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Associations between insomnia and reward learning in clinical depression

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Abstract

Background. Depression and insomnia commonly co-occur. Yet, little is known about the mechanisms through which insomnia influences depression. Recent research and theory highlight reward system dysfunction as a potential mediator of the relationship between insomnia and depression. This study is the first to examine the impact of insomnia on reward learning, a key component of reward system functioning, in clinical depression.

Methods. The sample consisted of 72 veterans with unipolar depression who endorsed sleep disturbance symptoms. Participants completed the Structured Clinical Interview for DSM-IV, self-report measures of insomnia, depression, and reward processing, and a previously validated signal detection task (Pizzagalli et al., 2005, Biological Psychiatry, 57(4), 319–327). Trial-by-trial response bias (RB) estimates calculated for each of the 200 task trials were examined using linear mixed-model analyses to investigate change in reward learning.

Results. Findings demonstrated diminished rate and magnitude of reward learning in the Insomnia group relative to the Hypersomnia/Mixed Symptom group across the task. Within the Insomnia group, participants with more severe insomnia evidenced the lowest rates of reward learning, with increased RB across the task with decreasing insomnia severity.

Conclusions. Among individuals with depression, insomnia is associated with decreased ability to learn associations between neutral stimuli and rewarding outcomes and/or modify behavior in response to differential receipt of reward. This attenuated reward learning may contribute to clinically meaningful decreases in motivation and increased withdrawal in this comorbid group. Results extend existing theory by highlighting impairments in reward learning specifically as a potential mediator of the association between insomnia and depression.

Major depressive disorder (MDD) is a heterogeneous disorder marked by a variety of symptoms, including sleep disturbance (Goldberg, 2011). A majority of individuals with MDD report sleep problems, such as insomnia or hypersomnia (APA, 2013; Geoffroy et al., 2018). Insomnia is characterized by persistent difficulties with falling (i.e. early insomnia) or staying asleep (i.e. middle insomnia), early morning awakening (i.e. late insomnia), or non-restorative, poor-quality sleep (APA, 2013), while hypersomnia is defined by excessive sleep during the night or day (APA, 2013). Approximately two-thirds of individuals with depression report insomnia, with as many as 90% endorsing poor sleep quality (Franzen & Buysse, 2008). In contrast, hypersomnia is found in approximately 15% of patients with depression (Franzen & Buysse, 2008).

The term 'insomnia' is used to describe both a symptom (e.g. a diagnostic criterion within MDD) and a distinct DSM disorder. In this paper, we use the term insomnia to refer to the symptom (i.e. not disorder) of insomnia, unless specifically noted. Due to its status as a symptom of depression, initial models assumed that depression was causally related to the development of insomnia. However, it has become clear that the relationship between depression and insomnia is bidirectional (Alvaro, Roberts, & Harris, 2013). For example, insomnia has been found to precede depression onset and increase depression risk (e.g. Breslau, Roth, Rosenthal, & Andreski, 1996; Buysse *et al.* 2008; Chang, Ford, Mead, Cooper-Patrick, & Klag, 1997). The temporal association of insomnia with subsequent depression appears across the lifespan, including in adolescent, adult, and geriatric populations (Baglioni et al., 2011; Bao et al., 2017; Roberts & Duong, 2014). There is also preliminary evidence that treating insomnia may improve depressive symptoms (e.g. Karlin, Trockel, Taylor, Gimeno, & Manber, 2013; Taylor & Pruiksma, 2014) and that improvements in insomnia may mediate depression treatment response (Manber et al., 2016). Taken together, these findings support a transactional relationship between these constructs and suggest that insomnia may influence the onset, severity, and course of depressive symptoms (Fang, Tu, Sheng, & Shao, 2019).

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Despite this, little is known about the pathways through which insomnia may influence depression, as well as negative clinical outcomes in depression treatment. Recent models of this comorbidity have identified reward system dysfunction as an important mediator of the relationship between insomnia and depression (Boland, Goldschmied, Wakschal, Nusslock, & Gehrman, 2020). Reward processing deficits are well established in depression and are linked to the experience of anhedonia specifically (i.e. loss of interest or pleasure in all or almost all daily activities; APA, 2013; Keedwell, Andrew, Williams, Brammer, & Phillips, 2005; Pelizza & Ferrari, 2009; Pizzagalli *et al.*, 2009; Whitton, Treadway, & Pizzagalli, 2015; Zhang, Chang, Guo, Zhang, & Wang, 2013). Moreover, sleep regulation and reward system pathways share significant neurobiological overlap (Fang et al., 2019; Palagini, Bastien, Marazziti, Ellis, & Riemann, 2019). Specifically, MDD is associated with decreased midbrain dopamine signaling, which contributes to reward learning impairments (Kaiser et al., 2018; Kumar et al., 2018). Similar dopaminergic activity has been implicated in sleep/wake regulation and REM sleep (Boland et al., 2020; Palagini et al., 2019). Finally, both insomnia and depression/anhedonia have been independently associated with impairments in reward processing, including reward learning (e.g. Casement, Keenan, Hipwell, Guyer, & Forbes, 2016; Engle-Friedman *et al.* 2003; Finan *et al.* 2019; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008c). Accordingly, enhancing our understanding of the interrelationships among insomnia, reward functioning, and depression may inform new treatment targets.

Depression is associated with alterations in multiple components of reward processing. These include impairment in: appetitive motivation (i.e. anticipation of rewards), reward seeking, effort expended to obtain rewards, decision-making based on reward magnitude and availability, and integration of reinforcement history (e.g. Pizzagalli *et al.* 2008c; Rawal, Collishaw, Thapar, & Rice, 2013; Treadway, Bossaller, Shelton, & Zald, 2012; Whitton *et al.* 2015). Depression has also been associated with decreased reward learning (Pizzagalli et al., 2008c; Vrieze et al., 2013), which involves the ability to make and retain associations between neutral stimuli and rewarding outcomes and to adjust one's behavior based on positive reinforcement (Liverant et al., 2014). Evidence from behavioral and neurobiological studies suggests that depressed individuals demonstrate weakened acquisition of reward learning relative to non-depressed participants (Kumar et al., 2018; Pizzagalli et al., 2008c; Smoski et al., 2009). Among depressed individuals, elevated anhedonia is associated with reduced reward learning, highlighting the key role of the anhedonic phenotype in the relationship between depression and reward learning (Pizzagalli et al., 2008c; Vrieze et al., 2013). Successful MDD treatment is associated with the normalization of reward learning, whereas reduced reward learning pre-treatment predicts continued MDD diagnosis post-treatment (Vrieze et al., 2013).

Although there is strong evidence for reward processing deficits in MDD, less is known about the relationship between insomnia and reward system dysfunction. Preliminary findings suggest that insomnia is associated with impairments in anticipatory reward processing, as well as effort expended for reward. For example, in healthy adolescents, fewer minutes of sleep, later sleep onset, and lower sleep quality were associated with hypoactivity in the caudate during reward anticipation (Holm et al., 2009). Additional neuroimaging research suggests that neural reward processing, specifically dorsal medial prefrontal cortex activity during reward anticipation, mediates the relationship between insomnia and depression (Casement et al., 2016). Similarly, Burani et al. (2019) found associations between sleep disturbance, blunted reward processing (as indexed by event-related potentials/RewP during a monetary reward task), and depression 1 year later in a sample of adolescent girls. Results suggested that both sleep and blunted reward activation predicted depression risk, and sleep problems moderated the relationship between reward processing and depression (i.e. reward activation predicted depression only at higher levels of sleep disturbance).

In line with these findings, a recent theory, the Integrated Sleep and Reward Model (ISR; Boland et al., 2020), highlights reward system functioning as an important mediator of the relationship between insomnia and depression. The ISR model suggests that insomnia decreases effort to pursue rewards and impairs reward learning via interference with the use of reward-related cues to inform reward-based decision-making and behavior. This model further suggests a dose/response relationship between sleep disturbance and reward system dysfunction. Consistent with this theory, recent findings demonstrated increased effort for anticipated rewards following insomnia treatment in depressed individuals with earlier peak alertness (i.e. morning chronotype; Boland, Bertulis, Leong, Thase, & Gehrman, 2019). Thus, these initial findings and the ISR model suggest that insomnia may weaken critical components of reward processing among individuals with depression. However, to date, no study has examined the specific effects of insomnia on reward learning in clinical depression.

Despite increased attention to the potential interrelationships among insomnia, reward system dysfunction, and depression, the impact of insomnia on different aspects of reward system functioning has not been fully explicated. This research is the first to examine associations between self- and clinician-rated insomnia (compared to other sleep disturbance symptoms including hypersomnia and mixed symptoms) and reward learning using self-report of reward functioning (Aim 1) and a signal detection task assessing reward learning (Aim 2) in a sample of veterans with unipolar depression. In line with existing theory and research, we predicted that insomnia would be associated with diminished self-reported reward functioning, as well as less effective reward learning on the signal detection task.

Method

Participants

A sample of veterans ($N = 72$) with unipolar depression was recruited from a VA Healthcare System. Participants were required to be ⩾18-years-old, fluent in English, and to endorse depression-related sleep impairment on the Structured Clinical Interview for DSM-IV Axis I Disorders – Clinician Version (SCID-CV; First, Spitzer, Gibbon, & Williams, 2002). Exclusion criteria included (a) lifetime bipolar disorder diagnosis; (b) current psychotic symptoms or lifetime psychotic disorder; (c) current suicidal/homicidal intent and/or plan; (d) unstable psychiatric symptoms (e.g. psychiatric hospitalization within 2 months); and (e) limited mental competency and/or inability to provide informed consent.

Within the sample, 79.2% ($n = 57$) endorsed insomnia symptoms (Insomnia) and 20.8% ($n = 15$) endorsed hypersomnia or mixed sleep disturbance symptoms (Hypersomnia/Mixed).

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Insomnia and Hypersomnia/Mixed participants did not differ significantly on any demographic or clinical variables (see Table 1). For Aim 1, complete self-report data on outcomes of interest were available from 94.4% ($n = 68$) of participants. For Aim 2, analyses were conducted on a reduced sample of 50 (37 Insomnia and 13 Hypersomnia/Mixed) participants with valid signal detection data.

Diagnostic assessment

The Structural Clinical Interview for DSM-IV Axis I Disorders – Clinician Version (SCID-CV; First et al., 2002) assessed the presence/absence of psychiatric disorders. The SCID-CV MDD module's sleep item indexed sleep disturbance symptoms.

Self-report measures

Beck Depression Inventory-II (BDI-II)

The BDI-II (Beck, Steer, & Brown, 1996b) is a 21-item self-report measure of depression severity. Items are rated on a four-point Likert scale, with higher scores indicating greater depression. The BDI-II has demonstrated excellent psychometric properties (Beck, Steer, Ball, & Ranieri, 1996a; Dozois, Dobson, & Ahnberg, 1998).

The Anhedonic Depression (AD) subscale of the Mood and Anxiety Symptom Questionnaire (MASQ)

The MASQ AD (Watson et al., 1995b) subscale assessed anhedonia. The subscale consists of 22 items, measuring reduced positive affect and loss of interest, rated on a five-point Likert scale. Higher scores indicate greater anhedonia. The MASQ AD subscale has demonstrated excellent reliability and validity (e.g. Watson et al., 1995a).

Behavioral Inhibition System/Behavioral Activation System Scale (BIS/BAS

The BIS/BAS (Carver & White, 1994) is a 20-item self-report measure of behavioral inhibition and activation. Items are rated on a four-point Likert scale. The BAS subscales: Reward Responsiveness, Drive, and Fun Seeking were examined as measures of self-reported dispositional BAS/reward system activation. Higher scores indicate greater activation. The BIS/BAS has demonstrated excellent psychometrics in clinical samples (e.g. Campbell-Sills, Liverant, & Brown, 2004).

Composite Measure of Insomnia Symptom Severity

A three-item continuous measure of insomnia symptom severity was created using items from the BDI-II, the Posttraumatic Stress Disorders Checklist – Civilian Version (PCL-C; Weathers, Litz, Herman, Huska, & Keane, 1993), and the Minnesota Nicotine Withdrawal Scale (MNWS; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The latter two measures were administered as part of a larger study. BDI-II Item 16 assessed 'changes in [participants'] sleep patterns' in the past 2 weeks. The item was rated using the following scale: 0 (*I have not experienced any change in my sleep pattern*), 1 (*I sleep somewhat less than usual*), 2 (*I sleep a lot less than usual*), or 3 (*I wake up 1–2 h early and can't get back to sleep*). Due to the study focus on insomnia severity, when participants endorsed sleeping more than usual in the past 2 weeks, responses were coded as zero. PCL-C Item 13 assessed participants' 'trouble falling or staying asleep' in the past month. This item was rated from 1 (*not at all*) to 5 (*extremely*). MNWS Item 7 assessed 'insomnia, sleep problems, and awakening at night' in the last 24 h. It was rated from 0 (*none*) to 4 (*severe*). Item responses were converted to *z*-scores and averaged to create a composite measure of self-reported insomnia severity. Cronbach's α ($\alpha = 0.76$) demonstrated good internal consistency for the composite scale.

Computerized Reward Learning Task

A previously validated signal detection task assessed reward learning (Pizzagalli, Jahn, & O'Shea, 2005; Pizzagalli et al., 2008c). The task included two 100-trial Blocks. Each trial consisted of: a fixation point presented for 500 milliseconds (ms), a cartoon face without a mouth presented for 500 ms, a mouth displayed within the face for 100 ms, and then the reappearance of the cartoon face without a mouth until a response was made. The mouth was either short (11.5 mm) or long (13 mm). Individuals were asked to identify if the short/long mouth was presented using designated keys. Participants were unaware that an asymmetrical reinforcer ratio was used to reward correct identifications; the rich stimulus received positive feedback ('Correct! You won 5 cents') three times more than the lean stimulus (30 *v.* 10 trials per Block). The rich stimulus (i.e. short *v.* long mouth) was counterbalanced across participants.

The main task outcome variable was response bias (RB), which captures the preference for the more frequently rewarded stimulus and was calculated as:

$$\text{Response Bias: } \log b = \frac{1}{2}\log\left(\frac{\text{Rich}_{\text{correct}} \times \text{Lean}_{\text{incorrect}}}{\text{Rich}_{\text{incorrect}} \times \text{Lean}_{\text{correct}}}\right)$$

To allow calculation in cases with a zero in a cell, 0.5 was added to each cell in the detection matrix as recommended (Hautus, 1995; Pizzagalli et al., 2008c). Trial-by-trial RB estimates were calculated to produce a continuous index of reward learning across the 200 trials.

Discriminability (d') indexed ability to differentiate between the two stimuli (i.e. short/long mouth), a measure of task difficulty. d' was calculated as:

$$\log d = \frac{1}{2}\log\left(\frac{\text{Rich}_{\text{correct}} \times \text{Lean}_{\text{correct}}}{\text{Rich}_{\text{incorrect}} \times \text{Lean}_{\text{incorrect}}}\right)$$

Reaction Time (RT) was the time (ms) following the presentation of the rich/lean stimulus to participant response.

Procedure

Initial inclusion/exclusion criteria were assessed via telephone screen. Participants then came to the lab and provided informed consent. Next, the SCID-CV was administered, and participants completed questionnaires, followed by the computerized task. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 and were reviewed by a VA healthcare system Institutional Review Board.

Data reduction and analytic plan

Identification of task outliers

According to standard scoring procedures (Pizzagalli et al., 2005), task data were screened for outliers. Participants were excluded if

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Table 1. Descriptive, psychiatric, and medical characteristics of the participant sample as a function of sleep status (Insomnia *v*. Hypersomnia/Mixed)

	Insomnia ($n = 57$)		Hypersomnia/mixed ($n = 15$)		
Characteristic	Mean (s.d.)	*n* (%)	Mean (s.d.)	*n* (%)	*p* value
Age (years)	51.26 (10.38)		49.07 (14.55)		0.59
Education (years)	13.69 (1.79)		13.53 (2.03)		0.77
Gender					0.94
Male		49 (86.0)		13 (86.7)	
Female		8 (14.0)		2 (13.3)	
Race/ethnicity					0.60
White/Caucasian		47 (82.4)		12 (80.0)	
Black/African American		6 (10.5)		1 (6.7)	
Latinx		2 (3.5)		0 (0.0)	
Asian/Pacific Islander		1 (1.8)		1 (6.7)	
Other/multiracial		1 (1.8)		1 (6.7)	
Marital status					0.50
Never married		15 (26.3)		5 (33.3)	
Married		9 (15.7)		4 (26.7)	
Divorced/separated		29 (50.8)		5 (33.3)	
Widowed		4 (7.0)		1 (6.7)	
Current smoker		24 (42.1)		8 (53.3)	0.44
Depression diagnoses					
MDD		55 (96.4)		14 (93.3)	0.59
Dysthymia		5 (8.8)		2 (13.3)	0.60
Comorbid PTSD		32 (56.1)		7 (46.7)	0.51
BDI-II	29.98 (9.46)		33.13 (10.45)		0.27
Anti-depressant use		38 (66.7)		10 (66.7)	1.00
β-Blocker use		2 (3.5)		0 (0.0)	0.46
Benzodiazepine use		7 (12.3)		3 (20.0)	0.44

Depression, including major depressive disorder (MDD) and dysthymia, and posttraumatic stress disorder (PTSD) diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID); BDI-II, Beck Depression Inventory-II.

they had: <80% of valid trials (invalid trials = RT < 150 or >2500 ms) within a Block; <25 rich reward per Block; >30 invalid trials within either Block; and <60% accuracy per Block. Using these criteria, 29.2% ($n = 21$) of participants were excluded from RB analyses, a rate consistent with previous studies in mood disorder and Veteran psychiatric samples (e.g. AhnAllen et al., 2012). Participants with data excluded from RB analyses did not differ from participants with valid task data on: Insomnia *v.* Hypersomnia/Mixed group, insomnia or depression symptoms, BAS scores, or MASQ scores ($ps > 0.05$).

Data analytic plan

Our first aim was to examine the association between insomnia and self-report measures of reward functioning. Independent samples *t* tests explored differences between the Insomnia and Hypersomnia/Mixed groups on the BAS and MASQ. Among the Insomnia group, Pearson's *r* correlations examined associations between insomnia severity and BAS and anhedonia.

Our second aim was to examine associations between insomnia and RB during the task. Task validity analyses included a Group (Insomnia, Hypersomnia/Mixed) × Block (Block 1, Block 2) mixed-model ANOVA to explore potential group differences in *d'*. A similar mixed-model ANOVA, including the repeated measure of Stimulus, was conducted to examine RT.

Next, linear mixed-model analyses were used to examine changes in trial-by-trial RB estimates across 200 trials. Consistent with Shek and Ma's (2011) recommendations, we first examined an unconditional mean model to evaluate intraindividual variability in reward learning. We then conducted an unconditional linear growth curve model to examine intraindividual variation across trials. Within this model, we considered both linear and quadratic change in RB over time. Linear and quadratic time variables were rescaled by dividing by 100. The association between insomnia and reward learning over time was examined within two models. The first model examined a categorical insomnia variable (Insomnia *v.* Hypersomnia/Mixed = reference group). The second model examined the composite insomnia

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severity scale and only included Insomnia participants. Restricted maximum likelihood was used for model estimation, and an unstructured covariance structure was used to account for within-subject correlated error terms.

Results

Insomnia and self-reported anhedonia and reward functioning

Differences between sleep symptom groups on self-reported measures of reward system functioning are presented in Table 2. Contrary to hypotheses, Insomnia (*v.* Hypersomnia/Mixed) participants reported greater BAS Drive. No other significant differences were found.

Among Insomnia participants, significant negative correlations emerged between insomnia severity and BAS Drive ($r = -0.29$, $p = 0.03$) and Fun Seeking ($r = -0.28$, $p = 0.04$). The association between insomnia severity and BAS Reward Responsiveness did not reach statistical significance ($r = -0.24$, $p = 0.08$). Insomnia severity was positively associated with MASQ Anhedonia ($r = 0.37$, $p = 0.005$).

Reward learning task validity analyses

Discriminability (d')

No significant effects emerged from the Group × Block ANOVA examining *d'*, indicating no group differences in task difficulty.

Reaction time (RT)

The ANOVA examining RT revealed a main effect for Block, $F_{(1,48)} = 8.06$, $p = 0.007$, partial $\eta^2 = 0.14$, due to an expected decrease in RT in Block 2 ($M = 595.51$ ms, S.E. = 27.75 ms) *v.* Block 1 ($M = 658.44$ ms, S.E. = 31.79 ms). There was a significant main effect for Stimulus, $F_{(1,48)} = 23.80$, $p < 0.001$, partial $\eta^2 = 0.33$, with predicted faster RT to the rich ($M = 606.55$ ms, S.E. = 26.58 ms) *v.* lean ($M = 647.10$ ms, S.E. = 29.34 ms) stimulus. The Block × Stimulus interaction was also significant, $F_{(1, 48)} = 7.73$, $p = 0.008$, partial $\eta^2 = 0.14$, indicating that RT decreased more from Block 1 to 2 in response to the rich ($M = 647.07$ ms, S.E. = 32.04 ms *v.* $M = 566.04$ ms, S.E. = 24.87 ms) *v.* lean stimulus ($M = 669.81$ ms, S.E. = 32.18 ms *v.* $M = 624.38$ ms, S.E. = 31.47 ms). Effects with Insomnia Group were non-significant, suggesting no relationship with RT.

Insomnia and trial-by-trial RB

Unconditional mean model

The mean RB score across participants and trials was 0.10 (S.E. = 0.02). Results indicated significant within-subject variance in RB (estimate = 0.02; S.E. = 0.0003; Wald $Z = 70.53$, $p < 0.001$) and significant between-subject variance in RB (estimate = 0.02; S.E. = 0.005; Wald $Z = 4.93$, $p < 0.001$). The intraclass correlation was 0.49.

Unconditional growth model

The unconditional growth model revealed a non-significant intercept effect ($B = 0.007$, S.E. = 0.04, $p = 0.85$), indicating that participants did not differ significantly in Trial 1 RB. As expected, the model revealed significant linear ($B = 0.14$, S.E. = 0.02, $p < 0.001$) and quadratic ($B = -0.0004$, S.E. = 3.41×10^{-5}, $p < 0.001$) effects of time. The positive linear time effect indicated that RB increased during the task, while the negative quadratic time effect indicated that the rate of learning slowed over time.

Insomnia predictor models

Estimates of fixed effects from the model examining the Insomnia/Hypersomnia/Mixed groups are presented in Table 3. At Trial 1, groups did not differ in RB. Significant linear and quadratic time effects showed that the Hypersomnia/Mixed group evidenced reward learning across the task, which decreased over time, while the Insomnia group demonstrated significantly less reward learning (*v.* Hypersomnia/Mixed) during the task. In addition, the Insomnia group evidenced a more consistent (albeit attenuated), linear learning rate relative to the Hypersomnia/Mixed group, which demonstrated a peak in learning after approximately ¾ of the 200 trials, followed by a slight decrease in learning rate (Fig. 1).[1]

Estimates of fixed effects from the model examining insomnia symptom severity among the Insomnia participants are presented in Table 3. Insomnia severity was not significantly associated with Trial 1 RB. Significant insomnia × linear time and insomnia × quadratic time effects indicated that more severe insomnia was associated with less reward learning during the task, though the positive insomnia × quadratic time interaction indicated that reward learning rate did not decrease over time as much among individuals with more severe insomnia symptoms (Fig. 2).[2]

Discussion

This is the first study to examine the relationship between insomnia and reward learning among individuals with clinical depression. Consistent with recent theory and research (e.g. Boland et al., 2020), findings demonstrated decreased RB (i.e. diminished rate and magnitude of reward learning) in the Insomnia relative to the Hypersomnia/Mixed group across the task (Pizzagalli et al., 2005). In addition, results with the composite measure of insomnia symptom severity revealed that participants with more severe insomnia evidenced the lowest rates of reward learning, followed by participants with average and less severe insomnia symptoms, respectively. This latter finding supports a dose/response

†The notes appear after the main text.

[1]All LMM analyses were re-run separately controlling for: smoking status, gender, racial/ethnic self-identification, and the severity of non-sleep-related depression symptoms. None of these covariates nor the interaction of the covariates with linear and quadratic time was significantly associated with reward learning. Further, inclusion of these covariates did not alter the significant linear time × insomnia or quadratic time × insomnia interactions in analyses comparing participants in the Insomnia *v.* Hypersomnia/Mixed groups. The pattern of interaction effects was also unchanged in analyses examining insomnia symptom severity, although the strength of the linear time × insomnia interactions was somewhat attenuated in the models including gender, race/ethnicity, and depression symptom severity as covariates, likely due to reduced power to detect effects. Please see the online Supplemental materials for additional detail on these analyses.

[2]To explore potential differences in the pattern of association between acute *v.* chronic sleep impairment and reward learning, analyses were also conducted examining the three insomnia symptom severity items separately. Greater impaired sleep in the past 24 h as measured by Item 7 of the MNSW was associated with less reward learning over the course of the task [$B = -0.13$, S.E. = 0.03, df = 41.20, $t = -4.40$, $p < 0.001$, 95% CI (−0.19 to −0.07)]. More severe insomnia symptoms over the past 2 weeks as measured by Item 16 of the BDI-II were not significantly associated with reward learning [$B = 0.02$, S.E. = 0.02, df = 41.73, $t = 1.00$, $p = 0.32$, 95% CI (−0.02 to 0.05)]. Finally, greater insomnia symptom severity during the past month as measured by Item 13 of the PCL-C was associated with greater reward learning over the course of the task [$B = 0.09$, S.E. = 0.03, df = 41.75, $t = 2.85$, $p = 0.007$, 95% CI (0.02–0.15)]. Though over-interpretation of these analyses is cautioned against, they may indicate that the association between insomnia symptom severity and deficits in reward learning in the Insomnia group is driven by the effects of acute rather than chronic sleep impairment (see online Supplemental materials for additional detail on these analyses).

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Table 2. Group differences for self-report measures of behavioral activation and anhedonia among Insomnia and Hypersomnia/Mixed participants

	Insomnia	Hypersomnia/mixed			
Questionnaire	Mean (s.d.)	Mean (s.d.)	*t*	*p*	*d*
BAS Reward Responsiveness	15.45 (2.62)	14.80 (2.93)	0.83	0.41	0.23
BAS Drive	10.05 (2.98)	8.27 (2.57)	2.11	0.04	0.64
BAS Fun Seeking	10.29 (2.90)	9.27 (3.08)	1.20	0.24	0.34
MASQ Anhedonia	87.01 (9.96)	91.40 (8.62)	1.55	0.13	0.47

BAS, Behavioral Activation System; MASQ, Mood and Anxiety Symptom Questionnaire.

Table 3. Estimates of fixed effects for the model examining reward learning among Insomnia and Hypersomnia/Mixed participants and in relation to insomnia symptom severity

Parameter	*B*	s.e.	df	*t*	*P*	95% CI
Model 1 (Insomnia *v.* Hypersomnia/Mixed participants)						
Intercept	0.02	0.07	48.40	0.28	0.78	−0.12 to 0.16
Insomnia	−0.02	0.08	48.40	−0.21	0.83	−0.18 to 0.15
Linear time	0.28	0.05	57.21	6.12	<0.001	0.19–0.38
Quadratic time	−0.0009	6.66×10^{-5}	9898	−14.31	<0.001	−0.001 to −0.0008
Insomnia × linear time	−0.20	0.05	57.21	−3.65	0.001	−0.30 to −0.09
Insomnia × quadratic time	0.0008	7.74×10^{-5}	9898	10.21	<0.001	0.0006–0.0009
Model 2 (insomnia symptom severity)						
Intercept	−0.004	0.04	35.31	−0.09	0.93	−0.09 to 0.08
Insomnia	0.03	0.07	35.31	0.46	0.65	−0.11 to 0.18
Linear time	0.11	0.03	41.81	3.43	0.001	0.05–0.17
Quadratic time	−0.0002	4.19×10^{-5}	7324	−5.61	<0.001	−0.0003 to −0.0001
Insomnia × linear time	−0.11	0.05	41.81	−2.38	0.02	−0.21 to −0.02
Insomnia × quadratic time	0.0004	6.93×10^{-5}	7324	5.59	<0.001	0.0003–0.0005

In Model 1, insomnia reference group = Hypersomnia/Mixed participants; in Model 2, insomnia = composite measure of insomnia symptom severity.

relationship between insomnia and reward learning impairments among those with depression and insomnia.

Findings using both categorical and dimensional insomnia assessments suggest that, among individuals with unipolar depression, insomnia is associated with decreased ability to learn associations between neutral stimuli and rewarding outcomes and/or modify behavior in response to differential receipt of reward (Liverant et al., 2014). This may suggest that depressed individuals with insomnia do not learn to associate rewarding experiences (e.g. positive interactions) with activities/behaviors in daily life (e.g. attending a party) to the same extent as depressed individuals without insomnia. This altered learning of environmental rewards may then contribute to clinically meaningful changes in withdrawal behavior (Jacobson, Martell, & Dimidjian, 2001).

Study results add to the limited existing literature showing relationships among insomnia, reward processing, and depression in adolescents. Specifically, previous research in this population has found associations between poorer sleep, neurobiological indicators of anticipatory reward functioning, and risk for depression (Burani et al., 2019; Casement et al., 2016; Holm et al., 2009). Thus, the current investigation adds to this growing research by explicating the relationship between insomnia and *reward learning specifically* among adults with clinical depression and insomnia.

Our results are also broadly consistent with the new ISR model and its identification of reward system functioning as a key mediator in the association between insomnia and depression (Boland et al., 2020). This model hypothesizes that insomnia attenuates effort to pursue rewards and impedes reward learning by interfering with the use of contextual information to inform decision-making and behavioral responding, leading to subsequent increases in depression. Findings demonstrating decreased reward learning in the Insomnia group, as well as greater reward learning impairments among those with more severe insomnia, provide empirical support for components of this model, while underscoring a potentially important role for reward learning deficits in this comorbidity.

Extensive neurobiological and experimental research has established dysfunction in the acquisition of reward learning and underlying reward circuitry in depression (Keedwell et al., 2005; Pizzagalli et al., 2009; Zhang et al., 2013), particularly among individuals experiencing anhedonia (Pizzagalli et al., 2008c; Smoski et al., 2009; Whitton et al., 2015). The current investigation critically extends this knowledge base, suggesting that co-occurring insomnia may exacerbate reward learning

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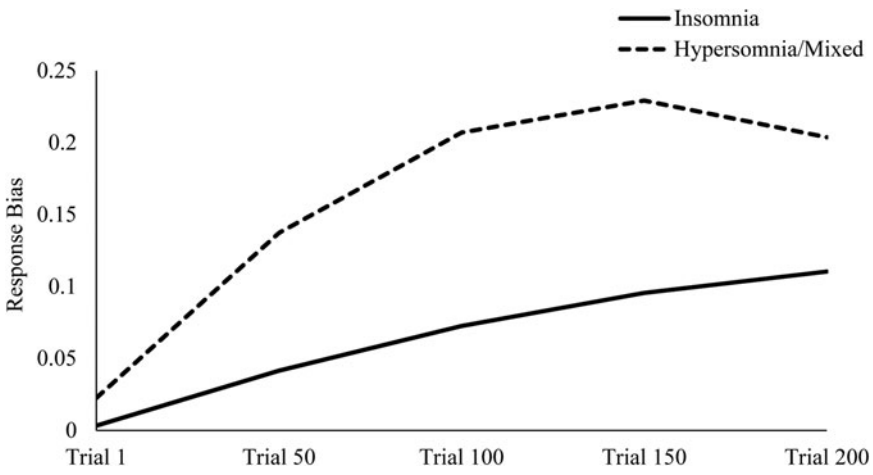

Fig. 1. Differences in trial-by-trial response bias estimates over the course of the computerized reward learning task between Insomnia and Hypersomnia/Mixed participants.

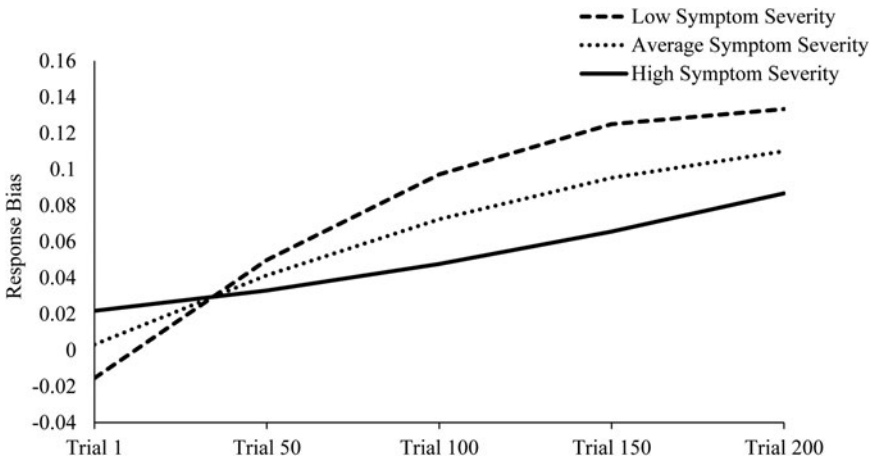

Fig. 2. Trial-by-trial response bias estimates over the course of the computerized reward learning task as a function of insomnia symptom severity among the Insomnia participants ($n = 37$). *Note.* The mean score for Insomnia participants on the composite measure of insomnia symptom severity was 0.19 (S.D. = 0.59). Response bias was examined at the mean insomnia symptom severity score, at +1 S.D. from the mean, and at −1 S.D. from the mean, to reflect average, high, and low symptom severity, respectively.

impairments found among individuals with depression (Pizzagalli et al., 2008c). Thus, this group may be at higher risk of more severe reward learning dysfunction (Franzen & Buysse, 2008).

Psychotherapeutic and pharmacological treatments for insomnia have been shown to ameliorate depression (Karlin et al., 2013; Manber et al., 2008; Taylor & Pruiksma, 2014). Our findings support reward learning as a potential mechanism of action underlying these antidepressant effects. Consistent with this interpretation, a recent pilot, open-label trial of Cognitive Behavioral Therapy for Insomnia (CBT-I) in depressed veterans found that, among those with a morning chronotype, CBT-I was associated with increased effort expended in pursuit of rewards from pre- to post-treatment (Boland et al., 2019). When combined, this research may also support the transdiagnostic utility of insomnia treatments to address reward system dysfunction in other disorders characterized by these impairments and/or anhedonia (e.g. PTSD and schizophrenia; Juckel *et al.* 2006; Nawijn *et al.* 2015).

Notably, results using the validated reward-learning task (Pizzagalli et al., 2005) were inconsistent with self-report findings, which failed to show significant differences between the Insomnia (*v.* Hypersomnia/Mixed) groups and BAS reward responsiveness and fun seeking. This inconsistency may be due to limitations of the BIS/BAS scale as an index of alterations in reward system functioning. Specifically, the BIS/BAS is a personality measure designed to assess temperamental activation of the behavioral activation system (Campbell-Sills et al., 2004; Carver & White, 1994). In contrast, the reward-learning task's repeated assessments of changes in RB in response to differential receipt of reinforcement delivered *in vivo* during the task may provide a more accurate characterization of the relationship between insomnia and behavioral reward responsivity (e.g. reward learning).

Contrary to hypotheses and recent theory (Boland et al., 2020), BAS drive subscale scores were significantly elevated in the Insomnia *v.* Hypersomnia/Mixed group. Of note, recent preclinical research has suggested unique effects of sleep deprivation on appetitive behavior particularly (i.e. Puhl, Boisvert, Guan, Fang, & Grigson, 2013; Wang *et al.* 2020). Thus, it is possible that, among depressed individuals, insomnia may produce specific antidepressant effects on drive/reward seeking. However, in contrast to this between-groups finding, correlational results in the Insomnia group found negative correlations between insomnia and BAS drive and fun-seeking subscale scores. Thus, among depressed individuals with clinically significant insomnia (e.g. already reduced sleep time), more severe insomnia symptoms were associated with self-report of decreased motivation for reward, including behavioral pursuit of rewards, spontaneous appetitive behavior, and desire for novel reinforcers. Given these conflicting findings, future research is needed with non-self-report assessments of appetitive behavior to elucidate the potential impact of insomnia on reward seeking specifically among individuals with depression, a condition marked by key deficits in this domain (e.g. Treadway et al., 2012).

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Despite the study's extension of existing literature, several limitations should be noted. This study used the SCID-CV and a composite measure of insomnia symptom severity composed of items from separate self-report measures to index insomnia. Future research should include additional validated self-report and physiological (actigraphy, polysomnography) measures of insomnia and reward system functioning (e.g. other neuroimaging and behavioral tasks, ecological momentary assessment) to fully characterize the relationship between insomnia and reward functioning in depression. Importantly, this investigation utilized an extensively validated signal detection task to assess reward learning (Pizzagalli, Goetz, Ostacher, Iosifescu, & Perlis, 2008b; Pizzagalli et al., 2008c). Unlike previous studies that have used mean RB to index reward learning aggregated across 100-trial Blocks, this study employed novel multi-level regression analyses of trial-by-trial RB estimates (calculated for each of the 200 trials), allowing for a nuanced investigation of reward learning rates across the task relative to previous studies (e.g. Pergadia et al., 2014; Pizzagalli et al., 2008a).

In addition, the study did not include a group of depressed individuals without sleep symptoms, limiting our ability to investigate the specific contribution of depression. However, given that as many as 90% of individuals with depression report sleep symptoms, results from such a comparison group may not be generalizable. In contrast, the current design allowed us to isolate the unique effects of insomnia plus depression as compared to those with depression and other sleep disturbance symptoms, increasing external validity. Lastly, the sample was primarily composed of veterans who identified as male and White. Thus, caution should be used when generalizing results to other populations.

In sum, study findings are novel and add critically to existing literature exploring the interrelationships among insomnia, reward system functioning, and depression. This investigation is the first to demonstrate reward learning impairments among individuals with insomnia and depression and highlights reward learning as a treatment target for this common comorbidity (Franzen & Buysse, 2008). Future research is needed utilizing multimodal assessments of insomnia and reward functioning in diverse samples to inform the transdiagnostic utility and mechanisms of action of insomnia treatments among individuals with depression and other disorders marked by the phenotypes of anhedonia and reward system dysfunction (Whitton et al., 2015).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172100026X

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Conflict of interest. Over the past 3 years, Dr Pizzagalli has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Engrail Therapeutics, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes, and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, Millennium Pharmaceuticals. In addition, he has received stock options from BlackThorn Therapeutics. Dr Pizzagalli has a financial interest in BlackThorn Therapeutics, which has licensed the copyright to the Probabilistic Reward Task through Harvard University. Dr Pizzagalli's interests were reviewed and are managed by McLean Hospital and Partners HealthCare in accordance with their conflict of interest policies. No funding from these entities was used to support the current work, and all views expressed are solely those of the authors. All other authors report no financial conflicts of interest.

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