognitive process beyond resting-state factors influencing blink rate is being engaged. Similarly, those who anticipated winning *more* money had *lower* blink rate during Reward Anticipation. Findings supported an inverse relationship between reward anticipation with behavioral effort and anticipated monetary reward.

In similar fashion, when predicting Reward Receipt EBR from Baseline EBR (model 2), there were main effects for behavioral effort and anticipated money such that *higher* values resulted in *lower* blink rate during Reward Receipt. It should be noted that behavioral effort (indexed by number of balloons popped) corresponds directly to reward earned (e.g.,10 balloons popped = $1.00, 20 balloons popped = $2.00; i.e., examining reward earned as a variable would produce identical results to the variable for behavioral effort); therefore, it is unclear whether the associations with reward anticipation EBR and reward receipt EBR are due to the valuation of effort and/or valuation of reward. In any case, blink rate appears sensitive to individual differences in reward sensitivity.

When examining the relationship between Reward Anticipation EBR and Reward Receipt EBR (model 3), state positive affect had a moderation effect such that *higher* state positive affect *strengthened* the relationship between Reward Anticipation EBR and Reward Receipt. Likewise, *lower* positive affect *weakened* the relationship. In this sense, state positive affect may act as a sort of cognitive "glue" binding reward anticipation and reward receipt processes. Moreover, state positive affect appears to have a unique effect in strengthening the relationship between reward anticipation and reward receipt; by contrast, state negative affect as well as the reward-related variables examined (i.e., expectations, behavioral effort) did not have that moderating effect. Lastly, Baseline EBR, Reward Anticipation EBR, and Reward Receipt

EBR were not associated with state negative affect or anticipated behavioral performance in any analysis.

Overall, Reward Anticipation EBR and Reward Receipt EBR were inversely associated with Anticipated Monetary Reward and Behavioral Effort. That these results were in the opposite direction expected suggests that either striatal dopamine does not have a linear positive relationship with blink rate, as previously assumed, and/or that changes in blink rate are inversely associated with a parallel process, such as task engagement. Consistent with the latter explanation, some have proposed that blink rate suppression aims to preserve the continuity of the information stream (Volkmann, Riggs, & Moore, 1980); thus, blink rate decreases when conditions demand or engage high attentional effort (Fairclough & Venables, 2006; Maffei & Angrilli, 2018). Increased blink rate has been associated with lower subjective ratings of task engagement (Fairclough & Venables, 2006), with lower cognitive and/or visual demand of tasks (Benedetto et al., 2011; Fairclough, Venables, & Tattersall, 2005; Recarte, Pérez, Conchillo, & Nunes, 2008), with time on task (Maffei & Angrilli, 2018; Wascher, Heppner, Möckel, Kobald, & Getzmann, 2015), and with performance declines on vigilance tasks (Maffei & Angrilli, 2018; McIntire, McKinley, Goodyear, & McIntire, 2014). Individuals with schizophrenia are known to have deficits in attention, including impaired orienting, vigilance, selective attention, and ability to filter out irrelevant information (Green, 2006; Nieoullon, 2002); therefore, it is reasonable to expect that increased blink rate in this psychotic disorder sample may reflect decreased engagement with these visual stimuli. In fact, some work has demonstrated that blink rate is also modulated by task difficulty for auditory stimuli (Oh et al., 2012) and cognitively demanding tasks such as internal counting (Holland & Tarlow, 1975) and digit span (Holland & Tartlow, 1972), suggesting that blink rate modulation is not specific to visual processing.

Consistent with the striatal dopamine hypothesis, and not mutually exclusive with the task engagement hypothesis, some evidence suggests that phasic changes in dopaminergic activity modulate allocation of attentional resources for stimulus processing. Thus, reductions in blink rate may reflect increased focusing of attentional resources; similarly, elevated blink rate may reflect decreased ability to modulate attentional resources. For example, Van Slooten, Jahfari, Knapen, and Theeuwes (2017) found that EBR inversely correlated with transient pupil response during reward anticipation in a non-psychiatric population; pupil dilation is generally interpreted to indicate increased effort allocation and research supports reduced pupil dilation in schizophrenia (e.g., Fish & Granholm, 2008; Granholm & Steinhauer, 2004). Future studies incorporating multiple modalities (e.g., neuroimaging with measures of blink rate) may help elucidate the specific neurobiological mechanisms that modulate blink rate.

Is There a Link Between Eye Blink Rate and Amotivation?

Consistent with expectations, amotivation moderated the relationship between Reward Anticipation EBR and Reward Receipt EBR, although only for self-reported symptoms and not for clinician-rated symptoms. *Higher* self-reported amotivation symptoms *weakened* the relationship between Reward Anticipation EBR and Reward Receipt EBR; this appears to map onto the finding that *lower* state positive affect also *weakens* that relationship. In support of this link, state positive affect had a medium-effect-sized, inverse correlation with self-reported amotivation. Notably, it is unclear how participants' pre-task state affect related to their "typical" or baseline level of affect, given that there was no measure of "trait" positive affect. Moreover, a large body of research supports the relationship between low trait positive affect and negative symptoms in schizophrenia spectrum disorders (for review, see Horan et al., 2008). In addition, self-reported amotivation had a moderate effect-sized, inverse correlation with anticipated

monetary reward suggesting a possible influence of negative symptoms on expectations regarding reward.

Emil Kraepelin conceptualized schizophrenia (then called dementia praecox) as "a weakening of those emotional activities which permanently form the mainsprings of volition" (Kraeplin 1919, cf. Foussias & Remington, 2010). The present findings lend novel nuance to this conceptualization. Amotivation may be exerting its effects by disrupting the "glue" process that occurs between reward anticipation and reward receipt. This might explain the consistent finding that individuals with schizophrenia have intact "in-the-moment" and reduced "non-current" levels of pleasure and enjoyment in response to rewarding stimuli (e.g., Cohen & Minor, 2008; Kring & Barch, 2014; Strauss & Gold, 2012). As further support of this disconnect, it is interesting that behavioral effort was not associated with anticipated performance, anticipated monetary reward, or negative symptoms although it was associated with Reward Receipt EBR and with change in the association between Baseline EBR and Reward Anticipation EBR.

It is somewhat unclear why self-reported amotivation was associated with blink rate whereas clinician-rated amotivation was not. One possibility is that there was simply more variability in the self-report measure (6 items; score range: 0-24) than the clinician-rated measure (2 items; score range: 0-12), which could have made the self-report measure more sensitive to individual differences. A second possibility is that the measures utilized in the current study assess different aspects of amotivation. Whereas the BNSS (clinician-rated measure) divides amotivation into two items – internal experience (i.e., drive) and amotivation behavior (i.e., frequency) – and includes motivation for social relationships in a separate item, the Clinical Assessment Interview for Negative Symptoms (CAINS) – on which the MAPS self-report was based – combines internal experience and behavior and separates items by life area (e.g.,

motivation for work/school, motivation for recreation/leisure activities, motivation for social activities). Consistent with the notion that these measures assess different constructs or, at least, that they assess the same construct differently, there was no correlation between BNSS clinician-rated symptoms and MAPS self-reported symptoms. Moreover, a recent psychometric study demonstrated less convergence between the CAINS and BNSS interviews for rating experiential symptom items (avolition, asociality, and anhedonia) compared to expressive symptom items (alogia, blunted affect) (Strauss & Gold, 2016). A third, perhaps additive, possibility is that the lack of correlation may reflect differences between self-reported and clinician-rated symptoms. The present study suggests that amotivation as measured by the MAPS (and possibly CAINS) may be more sensitive than the BNSS. Future research could replicate and extend this finding by administering the self-reported and clinician-rated versions of the CAINS in addition to the clinician-rated BNSS to ascertain whether the effect found in the present study is due to differences in self-reported versus clinician-rated symptoms or due to differences in the way amotivation is assessed by each clinician-rated negative symptom measure.

Limitations and Future Directions

It is unclear why the present paradigm found inverse relationships with reward responsivity whereas previous research found positive relationships (Akbari Chermahini & Hommel, 2012; Peckham & Johnson, 2015). In addition to the explanations for the present findings provided above, there are important differences between these studies. First, neither of the previous studies had a "return to baseline" task phase nor a cycle repetition, so they did not have a control condition for time on task. Second, the present study did not include a healthy control group, so it is possible that a healthy control group would have displayed a positive relationship between blink rate and reward responsivity. Given that individual differences in blink rate in the present

study indicated that *higher* behavioral effort was associated with *lower* blink rate combined with the expectation based on existing theories and studies using other effort tasks that healthy controls and bipolar 1 disorder participants would likely demonstrate even higher effort, this would not explain the differences.

One consideration for future studies is that other windows of EBR measurement may be more appropriate for measuring striatal dopamine responses whereas longer windows may be more appropriate for other reward-related processes (e.g., task engagement). For example, it may be that dopamine-related changes occur at a shorter time scale (i.e., within the first few seconds of phase onset). The one-minute time window of the present study was selected based on previous literature (e.g., Peckham & Johnson, 2015). Future studies might examine rate of change in blink rate over time in relation to proximity to effect of interest. In addition, other blink-related indices may better capture the intended effects (e.g., latency to first blink, blink duration, blink amplitude, proportion of blinks in trials [for shorter intervals]), as have been explored in some other studies (Fairclough & Venables, 2006; Wascher et al., 2015). EOG data were collected for a sub-sample of participants and will be integrated with a larger sample of participants to explore optimal blink-related indices. All this said, blink rate was inversely associated with behavioral performance and anticipated rewards, suggesting it is significantly related to aspects of reward and performance.

The present findings also highlight a more theoretical question about the appropriate comparison conditions for an effort-based reward task such as this one. While it may have been tempting to conclude that a decrease in blink rate from Baseline to Task Anticipation or Reward Anticipation indicated blunted dopamine response, the present paradigm allowed for exploration of other potential explanations. Without the pre-task Baseline condition employed in the present

study, there would appear to have been a pure linear increase across task phases, from Task Anticipation through Post-Reward Rest. Careful consideration during experimental designs or careful selection of a comparison group impact the theoretical questions that may be examined. Future studies might examine whether the same effects occur under different types of reward (e.g., social, food, pleasant videos or images) or whether effects differ under reward loss and/or neutral conditions.

Given that the Reward Anticipation EBR and Reward Receipt EBR phases were not significantly higher than the Baseline EBR phase, it is possible that the "rewarding" phases of the task were not as reinforcing as intended. Peckham and Johnson (2015) played pleasant music during their reward receipt phase in order to amplify the sense of rewarding-ness. The decision not to play music was made in effort to ensure that any EBR changes observed were due to the sense of reward produced by the task and not conflated with possible mood induction effects of pleasant music. Future studies might examine different ways to amplify the sense of reward felt from engaging in the task.

It is possible that the "task engagement" effects were not due to engagement with the "rewarding-ness" of the task and instead due primarily to the fact that the Task Anticipation and Reward Anticipation phases had a dynamic screen (i.e., displaying a countdown) whereas the screen during the Reward Receipt and Post-Reward Rest phases were static. This static-versus-dynamic screen explanation does not account for the strong inverse correlations between aspects of monetary reward (anticipated reward, money earned) with blink rate during reward anticipation (which had a dynamic screen) and with reward receipt (which had a static screen); in addition, there was no correlation between anticipated monetary reward with blink rate during task anticipation (which had a dynamic screen). Moreover, this does not fully account for the

differences between the reward receipt and post-reward rest phases observed during the present task, as both are static and the Reward Receipt phase immediately followed Post-Reward Rest phase.

It is possible that inclusion of a healthy control sample would help distinguish whether the several confounding factors associated with a SSD population (e.g., smoking status) contributed to the present results. In addition, inclusion of a control group would permit comparison of whether the SSD group showed relatively better or worse task engagement during the Reward Anticipation and Reward Receipt task phases. There was no healthy control sample due in part to 1) no readily identifiable comparison sample (e.g., smokers, nonsmokers; individuals matched on socioeconomic and occupational status) and 2) recruitment difficulty and time restrictions on data collection that led to the decision to emphasize data collection for a patient sample. Moreover, although it is not expected that bipolar I disorder participants without psychotic features would perform similarly to individuals with SSD, Peckham and Johnson (2015) did not find group differences between bipolar I disorder and healthy control participants in their study despite finding significant correlations in the bipolar group with reward responsivity measures. That said, their bipolar I disorder participants were not experiencing a current mood episode, so results may have differed if participants had been experiencing a current manic, hypomanic, or depressive episode. Overall, the addition of a control group would put the present findings into better context.

It is possible that the present study was underpowered to detect some of the effects expected. In effort to boost sample size, VA Connecticut was added as a second site. Due to resource demands, time constraints, and following guidance from my committee, the decision was made to discontinue data collection. While this sample size is in the range typical of many SSD

samples for experimental designs of this nature, it may be insufficient to detect effects of smaller magnitude. Future studies would benefit from increased sample size.

Due to the nature of the testing environments, it was impossible to control for all possible confounds – e.g., natural lighting and temperature. Every effort was made to keep known factors within a normal range – brightly lit, comfortable temperature, relatively quiet; however, such effects cannot be ruled out.

As with most studies of SSD samples, one possible confound is that almost all participants were prescribed at least one dopamine receptor-blocking antipsychotic medication, which could affect reward-related responses (Abler, Erk, & Walter, 2007; Juckel et al., 2006). Medication dosage could not be statistically controlled in the present study due to excessive missing data on medication names and doses. Despite the potential impact of medication, it would be highly unlikely that the findings would be related purely to antipsychotic action since fMRI studies have found blunted striatal responses in both medicated and unmedicated schizophrenia samples experiencing their first episode (e.g., Esslinger et al., 2012; Schlagenhauf et al., 2009) and medication naïve individuals in the prodromal phase of illness (Piskulic et al., 2012; Wotruba et al., 2014; Yung & McGorry, 1996). Moreover, antipsychotics tend to influence baseline levels of neurotransmitter, not phasic neurotransmitter levels; thus, EBR change between task phases is less likely to be impacted. Furthermore, antipsychotics do not appear to adequately ameliorate negative symptoms, even when those antipsychotics show improvements in positive symptoms (Fervaha et al., 2015; Fervaha et al., 2016); therefore, it is unlikely that the results in this task were driven by medication effects.

Another limitation is that the majority of participants smoked cigarettes (16/28 [57%] current smokers; 7/28 [25%] are former smokers), which was consistent with SSD population

rates more broadly. Given the high rates of comorbidity in this population, it is believed that allowing for smokers more accurately represents the population of interest. Among those in the present study who currently smoked, there was a trend-level correlation between smoking more cigarettes per day and higher blink rate during Post-Reward Rest, though this phase was not used in the moderation analyses. Age of first cigarette had a trend-level associated with higher blink rate during Pre-Task Baseline, though the implications of this finding are unclear. Moreover, there were no group differences between smokers and nonsmokers on blink rate in any task phase.

Regarding ties to reward responsivity, it could be argued that participants were overestimating the amount of money they would win because they knew (e.g., based on word of mouth) or expected that they would win the maximum amount of $5 regardless of their performance (46% or 13 of 28 estimated that they would win $5.00). Since we tested several participants that resided together in group homes, it is possible that the information spread via word of mouth. However, the fact that three participants also anticipated making more than $5.00 would not make sense by that logic. Prior to the prompt to provide their estimates, all participants had been informed at least two times – verbally and in writing each time – that the maximum amount of bonus cash they could earn was $5 and that they earn that money by popping more balloons, earning 10 cents per balloon popped with their highest score from their two attempts used for their bonus. In addition, it stands to reason that knowing you were winning the full amount regardless of your efforts would lead to less effortful responses, not more effortful ones. In the present study, lower self-reported amotivation (i.e., higher MAPS scores or higher motivation) was associated with higher anticipated monetary rewards, which casts doubt on that explanation. Moreover, the script for providing the monetary reward was also specified in

a manner to maintain the deception and to emphasize rewarding effort rather than specific performance per se: “Your highest score was [accurate number of balloons] which amounts to [accurate monetary win], but I can tell you put in great effort, so I’m going to give you the full amount of $5.00. Is that ok with you?” Future studies might consider asking standardized questions during the debrief period to ensure that the deception regarding monetary reward was maintained.

Conclusions

Previous research suggested that EBR is a reliable and validated, though indirect, measure of striatal dopamine; however, the results of the present study suggest that this interpretation may either be inaccurate or, at least, not as straightforward as previously thought. Phasic EBR can be easily recorded and analyzed, measured in a number of different ways (with eye-tracker, electro-oculogram, video recording), and recorded in many different ecological conditions (e.g. during driving as an index of fatigue, or visual exploration for product choice, during sport activity and videogames, during emotional movies, etc.). These qualities highlight its potential as a useful measure in a diverse array of future studies.

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APPENDIX A. LSU INSTITUTIONAL REVIEW BOARD APPROVAL FORM

ACTION ON PROTOCOL APPROVAL REQUEST

Institutional Review Board
Dr. Dennis Landin, Chair
130 David Boyd Hall
Baton Rouge, LA 70803
P: 225.578.8692
F: 225.578.5983
irb@lsu.edu
lsu.edu/research

TO: Alex Cohen
Psychology

FROM: Dennis Landin
Chair, Institutional Review Board

DATE: April 24, 2017

RE: IRB# 3866

TITLE: Emotion in adult stable outpatients

New Protocol/Modification/Continuation: New Protocol

Review type: Full ___ Expedited _X_ **Review date:** 4/18/2017

Risk Factor: Minimal ___X___ Uncertain _____ Greater Than Minimal_____

Approved_____X_____ **Disapproved**_____

Approval Date: 4/21/2017 **Approval Expiration Date:** 4/20/2018

Re-review frequency: (annual unless otherwise stated)

Number of subjects approved: 100

LSU Proposal Number (if applicable):

Protocol Matches Scope of Work in Grant proposal: (if applicable)

By: Dennis Landin, Chairman _____

PRINCIPAL INVESTIGATOR: PLEASE READ THE FOLLOWING –
Continuing approval is CONDITIONAL on:

1. Adherence to the approved protocol, familiarity with, and adherence to the ethical standards of the Belmont Report, and LSU's Assurance of Compliance with DHHS regulations for the protection of human subjects*
2. Prior approval of a change in protocol, including revision of the consent documents or an increase in the number of subjects over that approved.
3. Obtaining renewed approval (or submittal of a termination report), prior to the approval expiration date, upon request by the IRB office (irrespective of when the project actually begins); notification of project termination.
4. Retention of documentation of informed consent and study records for at least 3 years after the study ends.
5. Continuing attention to the physical and psychological well-being and informed consent of the individual participants, including notification of new information that might affect consent.
6. A prompt report to the IRB of any adverse event affecting a participant potentially arising from the study.
7. Notification of the IRB of a serious compliance failure.
8. **SPECIAL NOTE: When emailing more than one recipient, make sure you use bcc.**

**All investigators and support staff have access to copies of the Belmont Report, LSU's Assurance with DHHS, DHHS (45 CFR 46) and FDA regulations governing use of human subjects, and other relevant documents in print in this office or on our World Wide Web site at http://www.lsu.edu/irb*

APPENDIX B. VA CONNECTICUT HEALTHCARE SYSTEM INSTITUTIONAL REVIEW BOARD APPROVAL FORM

VA CONNECTICUT HEALTHCARE SYSTEM
Human Research Protection Program

Initial Approval of a Human Research Project

Date: 8/3/17

To Principal Investigator: Joanna Fiszdon, Ph.D. **MIRB Number**: 02160

Project Title: Clarifying the mechanisms underlying negative symptoms in psychotic disorders

The following decisions have been made by the Human Studies Subcommittee regarding your project:

Risks to subjects are minimized. Risks are reasonable in relation to benefits. Selection of subjects is equitable. Provisions for safety monitoring are adequate. Provisions to protect privacy and confidentiality are adequate.

Consent Form was Reviewed and Approved: ☒ Yes ☐ Not Requested
Approval indicates that the HSS found that the information provided in the Consent Form is complete, accurate, and understandable to a research subject who possesses standard reading and comprehension skills.
The HSS has been assured that the informed consent will be obtained by the principal investigator or a trained and supervised designee under suitable circumstances.

Witness Signature is required on consent form: ☐ Yes ☒ No

Consent for Use of Picture and/or Voice is required: ☐ Yes ☐ No ☒ Not Requested

Waiver of Informed Consent (WIC) granted: ☐ Yes ☒ Not Requested
If yes, ☐ full study or ☐ screening (identifying potential subjects) only
☐ All subjects or ☐ one particular group (what group?)

Waiver of Written Informed Consent (WWIC) granted: ☒ Yes ☐ Not Requested
If yes, ☐ all subjects or ☒ one particular group (phone screening)

If yes, Consent Form approved ☐ Yes or *Information Sheet approved* ☒ Yes

HIPAA Authorization Required: ☒ Yes ☐ No
The HSS has been assured that the HIPAA Authorization will be obtained by the principal investigator or a trained and supervised designee under suitable circumstances.

Waiver of HIPAA Authorization (WoA) granted: ☒ Yes ☐ Not Requested
If yes, ☐ full study or ☒ screening (identifying potential subjects) only
☐ All subjects or ☐ one particular group (what group?)

Subjects are considered to be vulnerable to coercion: ☒ Yes ☐ No ☐ N/A
If yes, there are additional adequate safeguards ☒ Yes

Enrollment of non-Veterans is Justified and Approved: ☒ Yes ☐ No ☐ Not Requested

The project is a Clinical Trial: ☐ Yes ☒ No

Drug Information Record is on file: ☐ Yes ☒ N/A

Surrogate Consent Approved: ☐ Yes ☐ No ☒ Not Requested
Approval indicates that all of the following conditions have been met: a) the research cannot be done with only competent subjects; b) risk to the subjects is outweighed by benefit; c) an incompetent subject who resists will not have to participate; d) the basis for the decision regarding a subject's competency will be fully described.

Payment of subjects Approved: ☒ Yes ☐ No ☐ Not Requested
Approval indicates that the HSS found that the payment is reasonable and commensurate with the subject's contribution.

Documentation Requirements:
Research Alert in Medical Record ☒ Yes ☐ No
Creation or updating of Medical Record ☒ Yes ☐ No

Risk Level: ☒ Not greater than minimal ☐ Moderate ☐ High

Incorporates the elements of
VA FORM 10-1223
OCT 1995

March2014

Principal Investigator: Joanna Fiszdon, Ph.D.	MIRB #: 02160

This project was Approved by HSS at its meeting on 8/3/17 **Contingencies met on:** NA

The Research was approved by the **Subcommittee on Research Safety** on: 8/4/17
The **Research & Development Committee** was notified on: 8/30/17
Other Applicable subcommittees:

Neither you nor any of the identified co-investigators participated in the review and decision-making. **All applicable approvals have been obtained and you may now proceed with the research.**

Approval for this project expires on 8/2/18 and will be subject to continuing review before the expiration date. This review will require that you submit a Continuing Review Application to the HSS before the end of the current approval period.

According to Section VII of the VA initial application it is understood:

☐ Yale University IS engaged in this project and HIC approval will be sought.
☒ Yale University is NOT engaged in this project; no HIC approval will be sought.

The HSS reminds you of several important requirements:

1. The Consent Form(s) and HIPAA Authorization used must be the ones most recently approved by the HSS. Be sure that both are filled in completely.
2. The procedures and interventions must be those proposed in the protocol and approved by the HSS.
3. Any changes to the protocol or the Consent Form(s) must be proposed to the HSS in writing as a modification to an approved project, and must be approved before they are initiated.
   The HIPAA Authorization may be amended as necessary and, a copy forwarded to the Research Office.
4. All Consent Form(s) must be reviewed, and signed by the Principal Investigator.
   (Co-investigators may sign, if the PI is unavailable, however, the PI must co-sign as soon as possible).
5. Any Adverse Event that is both Serious and Unanticipated must be reported to the HSS within 5 business days of your becoming aware of it.
6. Any Unanticipated Problem Involving Risk to Subjects or Others must be reported to the HSS within 5 business days of your becoming aware of it.
7. Any Deviation from the approved protocol or Consent Form(s) must be promptly reported to the HSS.
8. For each signed HIPAA Authorization and Consent Form(s), there must be:
   - The original in your file
   - A copy given to the subject (or representative)
   - A copy retained for submission to the HSS with your request for Continued Approval
   - Non-veteran research subjects must be provided with a copy of the Notice of Privacy Practices (NOPP). A copy of the signed acknowledgement letter must be kept in the subject's research file.
   - If this study involves the use of an investigational drug, VA form 10-9012 must be scanned into the medical record for anyone who enrolls in this study.

If you have any questions, please contact Brendan Sullivan at (203) 932-5711, ext.3350.

Fred S. Wright, MD
Associate Chief of Staff for Research

8/30/17
Date

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March2014

APPENDIX C. MOTIVATION AND PLEASURE SCALE – SELF-REPORT (MAPS-SR)

Item	Anchors
Social pleasure	
1. In the past week, what is the most pleasure you experienced from being with other people?	0 (no pleasure) – 4 (extreme pleasure)
2. In the past week, how often have you experienced pleasure from being with other people?	0 (not at all) – 4 (very often)
3. Looking ahead to being with other people in the next few weeks, how much pleasure do you expect you will experience from being with others?	0 (no pleasure) – 4 (extreme pleasure)
Recreational or work pleasure	
4. In the past week, what is the most pleasure you experienced from hobbies, recreation, or from work?	0 (no pleasure) – 4 (extreme pleasure)
5. In the past week, how often have you experienced pleasure from hobbies, recreation, or from work?	0 (not at all) – 4 (very often)
6. Looking ahead to the next few weeks, how much pleasure do you expect you will experience from your hobbies, recreation, or work?	0 (no pleasure) – 4 (extreme pleasure)
Feelings and motivations about close, caring relationships	
7. When it comes to close relationships with your family members, how important have these relationships been to you over the past week?	0 (not at all important to me) - 4 (extremely important to me)

9. When it comes to having a close relationship with a romantic partner, how important has this type of relationship been to you over the past week?	0 (not at all important to me) - 4 (extremely important to me)
11. When it comes to close relationships with your friends, how important have these relationships been to you over the past week?	0 (not at all important to me) - 4 (extremely important to me)
Motivation and effort to engage in activities	
13. In the past week how motivated have you been to be around other people and do things with them?	0 (not at all motivated) – 4 (very motivated)
14. In the past week how much effort have you made to actually do things with other people?	0 (no effort) – 4 (very much effort)
15. In the past week how motivated have you been to go to work or school or look for a job or class to take?	0 (not at all motivated) – 4 (very motivated)
16. In the past week how much effort have you made to do things at work or school? (If you are not working or going to school, how much effort have you made to look for a job or go to school?)	0 (no effort)–4 (very much effort)
17. In the past week how motivated have you been to do hobbies or other recreational activities?	0 (not at all motivated) – 4 (very motivated)
18. In the past week how much effort have you made to actually do any hobbies or recreational activities?	0 (no effort)–4 (very much effort)

APPENDIX D. PRE-TASK QUESTIONNAIRE

1. How enthusiastic do you feel right now? 1 = very slightly or not at all to 7 = extremely
2. How confident do you feel right now? 1 = very slightly or not at all to 7 = extremely
3. How energetic do you feel right now? 1 = very slightly or not at all to 7 = extremely
4. How sad do you feel right now? 1 = very slightly or not at all to 7 = extremely
5. How nervous do you feel right now? 1 = very slightly or not at all to 7 = extremely
6. How frustrated do you feel right now? 1 = very slightly or not at all to 7 = extremely
7. How tired do you feel right now? 1 = very slightly or not at all to 7 = extremely
8. How difficult do you think this task will be? 1 = very slightly or not at all to 7 = extremely
9. How motivated are you to do well on this task? 1 = very slightly or not at all to 7 = extremely
10. How long ago was your last cigarette? 1 = within the last 15 minutes, 2 = within the last 30 minutes, 3 = within the last hour, 4 = within the last 2 hours, 5 = within the last 3 hours, 6 = more than 3 hours ago, 7 = I don't smoke
11. When was the last time you had a caffeinated drink? 1 = within the last 15 minutes, 2 = within the last 30 minutes, 3 = within the last hour, 4 = within the last 2 hours, 5 = within the last 3 hours, 6 = more than 3 hours ago, 7 = I don't drink caffeine
12. How many balloons do you think you will be able to pop in 5 minutes? ____
13. How much money do you think you will win? ____

APPENDIX E. POST-TASK QUESTIONNAIRE

1. How enthusiastic do you feel right now? 1 = very slightly or not at all to 7 = extremely
2. How confident do you feel right now? 1 = very slightly or not at all to 7 = extremely
3. How energetic do you feel right now? 1 = very slightly or not at all to 7 = extremely
4. How sad do you feel right now? 1 = very slightly or not at all to 7 = extremely
5. How nervous do you feel right now? 1 = very slightly or not at all to 7 = extremely
6. How frustrated do you feel right now? 1 = very slightly or not at all to 7 = extremely
7. How tired do you feel right now? 1 = very slightly or not at all to 7 = extremely
8. How difficult did you think this task was? 1 = very slightly or not at all to 7 = extremely
9. How motivated were you to do well on this task? 1 = very slightly or not at all to 7 = extremely
10. How many balloons did you pop compared to how many you thought you would?

    1 = I popped a lot fewer than I thought I would, 2 = I popped slightly fewer than I thought I would, 3 = I did about as well as I thought I would, 4 = I popped a little more than I thought I would, 5 = I popped a lot more than I thought I would
11. How much money do you think you will win?

    1 = I made a lot less than I thought I would, 2 = I made a little less than I thought I would, 3 = I made about as much as I thought I would, 4 = I made a little more than I thought I would, 5 = I popped a lot more than I thought I would

VITA

Jessica Elaina McGovern was born and raised in Reseda, CA. She received her Bachelor of Science degree in psychology with a minor in cognitive science from the University of California at San Diego (UCSD), graduating magna cum laude with a college honors distinction. At UCSD, she completed her honors thesis examining the relationship between attributions about own auditory hallucinations, mood, and self-esteem in individuals with schizophrenia under the mentorship of Dr. Eric Granholm. After graduating from UCSD, Jessica worked as a psychometrist on a longitudinal traumatic brain injury at the NIH Clinical Center where she further developed her interests in brain-behavior relationships under the mentorship of neuropsychologist Dr. John Dsurney. As a Clinical Psychology doctoral student at Louisiana State University, under the mentorship of Dr. Alex Cohen, Jessica honed her research interests in elucidating biopsychosocial mechanisms underlying negative symptoms (especially avolition) and improving treatments targeting such symptoms in individuals with severe mental illness. She completed her predoctoral internship in Clinical Psychology with an emphasis in Severe Mental Illness at the VA Connecticut Healthcare System under the mentorship of Drs. Joanna Fiszdon and Jason Johannesen. She will next be joining Dr. Michael Green's laboratory through the VA Greater Los Angeles MIRECC postdoctoral fellowship (in association with the University of California at Los Angeles) specializing in schizophrenia treatment and research.