Pavlovian and Instrumental Conditioning and Their Mutual Influence in Major Depressive Disorder: The Mood and Emotional Learning Dynamics (MELD) Framework

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Abstract

Major Depressive Disorder (MDD) poses a significant burden for individuals and society. It compromises quality of life, disrupts productivity, and strains social relationships. Pavlovian and instrumental conditioning play an important role in psychopathology, yet the independent and joint contributions of these forms of emotional learning to depressed mood are not well understood. In particular, studies of Pavlovian conditioning and Pavlovian-instrumental transfer (PIT) in MDD are few. Studying PIT in MDD may improve our understanding of how emotional learning influences depressive symptoms that is more reflective of how Pavlovian and instrumental conditioning operate in the real world. In this review, we first provide a narrative summary of past research investigating emotional learning in MDD, including computational modeling approaches. Based on these findings, we then build on an existing theoretical framework characterizing emotional learning and decision making in depression by incorporating the potential influence of Pavlovian conditioned cues on instrumental behaviour in individuals experiencing depressed mood. Specifically, we propose that, in MDD, adaptive instrumental behaviours are interrupted by the exaggerated inhibitory influence of aversive Pavlovian cues and insufficiently invigorated by appetitive Pavlovian cues. We conclude with recommendations for future research investigating emotional learning in MDD.

Keywords: Major Depressive Disorder, Pavlovian-instrumental transfer, Pavlovian conditioning, instrumental conditioning, reinforcement learning, emotional learning

Pavlovian and Instrumental Conditioning and Their Mutual Influence in Major Depressive Disorder: The Mood and Emotional Learning Dynamics (MELD) Framework

Major Depressive Disorder (MDD) poses significant social and economic costs to individuals, families, and society (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; Kessler, 2012; Lépine & Briley, 2011). It has been estimated that 322 million people are living with MDD worldwide, a prevalence which increased 18% between 2005 and 2015 (World Health Organization, 2017). MDD is the leading cause of disability globally and accounts for 40% of global disease burden attributable to all mental health conditions (Ferrari et al., 2013; Whiteford et al., 2013).

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), MDD is predominantly characterized by low mood and/or loss of interest or pleasure (American Psychiatric Association, 2013). Changes in appetite and sleeping patterns, fatigue or loss of energy, psychomotor agitation or retardation, feelings of worthlessness or excessive or inappropriate guilt, concentration difficulties, and thoughts of death or suicide are also common (APA, 2013). A precise characterization of the mechanisms underlying these symptoms may facilitate the development of more targeted and individualized treatments (Insel et al., 2010).

A large body of research has used cognitive science approaches to help characterize, predict, and improve treatment for MDD (Beck & Bredemeier, 2016; Grahek, Everaert, Krebs, & Koster, 2018; Kaiser et al., 2018; LeMoult & Gotlib, 2019; Teasdale, 1999a, 1999b; Teasdale, Segal, & Williams, 1995). However, contemporary accounts of the cognitive processes implicated in MDD often omit emotional learning (Grahek et al., 2018), the process by which actions and events or objects in the environment become associated with desirable or undesirable outcomes. A number of recent studies implicate emotional learning in MDD, including

computational psychiatry approaches that provide evidence for the contributions of latent aspects of Pavlovian and instrumental conditioning, and their mutual influence (Huys et al., 2016; Huys, Pizzagalli, Bogdan, & Dayan, 2013; Mukherjee, Filipowicz, Vo, Satterthwaite, & Kable, 2020; Nord, Lawson, Huys, Pilling, & Roiser, 2018). The mutual influence of Pavlovian and instrumental conditioning is referred to as Pavlovian-instrumental transfer (PIT), a phenomenon whereby Pavlovian conditioned stimuli invigorate, suppress, or guide the selection of instrumental behaviours. Emerging evidence suggests that PIT may be altered for individuals with MDD (Huys et al., 2016; Moutoussis et al., 2018; Nord et al., 2018).

Bishop and Gagne (2018) recently introduced the altered computations underlying decision making (ACDM) framework characterizing reinforcement learning and decision-making in depression and anxiety using a computational perspective (Bishop & Gagne, 2018). According to their framework, individuals with depression may underestimate the estimated probability and value of future positive events and overestimate the effort required to attain them. The authors note that a bias towards recalling negative rather than positive past experiences could inform pessimistic predictions of the likelihood of future positive events commonly seen in depression (Bjärehed, Sarkohi, & Andersson, 2010; MacLeod & Byrne, 1996; MacLeod & Salaminiou, 2001). Moreover, they propose that exaggerated anticipation of effort cost may contribute to anhedonia symptoms, consistent with previous research (Treadway, Bossaller, Shelton, & Zald, 2012; Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). A key proposition in their framework is that depression involves blunted anticipation of positive events ('wanting') rather than blunted sensitivity to consummatory reward ('liking'), a proposal that is also supported by previous studies (Bonnelle, Manohar, Behrens, & Husain, 2016; Bonnelle et al., 2015; Chong, Bonnelle, & Husain, 2016). We suggest that, while consistent with

a body of findings, this is not the whole picture. Following a review of studies investigating emotional learning in MDD, we build on the ACDM framework to integrate the roles of Pavlovian and instrumental conditioning and PIT in a new theoretical framework. The Mood and Emotional Learning Dynamics (MELD) framework provides a comprehensive account of how emotional learning and related psychological processes may perpetuate depressed mood in MDD.

To address the limitations outlined above, the current narrative review was carried out to synthesize previous studies investigating Pavlovian conditioning, instrumental conditioning (including computational models of reinforcement learning), and PIT studies in MDD before introducing the MELD framework to integrate past emotional learning findings and inform future research of emotional learning in depression. Our framework proposes that, for acutely depressed individuals with MDD, aspects of the environment that have previously been associated with negative outcomes may suppress actions intended to bring about desirable outcomes and prevent undesirable ones. Furthermore, the MELD framework suggests that, for individuals who are depressed, actions intended to bring about desirable consequences are not invigorated by aspects of the environment that have previously signaled a concurrent or subsequent positive outcome (where nondepressed individuals would experience invigoration of such actions). The assumptions of the MELD framework are informed by emotional learning studies in currently depressed individuals who have been diagnosed with MDD. Before reviewing this research, however, we will provide a brief overview of behavioural theories of depression focused on the role of positive and negative reinforcement (as opposed to cognitive theories that emphasize the roles of negative thoughts and beliefs in depression) that set the stage for recent research investigating emotional learning in MDD.

89 **Behavioural Theories of Depression**

90 A number of behavioural theories of depression emerged following seminal work of
91 Ferster and Skinner (1957) who formally proposed that the likelihood of a behaviour being
92 carried out will be more or less likely depending on whether the behaviour was previously
93 rewarded or punished, respectively (Clark & Beck, 1999). Early behavioural theories of
94 depression emphasized that adaptive behaviours can be reduced significantly in the absence of
95 (1) behaviours resulting in positive experiences that motivate the repetition of those behaviours
96 (i.e., positive reinforcement) and (2) behaviours resulting in successful avoidance of negative
97 experiences (producing a feeling of relief) that also motivate the repetition of those behaviours
98 (i.e., negative reinforcement). When behaviours appear to no longer result in reinforcement, this
99 loss of positive and negative reinforcers can produce an overgeneralized loss of interest and
100 pleasure and a tendency towards helplessness, respectively (Clark & Beck, 1999; Gotlib &
101 Hammen, 1992). Some of the most well-known behavioural theories of depression are those
102 introduced by Ferster (1973), Costello (1972), Lewinsohn (1974), and Seligman (1975), as
103 summarized below. These theories are presented to help provide context for recent research on
104 emotional learning in MDD.

105 **Ferster (1973): Reduced Frequency of (Reinforced) Behaviour**

106 In his conceptualization of depression, Ferster (1973) proposed that the defining feature
107 of the condition is the reduced frequency of adaptive behaviours resulting from a lack of
108 positively reinforced behaviours and/or an excess of punished behaviours. For example,
109 insufficient positive reinforcement may lead to reduced engagement in enjoyable activities like
110 meaningful social interactions and excessive punishment may result in reduced engagement in
111 adaptive avoidance or escape behaviours such as actively preventing or resolving interpersonal

conflict. Ferster (1973) noted that individuals with depression tend to perform *indirect actions* that are unlikely to alter or prevent an undesirable situation even though they are motivated by it (e.g., unconstructive complaints, demands that are unrealistic or not feasible), and less often perform *direct actions* which effectively address (e.g., reduce or terminate) undesirable circumstances. The performance of indirect actions and paucity of direct actions proposed to characterize depression may be explained by excessive punishment preventing direct actions and insufficient reinforcement of direct actions to guide and motivate adaptive behaviour. For example, an individual requesting their partner to go to the movies, attend a party with friends, go for a walk, or do some other activity are examples of direct actions performed to bring about positive experiences. If these requests are repeatedly denied (a lack of positive reinforcement), the individual interested in engaging in these activities may begin to perform indirect actions, such as complaining that their life is boring or that they are always cooped up at home. The goal is the same for these actions, but indirect actions are proposed to be more common for people who are depressed. Unfortunately, indirect actions are often even less likely to result in positive reinforcement, thereby failing to increase the positive reinforcement needed to alleviate depressed mood. Thus, Ferster's (1973) theory suggests the critical role of emotional learning (changes in behaviour resulting from reward and punishment) in depression.

Lewinsohn (1974): Reduced Effectiveness of Positive Reinforcers

Consistent with Ferster's (1973) theory, Lewinsohn (1974) proposed that individuals with depression experience a lack of response-contingent reinforcement that leads to the extinction of positively reinforced behaviours. He theorized that depression was determined by (1) the *availability* of positive reinforcers (e.g., few opportunities to see friends, no access to recreational activities, few contacts with superiors at work who praise work accomplishments)

and aversive experiences (e.g., chronic pain, frequent disdain from a partner), (2) the *adequacy/effectiveness of instrumental behaviours* to promote positive reinforcement or reduce/eliminate aversive experiences (e.g., poor social skills or problem solving), and/or (3) the *number/frequency* of positive reinforcers and aversive events (e.g., multiple losses such as a job, partner, home, etc.; Clark & Beck, 1999; Lewinsohn, 1974). Thus, if opportunities to engage in positively reinforcing behaviours are limited and/or there is a preponderance of aversive events, individuals are unlikely to experience the kind of reinforcement that can promote healthy approach and avoidance/escape behaviours and prevent unhealthy ones (Trew, 2011). Furthermore, reinforcement may not occur if an individual does not have the skills (or believes they do not have the skills) needed to facilitate the behaviour required to bring about reward or avoid punishment. In this case, aversive experiences may be more likely as a consequence of the individual being ineffective at facilitating desirable outcomes and preventing negative ones. Lastly, if the number and frequency of positive reinforcers are low and/or the number and frequency of aversive events are high, frequency of active behaviour in general is reduced, and the negative consequences that result from inaction are increased. According to Lewinsohn (1974), these patterns of behaviour and environmental conditions are central contributors to the depressed state. Again, this early behavioural theory of depression proposes that rewarding and aversive consequences of behaviour, and the changes in behaviour they cause, can lead to and perpetuate depressed mood, as further explored in recent research of emotional learning in MDD discussed below.

Costello (1972): Disrupted Chain of Behaviour

Costello (1972) sought to explain why the loss of one reinforcer (e.g., a close companion) would lead to a loss of interest in a variety of reinforcers (e.g., food and sex). He proposed that

depression results from a disruption in a chain of behaviour, whereby a break in a chain of reinforced behaviours can reduce all of the behaviours in that chain. For example, for someone who routinely prepares coffee in the morning to enjoy with a partner, the loss of that partner may not only result in the cessation of that ritual, but it may also cause a disruption in the motivation for the individual to get out of bed. This example depicts how the disruption of a component of the chain of behaviours can disrupt other components of the chain explaining certain depressive behaviours. Although disrupted behavioural chaining was central to Costello's (1972) theory, he also emphasized using concepts from Pavlovian conditioning (Pavlov & Gantt, 1928) that an unconditioned stimulus (US, a stimulus that is intrinsically painful or pleasurable), is increased in attractiveness or aversiveness by a conditioned stimulus (CS, an otherwise neutral stimulus that has come to be associated with pain or pleasure) that is presented before it. Thus, Costello's behavioural theory of depression also points to a role of Pavlovian conditioned stimuli in reduced positively reinforced behaviour in depression as we propose below in the MELD framework.

Seligman (1975): Learned Helplessness

The learned helplessness model proposed by Seligman (1975) posited that depression results from repeated uncontrollable and inescapable stressors that compromise an individual's sense of control over their life and circumstances (Clark & Beck, 1999). Seligman distinguished two types of learned helplessness, objective and subjective. Objective helplessness refers to situations in which the probability of an aversive outcome is the same regardless of one's response, i.e., there is nothing an individual can do to prevent the aversive event. Subjective helplessness, on the other hand, refers to an individual's *belief* that the probability of an aversive outcome is the same regardless of the response, whether this is accurate or not. Perhaps the most well-known investigation of learned helplessness was a study by Seligman and Maier (1967)

who tested whether already acquired Pavlovian CSs could influence later instrumental conditioning. In their experiment, subjects were first exposed to inescapable shock, and then placed in a shuttle box that would allow them to escape the shock (Seligman & Maier, 1967). Surprisingly, subjects that experienced inescapable shock prior to the instrumental conditioning paradigm did not learn to escape the shuttle box when given the opportunity to do so, i.e., the conditioned context prevented instrumental escape behaviour (Seligman & Maier, 1967). This is an example of Pavlovian-instrumental transfer (PIT), which we describe in detail in later sections of this review.

Emotional Learning in MDD

Until recently, relative to other diagnostic categories, MDD had received less attention in research exploring the clinical implications of altered emotional learning, particularly Pavlovian conditioning and PIT (Nees, Heinrich, & Flor, 2015). However, research to date characterizing emotional learning in MDD suggests that both Pavlovian and instrumental conditioning are implicated in depression (Craske, Meuret, Ritz, Treanor, & Dour, 2016; Dayan & Huys, 2008; Huys et al., 2016; Huys et al., 2013; Huys, Vogelstein, & Dayan, 2009). Furthermore, research exploring the interaction between these two types of emotional learning in the context of MDD has shed light on the complexity of emotional learning processes that may be implicated in depressive symptomology (Huys et al., 2016; Nord et al., 2018). Yet, a comprehensive review of emotional learning in MDD has not been undertaken. The following narrative review aims to address this gap by summarizing previous findings regarding Pavlovian and instrumental conditioning, as well as PIT, in MDD. Notably, there is considerable heterogeneity across individuals diagnosed with MDD in terms of ‘subtypes’ or patterns of depressive symptoms;

however, the studies reviewed here represent important groundwork toward a more fine-grained understanding of how emotional learning relates to different dimensions of depressed mood.

Pavlovian Conditioning

Pavlovian conditioning is thought to be an evolutionarily adaptive learning process that facilitates the encoding (the conversion of sensory input into a form that can be processed and deposited into memory) and consolidation (the crystallization of recent memories into long-term memory) of information predictive of desirable or undesirable outcomes (Boureau & Dayan, 2011; Rescorla, 1988). It constitutes the pairing of a neutral stimulus (the CS) with a significant event (the US) to facilitate a biological response in the presence of the CS (the conditioned response; CR) that can subsequently be elicited by the CS in the absence of the US. In addition to neutral cues and contexts, vivid visual imagery of a US can also produce a CR (Berridge, 2012; Dadds, Bovbjerg, Redd, & Cutmore, 1997; Holland, 1990). Such learning prepares an organism for future occasions when the US may be presented, as signaled by the presence of the CS. The CR is a *direct* consequence of the CS that facilitates approach (for desirable outcomes) or avoidance (for undesirable outcomes) (Boureau & Dayan, 2011). That is, it allows us to use cues to predict and approach or avoid good or bad events, respectively.

In human research, laboratory experiments used to study Pavlovian associations typically involve the repeated presentation of a CS, such as a coloured shape, with a significant event, such as the delivery of a monetary or food reward, that elicits a reflexive motivational/emotional response (e.g., increased skin conductance response [SCR]; Dickinson, 2015). Critically, Pavlovian conditioning is a *passive* learning process, whereby the CS and US are presented together irrespective of a participant's behaviour. If the formation of a Pavlovian association is successful, participants will demonstrate a CR to the CS after it has been paired one or more

times with the US, even in the absence of the US. Pavlovian conditioning paradigms typically also include a neutral stimulus that is unpaired with the US (CS-; e.g., an alternative coloured shape) as a control stimulus so that responses to these stimuli can be compared to assess the degree to which a specific Pavlovian association between the CS and US has been formed.

Several measures of Pavlovian conditioning can be derived from experimental Pavlovian conditioning tasks. Two measures commonly derived from Pavlovian conditioning tasks include the *acquisition* of a CR (learning the association between the CS and the US) and the maintenance or *extinction* of a CR once the CS no longer predicts the delivery of the US. Measuring the acquisition (or learning) of a Pavlovian association can be used to assess how susceptible an individual is to forming passive emotional associations between neutral stimuli or contexts and significant events (Dickinson, 2015), whereas measuring the rate of extinction of a CR helps to indicate how resistant an individual is to the diminishing or elimination of associations between a CS and a US once the CS is no longer predictive of the US. In other words, measuring extinction helps to assess an individual's ability to update the emotional value of a neutral stimulus once it no longer signals imminent threat or reward. In the following section, we review previous Pavlovian conditioning studies of currently depressed individuals with MDD.

Studies Examining Pavlovian Conditioning in MDD

We identified five previous studies that have examined Pavlovian conditioning in individuals who met diagnostic criteria for a current Major Depressive Episode (MDE; Greer, Trivedi, & Thompson, 2005; Jovanovic et al., 2010; Kuhn et al., 2014; Nissen et al., 2010; Otto et al., 2014). The following is an overview of these studies, including their findings and

248 comparative methodologies. A summary of the key characteristics of these studies are presented
249 in Table 1.

250 **Table 1**251 *Studies Examining Pavlovian Conditioning in MDD*

Authors	Sample characteristics (M [SD]) ^a			Stimuli	Dependent variable(s)	Results	Interpretation
Kuhn et al. (2014)	Pop'n	MDD	CTRL	US: Mild electric shock to right lower arm	Differential fear conditioning using fear-potentiated startle (eye-blink)	Acquisition: No difference between groups.	Acquisition: Normal differential fear conditioning in MDD.
	Age	37	40	immediately after 50% of CS presentations.	measured via electromyogram (EMG).	Extinction: No difference in startle response between two CSs for the MDD group, whereas difference remained for CTRL group ($d = 0.46$; medium effect).	Extinction: Enhanced in MDD. (Lower differentiation of CS vs. CS-during extinction.)
	%fem.	38.4 (12.4)	37.3 (10.5)				
	BDI	46%	48%				
		29.2 (10.5) [Severe]	1.9 (2.9) [Minimal]				
	HAM-D	28.6 (5.7) [Severe]	NA				
	BAI	13.8 (7.2) [Mild]	1.2 (2.0) [Minimal]	CS: Geometric shapes.	Conditioning measure: CS vs. CS-differential average startle response amplitude during target window of 40-90 ms post-stimulus across six trials each. Same measure used for acquisition and extinction phases.		
Nissen et al. (2010)	Pop'n	MDD	CTRL	US: Mild electric shock	Skin conductance response (SCR).	Acquisition: Stronger responses in MDD group to the CS than the CS- (greater differential conditioning) but not in CTRL, $d = 0.62$; medium effect).	Acquisition: Enhanced differential fear conditioning in MDD.
	n	23	35	immediately after 100% of CS presentations.	Conditioning measures: Averaged SCRs to the CS- subtracted from the averaged SCRs to the CS.		Extinction: NA
	Age	39.3 (9.8)	37.7 (9.0)				
	%fem.	65%	74%				
	BDI	26.3 (8.7) [Moderate]	1.4 (2.2) [Minimal]				
	BAI	17.8 (9.1) [Moderate]	1.7 (2.6) [Minimal]	CS: Geometric shapes (two for			

				CS and two for CS-).		Extinction: NA	
Otto et al. (2014)	Pop'n	MDD	CTRL	US: Mild electric shock	SCR.	Acquisition: Greater differential conditioning in the CTRL compared to the MDD group ($d = 0.72$; large effect).	Acquisition: Poorer differential conditioning in MDD.
	Age	41.2 (10.6)	29.6 (10.3)	to fingers immediately after 100% of CS	Conditioning measures: Simple conditioning. Averaged SCRs for the CS trials independent of the SCRs to CS- trials. Differential conditioning. Averaged SCRs to the CS- subtracted from the averaged SCRs to the CS.		
	%fem.	31%	49%				
	Dep.	NA	NA				
	Sx						
	Anx.	NA	NA	presentations during Day 1 training phase and no US on Day 2 testing phase.		Extinction: NA	Extinction: NA
Jovanovic et al. (2010)	Pop'n	MDD	CTRL	US: 250 ms air blast to the	Fear-potentiated startle (eye blink).	Acquisition: Both MDD and CTRL groups demonstrated higher percent startle potentiation to CS vs CS- and to CS vs. inhibitory stimulus. (No differences between MDD and CTRL groups.)	Acquisition: Normal differential fear conditioning in MDD.
	Age	40.4 (12.2)	45.7 (12.9)	larynx during the last 250 ms of 100% of CS presentations.	Conditioning measures: Averaged percent startle potentiation (100*(startle magnitude during CS trials-NA startle)/(NA startle)) for CS, CS-, and inhibitory stimulus (CS and CS- presented together).		
	%fem.	73%	59%				
	BDI	21.7 (6.4) [Moderate]	6.9 (5.19) [Minimal]				
	Anx.	NA	NA				
	Sx			CS: Geometric shapes.		Extinction: NA	Extinction: NA

Greer et al. (2005)	Pop'n Age %fem. HAM-D Anx. Sx	MDD 20 29.8 (7.3) 70% 23.2 (4.9) [Moderate] NA	CTRL 18 27.6 (6.3) 78% 3.9 (1.8) [No dep.] NA	US: Air puff applied to the left cornea. CS: Auditory tones.	Fear-potentiated startle (eye blink). Conditioning measures: Delay 500 trials: US delivered during last 150 ms of a 650 ms presentation of the CS. Trace 500 trials: 100 ms of a CS, 500 ms inter-stimulus trace interval, and then a 150 ms US. Trace 1000 trials: 100 ms of CS, 1000 ms inter-stimulus trace interval, and then a 150 ms US.	Acquisition: MDD group generated significantly fewer CRs than the CTRL group during the Delay 500 task ($d = 0.97$; large effect) and during a task in which the US was presented shortly after the CS ($d = 0.75$; large effect). MDD group generated significantly fewer CRs than the CTRL group on the first ($d = 0.73$; large effect) and second ($d = 0.94$; large effect) tasks completed (the tasks were counterbalanced). CTRL group showed increasingly more CRs produced throughout the tasks, whereas the MDD group showed no change from baseline CR production ($d = 0.81$; large effect).	Acquisition: Blunted in MDD. Extinction: NA
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Extinction: NA

252 *Note.* ^aExcept otherwise noted. CTRL = healthy control participants; MDD = Major Depressive Disorder; BAI = Beck Anxiety
253 Inventory; BDI = Beck Depression Inventory; HAM-D = Hamilton Depression Rating Scale; Anx. Sx = anxiety symptom scale; Dep.
254 Sx = depressive symptom scale; CS = Conditioned Stimulus; CR = Conditioned Response; US = Unconditioned Stimulus; SCR =
255 Skin Conductance Response; NA = Not applicable.

Characteristics of Previous Studies Examining Pavlovian Conditioning in MDD

All studies examining Pavlovian conditioning in MDD focused on aversive conditioning (Greer et al., 2005; Jovanovic et al., 2010; Kuhn et al., 2014; Nissen et al., 2010; Otto et al., 2014). Based on the four studies in which participants completed a depressive symptom scale, MDD groups had, on average, either moderate (Greer et al., 2005; Jovanovic et al., 2010; Nissen et al., 2010) or severe (Kuhn et al., 2014) depressive symptoms. There was significant heterogeneity between studies in terms of sample size, conditioning phase examined (i.e., acquisition vs. extinction), the type of US and CS used, the schedule and latency of US delivery, and the CR measured. The number of MDD participants included in these studies ranged from 13 (Otto et al., 2014) to 37 (Kuhn et al., 2014). All studies examined the acquisition of aversive Pavlovian associations and one compared patterns of extinction between MDD and control participants (Kuhn et al., 2014). Of these five previous studies, three employed mild shock as the US (Kuhn et al., 2014; Nissen et al., 2010; Otto et al., 2014) and two used air blasts (Greer et al., 2005; Jovanovic et al., 2010). Four studies used geometric shapes as the CS/CS- (Jovanovic et al., 2010; Kuhn et al., 2014; Nissen et al., 2010; Otto et al., 2014) and one study used auditory tones (Greer et al., 2005). Nissen et al. (2010) and Otto et al. (2014) delivered the US (mild electric shock) immediately after 100% of CS presentations, whereas Kuhn et al. (2014) delivered the US (mild electric shock) immediately after 50% of CS presentations. Jovanovic et al. (2010) delivered a 250 ms air blast to the larynx during the last 250 ms of 100% of CS presentations and Greer et al. (2005) used different delivery schedules across trial blocks, including one block in which air blasts were delivered during the last 150 ms of a 650 ms presentation of the CS; another block in which the CS was presented for 100 ms, followed by a 500 ms inter-stimulus trace interval, and then a 150 ms air blast was delivered; and another in

which the CS was presented for 100 ms, followed by a 1000 ms inter-stimulus trace interval, and then the delivery of a 150 ms air blast. In terms of CRs measured, three studies measured fear potentiated startle and two studies measured SCR. The considerable methodological heterogeneity between studies makes the interpretation of results across studies difficult; however, the following section provides a synthesis of study findings in the context of these methodological differences.

Findings from Previous Studies Examining Pavlovian Conditioning in MDD

Regarding overall findings from these five previous studies of Pavlovian conditioning in MDD, two showed that the acquisition of Pavlovian associations between neutral and aversive cues was blunted in MDD (Greer et al., 2005; Otto et al., 2014), one showed that acquisition was enhanced (Nissen et al., 2010), and in two studies, no differences in the acquisition of aversive Pavlovian associations were found in individuals with MDD compared to healthy control participants (Jovanovic et al., 2010; Kuhn et al., 2014). In the single study that examined the extinction of aversive Pavlovian associations conducted by Kuhn et al. (2014), participants with MDD showed enhanced extinction of the association between the CS and CS- relative to control participants whose averaged fear potentiated startle to the CS remained significantly higher than their averaged fear potentiated startle to the CS- during extinction. Thus, based on studies conducted to date, the role of aversive Pavlovian conditioning in MDD is unclear. More reliable findings on the acquisition of aversive Pavlovian associations as well as more studies exploring the extinction of these associations are needed.

When these studies are examined according to phase of Pavlovian conditioning measured, the CS/CS- and US used, the schedule and latency of US delivery, and the CR measured, it remains unclear whether individuals with MDD exhibit altered acquisition and/or

extinction of aversive Pavlovian associations. Studies that used mild electric shock as a US and geometric shapes as the CS/CS- showed enhanced (Nissen et al., 2010), normal (Kuhn et al., 2014), and blunted (Otto et al., 2014) acquisition of aversive Pavlovian associations. Studies that employed air blasts as the US (Greer et al., 2005; Jovanovic et al., 2010) also reported inconsistent acquisition results, including normal (Jovanovic et al., 2010) and blunted (Greer et al., 2005) acquisition, although different CSs (geometric shapes versus auditory tones) were employed. Studies in which the US was presented immediately following the CS in 100% of CS trials showed enhanced (Nissen et al., 2010) and blunted (Otto et al., 2014) acquisition. For studies that used a US delivered during the presentation of the CS, acquisition of an aversive Pavlovian association was normal (Jovanovic et al., 2010) or blunted (Greer et al., 2005). Greer et al. (2005) examined aversive Pavlovian conditioning in MDD using tasks that entailed delivery of the US after 500 or 1000 ms inter-trial interval between the presentation of the CR and the presentation of the US. They found that participants with MDD showed significantly blunted acquisition during the task with a 500 ms inter-trial interval and marginally significant blunting during acquisition on the task with a 1000 ms inter-trial interval (Greer et al., 2005). Examining the findings according to the CR measured also provides a mixed picture. The three studies that employed eye blinks as the CR found that acquisition was either normal (Jovanovic et al., 2010; Kuhn et al., 2014) or blunted (Greer et al., 2005).

In the single study that included a measure of extinction (Kuhn et al., 2014), it was found that during the extinction period individuals with MDD showed complete extinction learning as indicated by undifferentiated startle responses for the CS and the CS- whereas control participants maintained a differential fear potentiated startle between the CS and CS- throughout the extinction phase. This suggests that associations formed between a neutral cue and an

aversive event degrades faster and to a greater degree for depressed than nondepressed individuals once the neutral cue no longer predicts the aversive event (Kuhn et al., 2014). Based on this single study, conclusions regarding the nature of extinction in MDD cannot be drawn. However, it is noteworthy that, compared to the other studies reviewed here, the sample was relatively large (37 for the MDD group and 40 for the control group) and comorbid anxiety symptoms in the MDD group were comparatively low (in the mild range).

Limitations of Previous Studies Examining Pavlovian Conditioning in MDD

Studies of Pavlovian conditioning in MDD have employed heterogeneous methods with small sample sizes and produced inconsistent findings (Greer et al., 2005; Jovanovic et al., 2010; Kuhn et al., 2014; Nissen et al., 2010; Otto et al., 2014). All of these studies examined the acquisition of aversive Pavlovian associations in MDD, one examined the extinction of these associations, and none examined appetitive Pavlovian conditioning. The absence of appetitive Pavlovian conditioning studies in MDD is surprising given that abnormal processing of reward in MDD is well-established (Bylsma, Morris, & Rottenberg, 2008). Thus, perhaps most notably, future studies are needed to examine appetitive Pavlovian conditioning in MDD. Several instrumental conditioning studies included in this review as well as studies of reward sensitivity indicate that individuals with MDD show altered processing of appetitive stimuli; therefore, it appears reasonable to expect that appetitive Pavlovian conditioning could be an additional marker for MDD (Bylsma et al., 2008; Henriques & Davidson, 2000; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008; Vrieze et al., 2013). Furthermore, the heterogeneity across studies may be attributable in part to the diverse presentations of mood and related psychological symptoms (e.g., anxiety) across individuals with MDD, and a dimensional approach to

understanding Pavlovian conditioning among individuals with clinically significant depressive symptoms may be warranted.

Preliminary Summary: Pavlovian Conditioning in MDD

In sum, of the five previous studies identified that examined Pavlovian conditioning in MDD, all of which focused on aversive (as opposed to appetitive) conditioning, most included small samples, and findings for the acquisition and extinction of aversive Pavlovian associations were inconsistent. More studies are needed to clarify the nature of aversive and, most notably, appetitive Pavlovian conditioning in individuals with MDD. In the next section, we review instrumental conditioning studies in MDD, followed by a review of studies examining PIT in MDD. To bring these findings together, we then propose our framework used to characterize the dynamics of emotional learning in MDD.

Instrumental Conditioning

Instrumental conditioning occurs when an organism is more or less likely to engage in a particular behaviour depending on the consequence(s) of that behaviour (i.e., reinforcement or punishment; Dickinson, 2015). Reinforcement entails the presentation of a rewarding outcome (*positive* reinforcement) or the removal of an aversive outcome (*negative* reinforcement) as a consequence of behaviour, in turn making the behaviour more likely in the future. Punishment involves the presentation of an aversive consequence (*positive* punishment) or the removal of a rewarding consequence (*negative* punishment) as a result of behaviour. Subsequently, an organism becomes less likely to engage in that behaviour. In animal studies, prototypical examples of instrumental conditioning paradigms include scenarios in which animals learn to press a lever to receive food or escape a chamber to avoid shock (Fanselow & Poulos, 2005). In human studies, instrumental conditioning is typically operationalized using tasks that require

participants to respond a certain way to receive monetary reward or avoid monetary loss. Note that most instrumental conditioning paradigms studies involve decision-making (making a choice between different options). This makes it difficult to differentiate associative learning processes between action and outcome involved in instrumental conditioning from decision-making or choosing between better and worse options. Most paradigms used to assess instrumental conditioning can be described as probabilistic reinforcement learning tasks. These tasks are often designed as discrimination or gambling tasks, as described below.

Probabilistic reinforcement learning discrimination tasks are typically memory or perception tasks that require participants to make correct judgments about stimuli according to some criteria, such as whether a word appeared on a previous word list (in a recognition memory task; Henriques & Davidson, 2000) or which of two stimuli was presented on the screen after a very brief presentation (in a stimulus discrimination task; Pizzagalli et al., 2008). In these tasks, feedback is typically provided regarding correct or incorrect judgments and may be accompanied by varying magnitudes and frequencies of rewards or punishments (Lynn & Barrett, 2014). The basic assumption that informs the interpretation of participants' performance on these tasks is that their responses will be biased towards choices that maximize the size and frequency of rewards and minimize the size and frequency of non-reward or punishments (Frank & Claus, 2006).

Probabilistic reinforcement learning tasks may also be designed as gambling paradigms involving the presentation of a set of cards or options from which participants must make choices based on the different likelihood of receiving a reward and/or avoiding punishment (Schönberg, Daw, Joel, & O'Doherty, 2007). Learning typically occurs through trial-and-error, whereby participants learn to make choices that increase the likelihood of reward and decrease the

likelihood of punishment. Probabilistic reinforcement learning tasks may also measure reversal learning by incorporating ‘rule reversals’ that require participants to detect when advantageous and disadvantageous response probabilities are reversed and to adjust their strategy accordingly (i.e., select the newly advantageous option and avoid the newly disadvantageous option). In the following sections, we review the methodological characteristics, results, and potential limitations of previous studies employing probabilistic reinforcement learning tasks in MDD.

Studies Examining Instrumental Conditioning in MDD

We identified ten studies that have examined instrumental conditioning (and decision-making) in individuals diagnosed with MDD (Cella, Dymond, & Cooper, 2010; Chase et al., 2010; Henriques & Davidson, 2000; Mukherjee et al., 2020; Murphy, Michael, Robbins, & Sahakian, 2003; Must et al., 2006; Pizzagalli et al., 2008; Steele, Kumar, & Ebmeier, 2007; Taylor Tavares et al., 2008; Vrieze et al., 2013). Study characteristics and main findings are presented in Table 2.

406 **Table 2**407 *Studies Examining Instrumental Conditioning in MDD*

Authors	Sample characteristics (<i>M</i> [SD]) ^a			Task	Dependent variable(s)	Results	Interpretation
Chase et al. (2010)	Pop'n	MDD	CTRL	Probabilistic selection task.	Test phase avoid B versus select A performance:	Test phase avoid B versus select A performance:	MDD group did not exhibit statistically significant differences in the ability to adaptively alter their behaviour based on positive and negative feedback compared to the CTRL group.
		23	23				
	Age	46.2 (2.3)	47.4 (2.1)	<i>Training phase.</i>			
	% fem.	44%	48%	Participants	Percent of correct choices for A	No difference.	
	BDI	26.8 (1.8)	3.2 (0.5)	selected one letter from one of three stimulus pairs (AB, CD, EF) that were presented in random order. Each letter had a varying probability of being correct (A, 80%; B, 20%; C, 70%; D, 60%; E, 60%; F, 40%). Feedback ('correct' or 'incorrect') was provided.	(select) and B (do not select).	Percentage correct during task acquisition:	
	BAI	32.4 (2.4)	5.61 (0.9)		Percentage correct during task acquisition:	Learning rate:	However, MDD participants showed a 'blunting' effect evidenced by lower trial-by-trial adjustments following
		[Moderate]	[Minimal]		Percent of correct choices for all stimuli during the training phase.	MDD participants had numerically lower parameter values for both positive and negative learning rates (<i>d</i> = 0.64).	
		[Severe]	[Minimal]		Learning rate:	Reaction time:	
				<i>Test phase.</i>	Trial-by-trial adjustment of responses after positive and negative feedback, i.e., the ability of participants to select stimulus A and avoid stimulus B.	MDD participants responded slower on average (<i>d</i> = 0.72).	
				Participants completed the same procedure without feedback.			

				Reinforcement: Positive and negative feedback.	Reaction time: Average speed of responding across trials.		positive and negative feedback.
Cella et al. (2010)	Pop'n Age % fem. BDI Anx. Sx	MDD 19 35.8 (10.1) 42% 30.1 (7.2) [Severe] NA	CTRL 20 35.1 (9.3) 50% 0.9 (1.1) [Minimal] NA	Contingency shifting variant of the Iowa gambling task: Participants select cards from four concurrently available decks. Selections from each deck could result in a win or a loss. <i>Phase 1.</i> Participants always won £100 if they selected a card from the 'disadvantageous' decks (i.e. A and B) and always won £50 if they selected a card from the 'advantageous' decks (i.e., C and D). Each deck was also associated with a probability of a simultaneous loss. The amount of	Overall performance: Number of disadvantageous selections subtracted from number of advantageous selections for each block. Deck preferences: Ability of the participant to adapt to a change in which of four decks was advantageous (i.e., adapt to the change in which decks were advantageous to continue to win).	Overall performance: MDD participants made significantly more disadvantageous selections relative to advantageous selections in the latter blocks in Phase 1 ($d = 1.16$) and Phase 2 ($d = 1.11$) blocks compared to CTRL participants. Deck preferences: MDD participants performed significantly worse than CTRL participants after the advantageous and disadvantageous decks were	MDD group did not learn to select from advantageous decks or to alter their response strategy after a change in reward/loss contingencies.

losses varied between £150 and £350 for deck A (in 5/10 selections); £1250 for deck B (in 1/10 selections); between £25 and £75 for deck C (in 5/10 selections); and £250 for deck D (in 5/10 selections).

switched ($d = 0.97$).

Phase 2. Decks which were advantageous in Phase 1 become disadvantageous and vice versa. Participant had to update their responses accordingly to maximize wins.

Reinforcement:
Monetary wins and losses.

Pizzagalli et al. (2008)	Pop'n Age % fem.	MDD 23 43.7 (9.6) 44%	CTRL 25 38.4 (10.8) 44%	Discrimination paradigm: Participants were asked to indicate	Response bias: The tendency to indicate that the stimulus paired	Response bias: MDD subjects showed a significantly lower	Participants with MDD showed significantly
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BDI	32.1 (8.7)	3.4 (3.6)	whether a	with the more	overall response	reduced reward
	[Severe]	[Minimal]	schematic face with	frequent reward	bias ($d = 0.70$).	responsiveness,
Anx. Sx	NA	NA	a long or short	was presented,		i.e., an
			mouth was	i.e., the extent to	Discriminability:	impaired
			presented after a	which behaviour	No difference.	tendency to
			100 ms	is modulated by		modulate
			presentation.	reinforcement	Reaction time:	behaviour as a
			Feedback was	history.	MDD participants	function of
			provided after each		responded more	prior
			selection with or	Discriminability:	slowly than CTRL	reinforcements.
			without a monetary	The ability to	participants ($d =$	
			reward for the	perceptually	0.81).	
			correct response.	distinguish		
			Correct responses	between the two		
			for one of the two	stimuli, i.e., a		
			stimuli was	proxy of task		
			financially	difficulty.		
			rewarded three			
			times more	Reaction time:		
			frequently than the	Time to select one		
			other stimulus to	of the two stimuli.		
			produce a response			
			bias for the more			
			frequently			
			rewarded stimulus.			
			Reinforcement:			
			Monetary wins			
			only.			

Steele et al. (2007)	Pop'n	MDD	CTRL	Gambling paradigm: Pairs of playing cards were presented and participants were asked to indicate the 'correct' card. Feedback was provided indicating whether they won or lost. The feedback sequence was fixed and unrelated to the presented cards. This ensured all subjects received identical feedback irrespective of ability. Since there was no contingency to learn, only 'feedback' and not 'response' events occurred. For each subject, two behavioural values were derived (<i>bw</i> and <i>bl</i>), which reflected change in RT in response to 'win' ('correct')	Reaction time change (win): Average change in observed reaction time as a consequence of 'win' feedback.	Reaction time change (win): Reaction time after wins became faster for the CTRL relative to the MDD group ($d = 0.61$).	MDD group did not alter their response strategy following reward and punishment relative to the CTRL group.
	n	15	14				
	Age	45.9 (10.7)	43.0 (13.3)				
	% fem.	73%	50%				
	BDI	36.9 (13.3)	1.1 (1.9)				
		[Severe]	[Minimal]				
	Anx. Sx	NA	NA		Reaction time change (loss): Change in observed reaction time as a consequence of 'lose' feedback.	Reaction time change (loss): Reaction time after losses became slower for the CTRL relative to the MDD group ($d = 0.65$).	

				and ‘lose’ (‘error’) feedback, respectively. Reinforcement: Monetary wins and losses.			
Vrieze et al. (2013)	Pop’n n Age % fem. HAM-D Anx. Sx	MDD 79 45.0 (11.9) 61% 16.9 (4.9) [Moderate] NA	CTRL 63 44.5 (11.6) 60% NA NA	Discrimination paradigm: Identical to the task employed by Pizzagalli et al. (2008) (see description above). Reinforcement: Monetary wins only, as in Pizzagalli et al.’s (2008) study.	Response bias: The tendency to indicate that the stimulus paired with the more frequent reward was presented, i.e., the extent to which behaviour is modulated by reinforcement history. Discriminability: The ability to perceptually distinguish between the two stimuli, i.e., a proxy of task difficulty.	Response bias: Reduced reward learning ability in MDD compared to CTRL group ($d = 0.41$) Discriminability: No difference between groups.	MDD group did not alter their behaviour to improve accuracy for more frequently rewarded stimulus compared to the CTRL group.
Murphy et al. (2003)	Pop’n n Age % fem. HAM-D	MDD 27 38.9 (9.7) 52% 23.6 (4.2) [Severe]	CTRL 23 39.1 (10.8) 52% NA	Probability reversal task: In the first stage of the task (40 trials), participants were required to learn to	Pass rate: Eight consecutive responses to the ‘correct’ or maximally rewarded stimulus	Pass rate: No difference between groups in either stage of the task.	MDD group less likely than CTRL group to maintain response set following

MADRS	34.3 (5.4) [Severe]	NA	discriminate the most highly rewarded stimulus of two stimuli based on feedback ('correct' or 'wrong'). The first stimulus selected by a participant received 'correct' feedback for 80% of responses and 'wrong' feedback for 20% of cases. The stimulus that was not selected on the first trial receives 'wrong' feedback for 80% of cases and 'correct' feedback for 20% of cases. In the second phase of the task (40 trials), the reinforcement criteria were reversed.	achieved (pass) or not achieved (fail) in each stage.	Errors to criterion: No difference between groups in either stage of the task.	intermittent misleading negative feedback.
BDI	NA	3.6 (3.1) [Minimal]		Errors to criterion: Number of errors prior to achieving 8 consecutive responses to the 'correct' stimulus in each stage.	Latency to respond: MDD group showed marginally slower response times during phases 1 and 2 of the task compared to CTRL group.	MDD group more likely to switch their response to an 'incorrect' stimulus following probabilistic negative reinforcement for a 'correct' response.
BAI	26.0 (14.3) [Severe]	3.7 (5.9) [Minimal]		Latency to respond: Mean response time across trials for each stage of the task.	Maintenance of failure scores: MDD group showed significantly higher scores compared to CTRL group in stage 1 ($d = 0.71$) and stage 2 ($d = 0.60$).	
				Maintenance failure scores: Number of errors (i.e., responses to the 'incorrect' stimulus) made following attainment of criterion divided by the total number of trials that remained following the	Probability matching score: MDD group showed	

attainment of criterion.	significantly greater matching score than the CTRL group ($d = 0.68$).
Probability matching score: The number of trials on which a participant chose the 'incorrect' stimulus immediately following a negatively reinforced 'correct' response was divided by the total number of negatively reinforced 'correct' responses.	Perseveration errors: No difference between groups.
Perseveration errors: The number of consecutive responses to the 'incorrect' stimulus immediately following reversal of the	

					reinforcement contingencies.		
Henriques and Davidson (2000)	Pop'n	M38.9 (DD)	CTRL	Discrimination paradigm:	Response bias:	Response bias:	MDD group
	n	18	15	<i>Phase 1.</i>	False alarm rate divided by 1	The CTRL group showed	showed lower
	Age	33.4 (9.2)	32.7 (11.6)	Participants were presented with 24 target words.	minus the difference of hit rate and false alarm rate. Larger values indicate a more liberal response bias.	differences in response bias between the neutral and reward conditions that were larger than MDD those of the CTRL group ($d = 0.83$).	approach-related
	% fem.	61%	60%				behaviour in
	BDI	26.4 (5.8) [Moderate]	1.9 (2.6) [Minimal]	<i>Phase 2.</i> Colour detection (i.e., distractor) task in which participants were asked to indicate whether two consecutively presented circles were the same colour.	Sensitivity: Difference between hit rate and false alarm rate. Larger values reflect a greater sensitivity in discriminating between target and nontarget stimuli.		response to
	Anx. Sx	NA	NA	<i>Phase 3.</i> Participants were presented with target and distractor words and asked to indicate whether the words presented were from the target list. Feedback for correct and incorrect responses was provided alone		Sensitivity: CTRL participants were more accurate than MDD participants at discriminating between target and nontarget stimuli ($d = 0.86$).	reward than the CTRL group.

or paired with
monetary reward or
punishment,
respectively.

Reinforcement:
Monetary wins and
losses.

Mukherjee et al. (2020)	Pop'n Age % fem. BDI Anx. Sx	MDD 64 40.5 (13.5) 58% 30.0 (10.5) NA	CTRL 64 38.5 (11.7) 48% 2.9 (4.3) NA	Probabilistic reversal learning tasks: In separate reward and punishment tasks, participants pressed a keyboard button to select one of two fractal stimuli followed by a reward (picture of a quarter indicating \$0.25 gain) or punishment (a quarter with a red cross overlaid indicating \$0.25 loss) or no reward/punishment (a red dot). One of the two fractal stimuli was rewarded or punished 70% of the time and the	Proportion of rich choices: Choices of the fractal with the higher probability of more positive outcomes (i.e., reward or no punishment). Proportion of win-stay and lose-shift choices: Repetitions of the same choice when a selection resulted in reward/no punishment and switching fractal choices when a selection resulted in punishment/no reward.	Proportion of rich choices: MDD participants made significantly fewer rich choices in both the reward ($d = 0.38$) and punishment ($d = 0.48$) conditions. After reversal, the MDD group appeared to learn the contingencies more slowly in both the reward and punishment conditions. Proportion of win-stay and lose-shift choices: The proportion of win-stay choices was significantly lower for the	MDD participants showed lower sensitivity to learning from positive outcomes. MDD participants showed poorer reward and punishment reversal learning than CTRL participants. MDD participants made significantly fewer rich choices in both the reward and
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				<p>other 30% of the time. Participants were not informed of the reward/punishment structure but told that one stimulus would be rewarded/punished more often than the other. Unsignalled reversals of this association occurred every 30 trials (out of 90 total).</p> <p>Reinforcement: Monetary wins and losses.</p>	<p>Learning rate: How much participants incorporated trial-by-trial feedback</p> <p>Value sensitivity: How sensitive participants were to value differences between the different fractal trials.</p>	<p>MDD group in both the reward ($d = 0.56$) and punishment ($d = 0.61$) conditions. The proportion of lose-shift responses did not differ between groups in the reward or punishment conditions.</p> <p>Learning rate: MDD group had lower fractal learning rates in reward and punishment conditions.</p> <p>Value sensitivity: Significant difference in punishment sensitivity and trending difference in reward sensitivity.</p>	<p>punishment conditions.</p>
Taylor Tavares et al. (2008)	<p>Pop'n n Age</p>	<p>MDD 13 38.3 (2.3)</p>	<p>CTRL 15 33.9 (2.3)</p>	<p>Probabilistic reversal learning task: Participants</p>	<p>Rate of errors per rule reversal: Total reversal</p>	<p>Rate of errors per rule reversal: No differences.</p>	<p>MDD group was more likely to change</p>

% fem.	77%	73%	select one of two	errors divided by		choice
MADRS	23.0 (1.7)	0.3 (0.3)	patterns presented	the total rule	Rate of	strategies
	[Mild to	[Symptoms	on a screen to learn	reversals.	behavioural	following
	moderate]	absent]	which selections		switches	negative
HAM-A	13.0 (1.6)	0.2 (0.2)	were correct based	Rate of	following	feedback than
			on trial-and-error.	behavioural	misleading	the CTRL
			Rules reversed	switches	negative	group.
			every 10-15 correct	following	feedback: Higher	
			responses.	misleading	probabilistic	
			Participants were	negative	switch rate in the	
			instructed to always	feedback:	MDD group ($d =$	
			choose the pattern	Number of	0.84).	
			that was correct	probabilistic		
			more often than the	switches divided	Mean reaction	
			other pattern.	by the total	time: No	
			Feedback (green	number of trials	differences.	
			smiley face or red	where misleading		
			sad face) was	negative feedback	Mean number of	
			provided after each	was presented.	correct responses	
			selection.		per run: No	
				Mean reaction	differences.	
			Reinforcement:	time: Average		
			Positive and	reaction time	Spontaneous	
			negative feedback.	across all trials.	errors: No	
					differences.	
				Mean number of		
				correct responses		
				per run: Average		
				number of correct		
				responses across		
				blocks.		

					Spontaneous errors: Mean number of spontaneous errors that could not be attributed to misleading feedback or rule reversal.		
Must et al. (2006)	Pop'n	MDD	CTRL	Iowa Gambling Task: Participants selected cards from four concurrently available decks. Selections from each deck resulted in a win or a loss.	Overall performance: Number of disadvantageous selections subtracted from number of advantageous selections for each block.	Overall performance: Patients with MDD made fewer advantageous decisions than the controls in the ABCD version ($d = 0.75$).	MDD participants failed to acquire a response bias to the more advantageous decks.
	n	30	20				
	Age	43.8 (9.6)	42.5 (10.7)				
	% fem.	60%	55%				
	HAM-D	15.0 (5.4) [Mild]	NA				
	HAM-A	8.2 (4.2) [Mild]	NA	Participants always won \$100 if they selected a card from the 'disadvantageous' decks (i.e. A and B) and always won \$50 if they selected a card from the 'advantageous' decks (i.e. C and D). Each deck was also associated with a probability of a simultaneous loss.			

The amount of losses varied between \$150 and \$350 for deck A (in 5/10 selections); \$1250 for deck B (in 1/10 selections); between \$25 and \$75 for deck C (in 5/10 selections); and \$250 for deck D (in 5/10 selections). A similar version of the task was completed subsequently that used decks labeled EFGH.

Reinforcement:
Monetary rewards and losses.

408 *Note.* ^aExcept otherwise noted. CTRL = healthy control participants; MDD = Major Depressive Disorder group; BAI = Beck Anxiety
 409 Inventory; BDI = Beck Depression Inventory; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating
 410 Scale; Anx. Sx = anxiety symptom scale; Dep. Sx = depressive symptom scale; NA = Not applicable.

Characteristics of Studies Examining Instrumental Conditioning in MDD

The number of MDD participants included in the identified studies investigating instrumental conditioning (and decision-making) in MDD ranged from 15 (Steele et al., 2007) to 79 (Vrieze et al., 2013) and their depressive symptom severity varied from mild (Must et al., 2006; Taylor Tavares et al., 2008) to moderate (Henriques & Davidson, 2000; Vrieze et al., 2013) to severe (Cella et al., 2010; Chase et al., 2010; Murphy et al., 2003; Pizzagalli et al., 2008; Steele et al., 2007) on average. In studies that reported anxiety symptoms, participants with MDD had anxiety symptom levels that were either mild (Must et al., 2006) or severe (Chase et al., 2010; Murphy et al., 2003) on average. Mean ages ranged from 33 to 46 years and the percent of female participants ranged from 42-73%.

Most of the reviewed studies employed tasks involving monetary reward and/or loss, including discrimination tasks involving probabilistic reward learning (Henriques & Davidson, 2000; Mukherjee et al., 2020; Pizzagalli et al., 2008; Taylor Tavares et al., 2008; Vrieze et al., 2013) or gambling paradigms (Cella et al., 2010; Must et al., 2006; Steele et al., 2007). In three studies, instrumental conditioning tasks that employed only ‘correct’ or ‘incorrect’ feedback (i.e., no monetary gain or loss) were used (Chase et al., 2010; Murphy et al., 2003; Taylor Tavares et al., 2008). The most common measures derived from the probabilistic reinforcement learning tasks employed in these studies were response bias/accuracy (more frequently selecting stimuli that were previously associated with greater reward/less punishment) and reaction time (e.g., changes in reaction time following wins versus losses). Four studies examined reinforcement reversal learning (Cella et al., 2010; Mukherjee et al., 2020; Murphy et al., 2003; Taylor Tavares et al., 2008).

Findings from Studies Examining Instrumental Conditioning in MDD

A consensus across most studies was that individuals with MDD did not use reinforcement to optimally inform their response strategies (Cella et al., 2010; Henriques & Davidson, 2000; Mukherjee et al., 2020; Must et al., 2006; Pizzagalli et al., 2008; Steele et al., 2007; Vrieze et al., 2013). MDD participants were also found in two studies to be more likely to change their response strategy following misleading negative feedback, e.g., following ‘incorrect’ feedback for a stimulus with a more advantageous reinforcement history overall (Murphy et al., 2003; Tavares et al., 2008). Another study reviewed here showed that while no negative bias in responding was observed, there was evidence for reduced trial by trial adjustment in participants with MDD compared to control participants during the training phase of their probabilistic reinforcement learning task (Chase et al., 2010).

In all of the studies that employed discrimination tasks, individuals with MDD were less likely to alter their behaviour in favour of positively reinforced (i.e., monetarily rewarded) choices (Henriques & Davidson, 2000; Mukherjee et al., 2020; Pizzagalli et al., 2008; Vrieze et al., 2013). Henriques and Davidson (2000) and Mukherjee et al. (2020) also examined how behaviour changed as a function of prior punishment (i.e., money lost). Henriques and Davidson (2000) did not find any difference between MDD and control participants in their tendency to alter decisions about stimuli that were previously associated with punishment (Henriques & Davidson, 2000). Mukherjee et al. (2020) found that the MDD group in their study demonstrated poorer reversal learning in the punishment condition and were less likely to choose more frequently unpunished choices than the control group. In two other studies that examined reversal learning, Cella et al. (2010) observed worse performance among the MDD group following switches between the advantageous and disadvantageous decks on the Iowa gambling task compared to control participants but Tavares et al. (2008) did not find a difference in the

rate of errors per rule reversal between participants in the MDD group versus the control group. In the studies that employed a gambling task, it was generally reported that individuals with MDD were less likely to make decisions that maximized wins and minimized losses according to prior reinforcement (Cella et al., 2010; Must et al., 2006; Steele et al., 2007).

Dependent variables commonly employed in these studies were response bias (i.e., the extent to which behaviour is modulated by reinforcement history; Henriques & Davidson, 2000; Mukherjee et al., 2020; Pizzagalli et al., 2008; Vrieze et al., 2013), overall tendency to make advantageous selections during a gambling task (Cella et al., 2010; Must et al., 2006; Steele et al., 2007), and patterns of reaction time following task feedback (Chase et al., 2010; Pizzagalli et al., 2008; Steele et al., 2007; Taylor Tavares et al., 2008). Studies that used response bias as an index of instrumental reward conditioning consistently showed that MDD participants were less likely to bias their responses towards more frequently/substantially rewarded stimuli (Henriques & Davidson, 2000; Mukherjee et al., 2020; Pizzagalli et al., 2008; Vrieze et al., 2013). This may suggest an overall greater rigidity in responses among individuals with MDD involving perseveration of responses regardless of choice outcomes. This interpretation is supported by the findings of Chase et al. (2010), which showed less trial-by-trial adjustment in responses among individuals with MDD compared to control participants. Studies that examined the tendency to make advantageous decisions over the course of a task according to both reward and punishment all showed that individuals with MDD performed worse than control participants (Cella et al., 2010; Must et al., 2006). Steele et al. (2007) showed that individuals with MDD were less likely to alter their reaction time as a function of task feedback, although Chase et al. (2010) found that depressed and nondepressed participants had similar patterns of reaction time adjustment after

correct vs. incorrect feedback (i.e., slower responses after ‘incorrect’ compared to ‘correct’ feedback), although depressed participants had slower reaction times overall.

Notably, the gambling tasks employed in instrumental conditioning studies of MDD involved conscious decision-making processes (Maia & McClelland, 2004), whereas the discrimination tasks are more likely to assess the acquisition of implicit associations between behaviours and reinforcing outcomes (Berry, Shanks, & Henson, 2008). Thus, the findings from studies that employed gambling paradigms may assess the influence of reinforcement on consciously informed choices, whereas the findings from studies that employ signal detection approaches may provide more insight about choices informed by less explicit information.

Limitations of Previous Studies Examining Instrumental Conditioning in MDD

Studies that examined instrumental conditioning in MDD using rewards and punishments employed secondary, rather than primary, reinforcers (i.e., money). In other words, the rewards and punishments employed in these studies were stimuli previously associated with one or more primary reinforcers. Therefore, future studies that employ primary (i.e., food or shock) rewards and punishments are needed to understand more comprehensively how individuals with MDD alter their behaviour in response to rewarding and punishing experiences. Furthermore, a limitation of the gambling tasks employed in these studies is that it is difficult to distinguish between participants’ responses to rewards versus punishments. Thus, the finding across these studies that participants were less likely to make advantageous choices (Cella et al., 2010; Must et al., 2006; Steele et al., 2007) could be due to a reduced ability to learn from reward, punishment, or both. Separate gambling paradigms or phases within paradigms that distinguish behavioural responses to rewards and punishments could help address this issue.

Preliminary Summary: Instrumental Conditioning in MDD

In sum, instrumental conditioning studies have demonstrated three main patterns of results. First, individuals with MDD may be less effective at using reinforcement history (both reward and punishment) to maximize advantageous choices and minimizes disadvantageous ones than nondepressed individuals on gambling tasks (Cella et al., 2010; Mukherjee et al., 2020; Murphy et al., 2003; Must et al., 2006; Taylor Tavares et al., 2008), including after a reversal in probabilistic contingencies (Cella et al., 2010; Mukherjee et al., 2020), and misleading negative feedback (Murphy et al., 2003; Taylor Tavares et al., 2008). The findings presented here also suggest that individuals with MDD do not develop response biases toward more frequently reinforced stimuli when required to discriminate based on visual perception (Pizzagalli et al., 2008; Vrieze et al., 2013) and verbal memory (Henriques & Davidson, 2000) in discrimination tasks. There is some evidence that participants with MDD were less likely to alter their response strategy or style following positive and negative consequences (e.g., less trial-by-trial response adjustment, slowed reaction time after negative feedback or increased reaction time following positive feedback) on decision-making tasks than nondepressed controls (Chase et al., 2010; Steele et al., 2007).

In light of recent developments in computational approaches to studying instrumental conditioning, including those used in studies of MDD, we provide below an overview of studies employing computational modeling of instrumental conditioning in MDD aimed at improving measurement and characterization of latent aspects of cognition that may underlie and/or contribute to depressive symptoms. A critical advantage of using computational modeling is that the parameters included in these models represent latent constructs implicated in MDD, such as reward sensitivity and learning rate, that can be computed and compared across tasks and studies, making it easier to compare findings (Bishop & Gagne, 2018; Kriegeskorte & Douglas, 2018).

We follow this section with a summary and synthesis of research incorporating both Pavlovian and instrumental conditioning in investigations of PIT that helped to inform the development of the MELD framework.

Contributions of Computational Models to Instrumental Conditioning Research in MDD

The use of computational psychiatry approaches to characterize reinforcement learning in depression has increased in recent years (Chase et al., 2010; Dombrovski, Szanto, Clark, Reynolds, & Siegle, 2013; Huys et al., 2013; Mukherjee et al., 2020). Computational models allow for the operationalization of formal parameters indicating aspects of cognition that are not apparent from behavioural responses but are latently operating and contributing to behaviour (Kriegeskorte & Douglas, 2018). They also allow for the testing of competing models of the degree to which they predict behaviour in different populations. Common models of reinforcement learning include the traditional Rescorla-Wagner (RW) model (Dombrovski et al., 2010), temporal difference (TD) models, and Q-learning models (Huys et al., 2013; Mukherjee et al., 2020). Examples of parameters representing latent aspects of cognition in these models include positive and negative prediction error (PE), reward and punishment learning rate and sensitivity, exploitation/exploration, memory, and delayed discounting of reward/punishment (Chase et al., 2010; Dombrovski et al., 2010; Huys et al., 2013; Mukherjee et al., 2020).

Most computational models incorporate a PE parameter representing the degree to which unexpected rewards generate a PE. Over time the cue-reward contingency is learned, after which the cue will elicit an expected value signal, or an expectation of the consequence (reward or punishment) of a given choice based on previous reinforcement. In the RW model, learning ceases after knowledge of the cue-reward contingency is acquired and, consequently, there is no PE after the contingency is learned. In TD models, however, a PE is produced whenever the cue

appears, including after the cue-reward contingency has been learned. Here, the magnitude of the PE reflects the expected magnitude of the predicted reward. In Q-learning models, a reward sensitivity or exploration/exploitation parameter is included to account for individual differences in these aspects of cognition distinct from learning rate, suggesting that reward sensitivity and exploration/exploitation make unique contributions to predicting behaviour that are not necessarily accounted for by learning rate. Findings from studies that employed computational models to investigate instrumental conditioning in MDD are presented below.

Chase et al. (2010) used a Q-learning model to examine reward and punishment learning rate during training and test phases of a probabilistic reinforcement learning task performed by individuals with MDD and nondepressed control participants. In the training phase of the task, participants selected one letter from one of three stimulus pairs (AB, CD, EF), each with a varying probability of being correct, and feedback ('correct' or 'incorrect') was provided (no reward or punishment) from which participants were expected to learn and select which letter was 'correct' most often. This was followed by a test phase in which participants completed the same task without feedback. Parameters in their model included positive and negative learning rate parameters (indicating efficiency of using PEs to update the expected value of a certain choice during future trials) and an exploration-exploitation parameter (indicating a participant's tendency to choose the option with the highest expected payoff or choose an option for which the payoff is not yet known). The learning rate parameters are included in the Q-learning model where the Q-value, representing the associative strength of the just-selected stimulus to a particular outcome, is updated as a function of whether the outcome was positive or negative, the learning rate, and the PE (outcome – expected outcome for that trial). The exploitation/exploitation parameter is used in the computation of the probability of selecting

either the stimulus known to result in a positive outcome or the stimulus for which the outcome is unknown. The authors found that MDD participants showed a reduced learning rate for both correct and incorrect feedback (i.e., for positive and negative PEs) in the reinforcement learning training phase but not in the test phase of their experiment. Furthermore, they found that poorer reward and punishment learning rate in the training phase was associated with greater anhedonia in all study participants (including MDD and control participants).

A study by Dombrovski et al. (2010) that used a modified RW model to examine parameters influencing reinforcement learning, using a probabilistic reversal learning task in suicide attempters, suicide ideators, nonsuicidal depressed elderly, and nondepressed comparison subjects. Consistent with the traditional RW model, they calculated the optimal expected values of choosing stimulus 1 or stimulus 2 based on a prior (the previously expected outcome) and a PE (the difference between the experienced outcome and the prior). Their model also included learning rate parameters for rewards and punishments and a memory parameter. Learning rate parameters captured the impacts of positive (reward) and negative (punishment) PE on the previous trial ($t - 1$) on the participant's subsequent choice (t), whereas the memory parameter reflected the effect of reward and punishment history on all previous trials on choice (low memory results in rapid switches of choice in response to reward/punishment on the last trial). The authors found that participants with MDD tended to exhibit a (marginally) lower punishment learning rate than control participants but reward learning rate did not differ between groups. These findings suggest that trial choices that resulted in negative (but not positive) PEs had a blunted influence on stimulus choice in the subsequent trial in MDD participants.

In a behavioural meta-analytic study by Huys et al. (2013), a Q-learning model was used to examine probabilistic reward learning task performance in participants with MDD compared

to nondepressed control participants. During the task, participants were required to discriminate between two visual stimuli and select the stimulus most likely to result in a rewarding outcome. The parameters of interest included (1) reward sensitivity and (2) a learning rate parameter that incorporated reward and punishment. This study revealed that the reward sensitivity parameter predicted altered behaviour in MDD more than learning rate and the authors therefore concluded that MDD is associated with blunted appetitive learning resulting from a reduced primary sensitivity to rewards as opposed to reduced reward learning rates.

Mukherjee et al. (2020) employed a Q-learning computational model to examine performance on two probabilistic reversal learning tasks in MDD and nondepressed control participants, including one task incorporating only reward/no reward feedback and another task incorporating only punishment/no punishment feedback. Parameters of interest in their models for both tasks were value sensitivity and learning rates. Their results showed that MDD participants had slower reward and punishment learning rates, lower punishment value sensitivity, and marginally lower reward value sensitivity than control participants. Notably, Mukherjee et al. (2020) found that the parameters used in their model better classified participants with MDD than simpler metrics of performance, including proportion of rich fractal choices, proportion of win-stay responses, and action perseveration.

In sum, these four previous studies used computational models to examine reward and/or punishment learning and sensitivity, as well as exploitation-exploration, in MDD with mixed results. Nonetheless, there was some consensus that individuals with MDD had lower reward and punishment sensitivity (Huys et al., 2013; Mukherjee et al., 2020) and learning rates (Chase et al., 2010; Dombrovski et al., 2010; Mukherjee et al., 2020) than nondepressed control participants. Importantly, there was evidence that emotional learning parameters included in

computational models were better at discriminating MDD from nondepressed control participants than simpler metrics of performance (Mukherjee et al., 2020). Thus, computational modeling of latent aspects of emotional learning in MDD may be superior to non-computational behavioural indices for identifying MDD.

Pavlovian-Instrumental Transfer

PIT refers to a process by which Pavlovian CSs can invigorate or suppress instrumental behaviour. Appetitive and aversive PIT effects are differentiated such that appetitive PIT occurs when an appetitive CS invigorates instrumental approach or inhibits instrumental withdrawal (Cartoni, Balleine, & Baldassarre, 2016) and aversive PIT takes place when an aversive CS inhibits instrumental approach or invigorates instrumental withdrawal (Huys et al., 2011). Appetitive and aversive PIT can also be described as the influences of appetitive and aversive expectations on behaviour, respectively (Geurts, Huys, Den Ouden, & Cools, 2013). Pavlovian CSs have been found to influence instrumental behaviour by (1) increasing the likelihood that an action (approach or withdrawal) associated with the Pavlovian US will be carried out and (2) inducing motivational states consistent with those elicited by Pavlovian US. Specific and general PIT are two putative subtypes of PIT. Specific PIT refers to situations in which both the Pavlovian and instrumental associations are formed with the exact same outcome (e.g., delivery of a shock) and the presence of the CS is found to alter (invigorate or suppress) instrumental behaviour associated with that specific outcome. For example, the presence of a CS previously paired with shock would be expected to invigorate instrumental avoidance behaviour intended to escape a shock. General PIT refers to situations in which the general motivational properties of a CS invigorates or suppresses instrumental behaviour even though the CS is different from the instrumental reinforcer/punishment, for example if the presence of a CS previously paired with

640 shock were to suppress an instrumental behaviour previously associated with the delivery of a
641 reward.

642 Most laboratory experiments designed to examine PIT involve separate Pavlovian and
643 instrumental training stages (either training stage may occur first), followed by the instrumental
644 task in the presence of the CS during extinction. During performance on a PIT task, the CS may
645 alter the number, frequency, or choice of an action (Holmes, Marchand, & Coutureau, 2010). A
646 graphical depiction of a human laboratory PIT task is presented in Figure 1.

Figure 1*Schematic Representation of a Pavlovian-Instrumental Transfer Task*

Note. Example of an aversive Pavlovian-instrumental transfer (PIT) task in which participants first learn to (a) associate one active behaviour (clicking the orange dot) with delivery of reward and another with no reward (clicking the yellow dot), the instrumental conditioning training phase; and (b) passively associate one neutral stimulus (blue and black fractal image; CS) with loss and another with no loss (green and black fractal image; CS-), the Pavlovian conditioning training phase. (c) Participants then perform a PIT task test phase during which they are asked to select one of the two dots (the trained instrumental behaviour) in the presence of the Pavlovian cues (CS and CS-). Participants do not receive any feedback during the PIT task. Performance on the instrumental learning task (without feedback) during the presentation of the CS versus the presentation of the CS- is compared to examine aversive Pavlovian control over instrumental reward behaviour.

Other studies that have examined PIT using prepotent responding as a form of pre-existing Pavlovian bias. It has been proposed that producing a response when seeking a reward (versus when avoiding punishment) and omitting a response when avoiding punishment (versus seeking reward) are built-in response tendencies that accompany Pavlovian learning (Guitart-Masip et al., 2012). Thus, in these paradigms, it is assumed that Pavlovian expectations of reward reflexively invigorate active go responses and expectations of punishment inhibit active go responses (Crockett, Clark, & Robbins, 2009; Dayan, Niv, Seymour, & Daw, 2006; Guitart-Masip et al., 2011).

A Hypothetical 'Real Life' Example of PIT in MDD

Instrumental Reward Conditioning. Martin, who was recently diagnosed with MDD, often texts friends and family for emotional support. They tend to be kind and supportive, which reinforces his tendency to reach out.

Aversive Pavlovian Conditioning. Since Martin became depressed, his productivity at work has declined, and his boss occasionally sends him emails criticizing his performance. As a result, Martin tends to experience a sense of dread when he hears or sees email notifications on his smartphone or computer.

Enhanced Aversive PIT. One evening, Martin was in bed feeling particularly stressed about work and decided to text his friend as a distraction. As he reached for the phone, an unexpected email notification popped up, and a feeling of dread overcame him. This feeling hampered his motivation to text his friend, and he retreated to his bed instead.

The above example illustrates how PIT may operate to reduce positive reinforcement in individuals with MDD, a critical factor in the onset and maintenance of depressed mood (Costello, 1972; Ferster, 1973; Lewinsohn, 1974; Seligman, 1975). Although Martin has

successfully acquired the instrumental behaviour of contacting friends and family for support, the aversive CR associated with email notifications interfered with his ability to perform this action and successfully obtain social support.

Studies Examining PIT in MDD

Human PIT is a relatively new area of research (Talmi, Seymour, Dayan, & Dolan, 2008), and paradigms examining PIT in humans has only recently been applied to individuals with MDD (Huys et al., 2016; Moutoussis et al., 2018; Nord et al., 2018). Investigations of PIT in MDD have included two studies that employed instrumental and Pavlovian training and PIT testing during a major depressive episode (Huys et al., 2016; Nord et al., 2018) as well as one study that investigated prepotent Pavlovian biases to respond for reward and omit a response to avoid no-reward during an instrumental conditioning task (Moutoussis et al., 2018). The characteristics and main findings of these studies are presented in Table 3.

696 **Table 3**697 *Studies Examining PIT in MDD*

Authors	Sample characteristics (<i>M</i> [<i>SD</i>]) ^a			Task phases	Conditioning measures	Results	Interpretation
Huys et al. (2016)	Pop'n	MDD	CTRL	Instrumental: Probabilistic reinforcement learning task with approach and withdrawal conditions in which participants were instructed to collect (approach) or discard (withdrawal) coloured mushrooms. The approach condition involved click-to-collect ("go") or withhold response to discard ("no-go"). The withdrawal condition involved click-to-discard ("go") or withhold response to keep ("no-go"). Each mushroom colour was associated with a different probability of being rewarded or punished based on	Appetitive approach PIT: Linear regression coefficient of the go probability across all instrumental stimuli for the neutral and positive CSs. Aversive approach PIT: Linear regression coefficient of the go probability across all instrumental stimuli for the neutral and negative CSs. Action specificity: Difference between the linear regression	Appetitive approach PIT: No difference. Aversive approach PIT: No difference. Action specificity: PIT was action-specific in controls but not patients; there was a trend-wise difference between MDD and CTRL groups.	In the depressed state the guidance of choices afforded by Pavlovian stimuli was reduced and lacked specificity.
	n	25	40				
	Age	28.3 (8.0)	27.3 (7.0)				
	%fem	68%	62%				
	BDI	23.4 (8.6)	2.8 (3.7)				
	BAI	[Moderate]	[Minimal]				
		13.5 (7.8)	4.3 (3.8)				
		[Mild]	[Minimal]				

				decisions to collect or discard.			coefficients in the approach and withdrawal blocks.
				Pavlovian: Passive observation of fractal images paired with a tone followed by a monetary win, loss, or no win/loss.			
				PIT. Probabilistic reinforcement learning task overlaid on Pavlovian fractal images.			
Moutoussis et al. (2018)	Pop'n Age %fem HAM-D Anx. Sx	MDD 39 33.7 (9.1) 56% 17.2 (3.4) [Moderate] NA	CTRL 22 34.0 (8.3) 50% 0.9 (1.0) [Normal range] NA	Instrumental: Go/no-go task required participants to learn through trial-and-error whether each of four fractal images required pressing a button (Go) or holding back on pressing (No-Go) to maximize positive outcomes (monetary win) and minimize negative outcomes (no win). Participants were instructed that the correct and incorrect actions would be	Instrumental: Several computational modeling parameters including appetitive and aversive sensitivity, learning rate, action bias, and lapse rate. Pavlovian: Pavlovian bias model parameter.	No differences between groups observed across the instrumental and Pavlovian model parameters.	MDD was not associated with pre-potent Pavlovian influence over instrumental actions to win or avoid losing.

				<p>followed by the ‘best’ and ‘worst’ outcomes 80% of the time, respectively. Participants were therefore required to learn what the ‘best’ and ‘worst’ action was for each stimulus, which could be Go-to-Win, Go-to-Avoid-Loss, NoGo-to-Win, or NoGo-to-Avoid-Loss.</p>			
Nord et al. (2018)	Pop’n n Age %fem BDI Anx. Sx	MDD 26 28.0 (8.8) 0.39 24.0 (9.3) NA	CTRL 28 26.8 (8.5) 0.46 3.4 (4.0) NA	See instrumental Pavlovian, and PIT task descriptions for the study by Huys et al. (2016) above.	Instrumental: Percent correct go and no-go responses in approach and withdrawal conditions separately.	Instrumental: No differences between groups. Pavlovian: No differences between groups. PIT approach condition: MDD group performed fewer ‘go’ responses in the context of Pavlovian stimuli associated with small ($d = 0.56$) and large ($d = 0.55$) losses.	Depression was associated with enhanced aversive Pavlovian influence over instrumental behaviour.

background, in the approach condition. PIT withdrawal condition: Probability of making a go response for each Pavlovian background in the withdrawal condition.	PIT withdrawal condition: MDD group performed more ‘go’ responses in the context of Pavlovian stimuli associated with small ($d = 0.59$) and large ($d =$ 0.70) losses.
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698 *Note.* ^aExcept otherwise noted. CTRL = healthy control participants; MDD = Major Depressive Disorder group; GAD = Generalized
 699 Anxiety Disorder; Diag. = mental disorder diagnosis; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; HAM-D =
 700 Hamilton Depression Rating Scale; Anx. Sx = anxiety symptom scale; Dep. Sx = depressive symptom scale; NA = Not applicable.

Characteristics of Studies Examining PIT in MDD

Three previous studies have examined PIT in individuals diagnosed with MDD. MDD participants in all of these studies were found to have moderate depressive symptoms, were 28 (Huys et al., 2016; Nord et al., 2018) and 34 (Moutoussis et al., 2018) years old on average, and were comprised of 39% (Nord et al., 2018), 56% (Moutoussis et al., 2018), and 68% (Huys et al., 2016) female participants. Two studies employed the same paradigm in which participants first underwent an instrumental training phase, then a Pavlovian training phase, and finally a PIT phase (Huys et al., 2016; Nord et al., 2018). For the instrumental training phase in these studies, participants either learned to (1) ‘click-to-collect’ certain coloured mushrooms and ‘withhold response to discard’ others in order to maximize rewards and minimize losses; or (2) ‘click-to-discard’ certain coloured mushrooms and ‘withhold response to keep’ others in order to maximize rewards and minimize losses. These two conditions were used to measure approach and withdrawal PIT, respectively. If successful, participants would learn which mushroom colours were associated with reward versus punishment when collected/discarded, developing approach and withdrawal biases according to each mushroom’s reinforcement history. In the study by Moutoussis et al. (2018), a prepotent Pavlovian bias during an instrumental conditioning task was examined, whereby participants learned to respond to fractal images with ‘Go-to-Win’, ‘Go-to-Avoid-Loss’, ‘NoGo-to-Win’, and ‘NoGo-to-Avoid-Loss’ conditions that would produce a monetary reward (win) or a monetary loss (no win). The Pavlovian influence in this study was the tendency to ‘Go-to-Win’ and ‘NoGo-to-Avoid-Loss’.

Findings from Studies Examining PIT in MDD

To investigate whether PIT may be altered in MDD, Huys et al. (2016) examined differences in action-specificity between individuals diagnosed with MDD and nondepressed

participants. Action-specificity in the context of PIT refers to the tendency for appetitive CSs to selectively invigorate active approach behaviours and aversive CSs to selectively invigorate active withdrawal behaviours. In the instrumental *approach* training phase of Huys and colleagues' (2016) PIT paradigm, participants learned to collect or not collect mushrooms according to the actions' associated consequences. Specifically, participants learned to (1) click on mushrooms for which (a) clicking frequently resulted in reward and infrequently resulted in punishment and (b) not clicking frequently resulted in punishment/infrequently resulted in reward ('go' to obtain reward/avoid punishment) or (2) refrain from clicking on mushrooms for which (a) not clicking was frequently rewarded/infrequently punished and (b) clicking was frequently punished/infrequently rewarded ('no-go' to obtain reward/avoid punishment). In the instrumental *withdrawal* training phase of their paradigm, participants learned to discard or keep mushrooms depending on reinforcement. This involved clicking on an empty box opposite mushrooms to discard ('go' to obtain reward/avoid punishment) and withhold clicking on the empty box to keep the mushroom ('no-go' to obtain reward/avoid punishment). Responses (or lack thereof) resulted in either reward or punishment during every trial with the same reinforcement schedule as the approach training.

The authors observed that in nondepressed individuals, PIT effects were action-specific. In the *approach* PIT task ('go' to collect or 'no-go' to not collect mushrooms), control participants were overall (i.e., averaged across all instrumental stimuli) more likely to produce a 'go to collect' response when an appetitive CS was presented and less likely to produce a 'go to collect' response when an aversive CS was presented (suggesting that appetitive CSs invigorated active approach and aversive CSs suppressed active approach responses), whereas instrumental training that involved *withdrawal* ('go to discard' mushrooms or 'no-go to keep'), participants

were overall more likely to produce an active withdrawal response when an aversive CS was presented and less likely to produce an active withdrawal response when an appetitive CS was presented. Notably, the authors found that greater action-specificity in the control group (i.e., an appetitive CS boosts active approach and inhibits active withdrawal; an aversive CS boosts active withdrawal and inhibits active approach) was driven more by PIT effects during approach than withdrawal (Huys et al., 2016). One explanation for this distinction could be that ‘go’ (i.e., active) responses are more likely in the face of potential rewards (signaled by appetitive CSs) and ‘no-go’ responses are more likely in the face of potential punishments (signaled by aversive CSs). This may have resulted in stronger PIT effects when active responses were associated with appetitive CSs and passive responses were associated with aversive CSs and weaker PIT effects when an active response was required in the presence of an aversive CS and passive response in the presence of an appetitive CS, contrary to pre-potent Pavlovian biases to produce a motor response in the presence of an appetitive stimulus and withhold a motor response in the presence of an aversive stimulus (Crockett et al., 2009; Dayan et al., 2006; Guitart-Masip et al., 2011; Guitart-Masip et al., 2012).

Unlike the pattern of results observed in control participants, PIT was not action specific in participants with MDD (Huys et al., 2016). For depressed participants, the valence of the CS did not appear to affect instrumental approach or withdrawal. The presentation of an appetitive or aversive CS was not associated with an increased likelihood of “clicking to obtain” or “clicking to discard”, respectively. The finding that the difference in PIT effects between MDD and control participants was most clearly observed for instrumental approach behaviours is consistent with behavioural theories of depression which propose that MDD is driven largely by

a lack of positively reinforced behaviours (i.e., fewer actions that bring about pleasurable consequences; Dimidjian, Barrera Jr, Martell, Munoz, & Lewinsohn, 2011).

In their study of PIT in participants with MDD compared to nondepressed participants, Moutoussis et al. (2018) did not observe differences in Pavlovian influences on instrumental behaviour, although their study assessed *pre-potent* Pavlovian biases as opposed to Pavlovian associations formed during training included in a PIT paradigm. Using a computational modeling approach, they examined whether individuals with MDD differed from control participants in terms of several parameters, with a Pavlovian bias parameter used to examine PIT (representing the tendency to produce a button press for rewards and withdraw a button press for punishments). The authors found that the Pavlovian bias to produce a button press for rewards and withdraw a button press for punishments did not differ between MDD and control participants (Moutoussis et al., 2018). Thus, MDD participants performed similarly to controls in their tendency to ‘go’ to obtain rewards and ‘no-go’ to avoid punishment.

An important consideration when comparing the disparate results of the studies by Huys et al. (2016) and Moutoussis et al. (2018) is that the latter study examined the influence of a pre-potent Pavlovian bias in motor responding on instrumental behaviour in MDD compared to nondepressed control participants. In contrast, Huys et al. (2016) examined the influence of a newly formed Pavlovian association between a visual stimulus and a rewarding or punishing outcome on instrumental behaviour. Furthermore, the instrumental actions in the two studies differ in that the study by Moutoussis et al. (2018) required a simpler instrumental action: ‘go’ or ‘no-go’ following the presentation of a fractal image to obtain a reward or avoid a punishment. The study by Huys et al. (2016), however, required more complex instrumental actions involving moving the cursor towards a stimulus and clicking on it (versus no action) in an approach phase

or moving a cursor away from a stimulus and clicking on an empty box opposite the stimulus (versus no action) in a withdrawal phase. Examining the pattern of responding *within* either of these phases may have produced similar results, whereby a ‘go’ response is more likely for previously rewarded stimulus (whether ‘clicking on’ to collect or ‘clicking away’ to discard) and a ‘no-go’ response is more likely for a previously punished stimulus (whether ‘not clicking on’ to not collect or ‘not clicking away’ to keep). However, these analyses were not completed. Thus, it may be that while individuals with MDD show a similar Pavlovian bias to nondepressed individuals in their motor responding during instrumental tasks (‘go’ to win and ‘no-go’ to avoid punishment), they do not show the same patterns of Pavlovian bias for newly formed stimulus-outcome associations and/or more complex instrumental actions.

In a recent study of aversive PIT by Nord et al. (2018), it was found that instrumental behaviours in individuals with MDD, whether involving approach or withdrawal, were significantly more influenced by aversive Pavlovian cues than was the case for nondepressed participants. Notably, groups performed comparably on the Pavlovian and instrumental conditioning tasks during training. However, during the aversive PIT task, MDD patients performed significantly *fewer* active approach responses (‘click’ to obtain) and significantly *more* active withdrawal responses (‘click’ to discard) when Pavlovian CSs predicted both small and large losses. Thus, aversive Pavlovian cues impaired performance in the approach condition and enhanced performance in the withdrawal condition. Again, Moutoussis et al. (2018) did not obtain results that were consistent with the study by Nord et al. (2018); they did not find any influence of the ‘NoGo-to-Avoid-Loss’ Pavlovian bias on instrumental behaviour in their study.

The results of Nord et al.’s (2018) study were not consistent with those of Huys et al. (2016), in that participants in with MDD did show action-specificity in their responses when

aversive Pavlovian CSs were presented. Nord et al. (2018) reported that the most likely explanation for these somewhat conflicting results is that, unlike Huys et al. (2016), they did not include participants who were taking psychotropic medication. Another difference between these studies was that 62% of participants in Nord et al. (2018) study had a comorbid anxiety disorder, whereas individuals with anxiety disorders were excluded from Huys et al. (2016) study. However, Nord et al. (2018) examined whether anxiety disorder comorbidity impacted their results and did not observe any effect. Thus, it is possible that unmedicated individuals with MDD exhibit exaggerated aversive Pavlovian influence over instrumental behaviour whereas psychotropic medication blunts this effect resulting in action-nonspecific effects of Pavlovian cues on instrumental behaviour in individuals with the disorder.

Preliminary Summary: PIT in MDD

In sum, there is mixed evidence to date indicating that individuals with MDD may show diminished action-specific influence of Pavlovian cues over instrumental behaviour (Huys et al., 2016) or exaggerated influence of aversive Pavlovian cues over instrumental behaviour (Nord et al., 2018) than nondepressed controls. Yet there was no evidence for a pre-potent Pavlovian response bias for individuals with MDD relative to healthy controls (Moutoussis et al., 2018). The results of these studies may suggest that paradigms employing measures of prepotent Pavlovian bias do not distinguish depressed from nondepressed individuals, whereas paradigms which include Pavlovian and instrumental conditioning training phases preceding the testing of PIT may better distinguish these groups.

Recommendations for Future Research Investigating PIT in MDD

Evidently, studies examining PIT in MDD are few, and more studies are needed to establish how Pavlovian CSs influence instrumental behaviour in depression. Thus far, a single

PIT paradigm has demonstrated altered Pavlovian control over instrumental behaviour in MDD. In this paradigm, monetary wins and losses were used to induce Pavlovian and instrumental conditioned associations (Huys et al., 2016; Nord et al., 2018). While reinforcement using monetary wins and losses is consistent with most previous studies of instrumental conditioning in MDD, all past studies on Pavlovian conditioning in MDD have used aversive primary USs. It may be worth exploring whether the aversive Pavlovian control over instrumental behaviour is enhanced in MDD when aversive primary punishments are associated with the CSs. For example, the use of a shock as an aversive Pavlovian US in a PIT study that employs an instrumental conditioning task involving monetary wins and losses would help clarify whether aversive Pavlovian control over instrumental behaviours is specific to situations when the Pavlovian US and reinforcer are the same (i.e., monetary rewards or punishments) or if aversive Pavlovian CSs in general show control over instrumental behaviours like approach and withdrawal (Cartoni, Puglisi-Allegra, & Baldassarre, 2013). Furthermore, as noted above, the results of the two studies that employed the same paradigm were inconsistent (Huys et al., 2016; Nord et al., 2018), highlighting that more replication studies are needed to more reliably establish how performance on this particular PIT tasks differs between individuals with MDD and nondepressed control participants. It may also be worthwhile to examining the effect of psychotropic medication on PIT in MDD, given that a possible explanation for the disparate results obtained by Huys et al. (2016) and Nord et al. (2018) is that treatment with psychotropic medication was an exclusion criterion only in the latter study.

The results of the study by Moutoussis et al. (2018) did not support a difference in pre-potent Pavlovian influence on instrumental behaviour between participants with MDD and the control group. This may suggest that individuals with MDD show intact pre-potent Pavlovian

bias (e.g., a pre-potent Pavlovian bias to have an approach motor response – ‘go’ – to obtain rewards and a withdrawal-congruent motor response – ‘no-go’ – to avoid punishment) but demonstrate either action-nonspecific (Huys et al., 2016) or aversively-biased (Nord et al., 2018) influence of Pavlovian cues that have been newly associated with a US. However, additional studies examining pre-potent Pavlovian influences on instrumental behaviour in MDD are clearly needed. Furthermore, it will be important to examine whether appetitive and aversive PIT differ according to various dimensions of the phenomenology of MDD. For example, anhedonia may selectively reduce the degree to which appetitive Pavlovian CSs elicit an approach response whereas cognitive aspects of MDD (e.g., helplessness) may be associated with enhanced aversive PIT in MDD (Husain & Roiser, 2018; Seligman & Maier, 1967).

Overall, there exists a significant gap in our understanding of how Pavlovian and instrumental conditioning interact to affect individuals with MDD. Although there is much work to be done, the first studies of PIT in MDD demonstrate that examining Pavlovian and instrumental conditioning and their mutual influence in a single paradigm shows promise for better understanding this complex disorder. To help reconcile the existing research of emotional learning in MDD, we propose the following framework to capture the nuanced interactions of Pavlovian and instrumental conditioning and how they may operate in MDD.

The Mood and Emotional Learning Dynamics (MELD) Framework

In this section, we present a theoretical framework of PIT in MDD. Our framework builds on findings from previous studies examining Pavlovian conditioning, instrumental conditioning, and PIT in MDD. The MELD framework is intended to fill a gap in the conceptualization of how Pavlovian and instrumental conditioning operate together to influence the reduced frequency of reinforcement in MDD (or subtypes of MDD), which is posited to

contribute its onset and maintenance (Dimidjian et al., 2011; Ferster, 1973; Jacobson, Martell, & Dimidjian, 2001; Lewinsohn, 1974). Largely consistent with research to date investigating PIT in MDD, we propose that individuals with MDD show exaggerated influence of aversive Pavlovian cues on instrumental behaviour generally (Nord et al., 2018) and blunted influence of appetitive Pavlovian cues on active approach behaviours in particular (Huys et al., 2016). Our framework focuses on the influence of Pavlovian associations formed during a Major Depressive Episode on instrumental behaviours; therefore, it does not portray the potential influence of pre-potent Pavlovian biases on instrumental behaviour as investigated by Moutoussis et al. (2018).

The MELD framework proposes a simplified pathway through which instrumental behaviour, triggered by the opportunity to obtain a pleasant outcome or avoid/escape a negative one, is determined under the influence of Pavlovian CSs. The framework also incorporates biases in attention and memory, which have been shown to play an important role in the psychopathology of MDD (Beck & Bredemeier, 2016; Kaiser et al., 2018; LeMoult & Gotlib, 2019). In the following sections, we elaborate on the various components of the framework and how they may be altered in MDD. A schematic of the MELD framework is presented in Figure 2.

Figure 2

Schematic Representation of the Mood and Emotional Learning Dynamics (MELD) Framework

Note. The MELD framework integrates Pavlovian and instrumental conditioning and their interaction (i.e., Pavlovian-instrumental transfer or PIT) as well as relevant psychological processes for demonstrating how dysfunctional emotional learning dynamics may perpetuate a lack of positive reinforcement and/or preponderance of punishment and in turn depressive symptoms in MDD.

906 **Elements of the MELD framework**

907 *Environmental and Motivational Factors Determine Instrumental Outcome Value*

908 Environmental contributions to the dynamics of emotional learning in MDD incorporated
909 in the MELD framework include an **opportunity for reinforcement** and the surrounding **cues**
910 **and context**, which may serve as Pavlovian CSs. Due to **negative attentional biases**, which
911 refers to the tendency to notice unpleasant aspects of the environment and attend to them longer
912 relative to pleasant aspects of the environment (Gotlib, Krasnoperova, Yue, & Joormann, 2004;
913 Koster, De Raedt, Goeleven, Franck, & Crombez, 2005), individuals with MDD are proposed to
914 detect fewer opportunities for reward and more opportunities for punishment, as well as fewer
915 environmental cues and contexts associated with desirable outcomes and more associated with
916 aversive outcomes (appetitive and aversive Pavlovian CSs, respectively; Anderson, 2016; Leong,
917 Radulescu, Daniel, DeWoskin, & Niv, 2017). An example of this may be an individual with
918 MDD who is considering where to order in a food court (opportunity for reinforcement) and
919 focuses their attention on the tense facial expressions of patrons waiting in long line ups
920 (aversive CS predicting unpleasant experience of waiting in the line) rather than the positive
921 facial expressions of people enjoying the food they ordered (appetitive CS predicting delicious
922 food).

923 As depicted in the MELD framework, once opportunities to obtain rewards or
924 avoid/escape punishments are detected, there is **recall of ‘liking’ or ‘disliking’ the outcome**,
925 which manifests as explicitly remembered or imagined declarative targets (Berridge & Aldridge,
926 2008). This reaction then produces varying degrees of **cognitive desire or aversion**, i.e.,
927 conscious desire for or aversion to an explicitly expected outcome such as delicious food or
928 waiting in a long lineup, respectively (Berridge & Aldridge, 2008). Recall of how much an

individual ‘liked’ or ‘disliked’ an outcome in the past and its influence on cognitive desire or aversion may also be referred to as the ‘remembered utility’ of the outcome, i.e., an individual’s retrospective evaluation of past experiences (Berridge, Robinson, & Aldridge, 2009; Kahneman, Wakker, & Sarin, 1997; Schacter et al., 2012; Wassum, Ostlund, Balleine, & Maidment, 2011). In MDD, we hypothesize that cognitive desire is attenuated, whereas cognitive aversion is potentiated, partly due to negative **memory biases** for the pleasantness or unpleasantness of experiences (Dillon & Pizzagalli, 2018; Gershman & Daw, 2017). The nature of negative memory biases in MDD and depressed mood include better memory for negative experiences and worse memory for positive experiences (Urban, Charles, Levine, & Almeida, 2018). Elaborating on the food court example, an individual with MDD who decided to wait in line for delicious food would be expected to recall the unpleasant experience of waiting in line better than the pleasant experience of enjoying the meal.

In addition to the detection of opportunities for reinforcement, surrounding Pavlovian CSs elicit conditioned responses (CRs) and contribute to the **motivational salience** of the instrumental outcome (Berridge et al., 2009). The motivational salience of an instrumental outcome refers to the degree to which a stimulus elicits approach (incentive salience) or avoidance (aversive salience). In the MELD framework, motivational salience is also determined by an individual’s **physiological state** (e.g., hunger, stress levels; Wassum et al., 2011). The influence of physiological state on motivational salience has been demonstrated in studies of reward devaluation, including findings that satiating hunger reduces the incentive salience of food cues (Balleine & Dickinson, 1998). Referring back to the food court example, the motivational salience of food (the instrumental outcome) would be influenced by the facial expressions of the food vendor’s patrons when they are enjoying the food (appetitive CS) and the

individual's level of hunger. In MDD, another relevant physiological state that would alter motivational salience is heightened stress, which can increase the motivational salience of aversive outcomes (van Marle, Hermans, Qin, & Fernández, 2009).

In the MELD framework, **instrumental outcome value** is based on both the motivational salience of an outcome (the degree to which the outcome elicits an implicit approach or avoidance response) and an individual's cognitive desire or aversion towards the outcome (the degree to which the outcome is explicitly represented as desirable or undesirable; Berridge et al., 2009; Olney, Warlow, Naffziger, & Berridge, 2018). The lower the instrumental outcome value, the lower the likelihood that the instrumental action will be carried out (i.e., **inaction** may result). If the instrumental outcome value is high, the process of **action selection** will follow.

Action selection

Action selection is the process through which an instrumental action (or inaction) is chosen to maximize the probability of a desired outcome (Balleine & Ostlund, 2007). Action selection is proposed to result from the **recall of past actions and their outcomes** (i.e., reinforcement history) as well as Pavlovian CSs that have been associated with approach or avoidance/withdrawal (i.e., **Pavlovian CSs bias action selection**; Berridge et al., 2009). Reinforcement history refers to how frequently and recently an action has been associated with a desirable or undesirable outcome. Greater frequency and recency results in a stronger association between the action and the outcome and a greater likelihood that the action will be carried out given the opportunity for reinforcement (Averbeck & Costa, 2017). However, reinforcement history also includes the context in which actions are performed. Pavlovian CSs can increase or decrease the likelihood that an action will be carried out if they have been associated with the

outcome of that action – another example of PIT (Corbit & Balleine, 2011; Ostlund & Balleine, 2008).

In MDD, negative memory biases are proposed to influence the recall of reinforcement history, including the frequency and recency of particular outcomes where negative outcomes are recalled as having occurred more frequently (Korn, Sharot, Walter, Heekeren, & Dolan, 2014). As reported above in our review of instrumental conditioning studies, misleading negative feedback has been found to be weighted more heavily than overall reinforcement history for determining choice for individuals with MDD (Murphy et al., 2003; Tavares et al., 2008). Furthermore, negative attentional biases are suggested to influence the detection of Pavlovian CSs associated with desirable and undesirable consequences in MDD, where aversive Pavlovian CSs are proposed to be detected more readily than appetitive Pavlovian CSs (Anderson, Leal, Hall, Yassa, & Yantis, 2014), biasing action towards avoidance/withdrawal responses as opposed to approach (Trew, 2011). However, it is possible that action selection will result in inaction, for example if no effective instrumental response can be recalled (Raes et al., 2005) or if a Pavlovian CS is sufficiently aversive (an example of aversive PIT; Dayan & Huys, 2008; Nord et al., 2018), as could be the case in MDD.

Effort tolerance versus estimated effort cost

If an effective instrumental action suitable to the context (as indicated by Pavlovian CSs that predict a successful outcome) is recalled, the next phase of the MELD framework includes competition between **effort tolerance** and **estimated effort cost**. Here, an individual's willingness to expend effort towards a particular outcome is pitted against the perceived effort required for the selected action (Treadway et al., 2012). In MDD, willingness to expend effort is expected to be low, whereas estimated effort cost is expected to be exaggerated (Cléry-Melin et

al., 2011; Hershenberg et al., 2016; Sherdell, Waugh, & Gotlib, 2012). However, if effort tolerance is greater than or equal to estimated effort cost, the action to obtain or avoid a pleasant or unpleasant outcome, respectively, will be carried out. An individual with MDD exploring options in a food court would be expected to estimate that patiently waiting for food will require an abundant amount of effort and their willingness to wait patiently may be low. If their willingness to wait patiently is less than the effort (or energy) required to do so, they are unlikely to wait in line. Alternately, if an individual with MDD does not estimate that waiting in a line will require much effort, their willingness to wait may be sufficient for them to do so.

Outcome sensitivity and updating of priors

Once an action has been carried out, the **success or failure** of the action and an individual's subjective experience of the outcome as pleasant or unpleasant (referred to in the MELD framework as **outcome sensitivity**) will influence the **updating of priors** for the action-outcome association (Berridge et al., 2009), as well as the cues and contexts that will now be associated with the outcome (again influenced by attentional bias). Updating of priors involves changes in (1) estimations of the pleasantness or unpleasantness of outcomes, (2) stimulus-outcome associations (i.e., Pavlovian conditioning), and (3) action-outcome associations (i.e., instrumental conditioning). Regarding the updating of priors for the pleasantness or unpleasantness of outcomes, stronger encoding and consolidation of positive and negative experiences will facilitate later recall of that experience for the purpose of estimating outcome value through cognitive desire/aversion, whereas weaker encoding and consolidation of positive and negative experiences will result in lower estimated outcome value. In MDD, increased punishment sensitivity and decreased reward sensitivity, as well as rumination of negative experiences that promotes consolidation of these memories, would be expected to promote recall

of negative experiences and their unpleasantness, and diminish the recall of positive experiences and their pleasantness (Hamilton & Gotlib, 2008; Levens & Gotlib, 2010; Watkins, Vache, Verney, & Mathews, 1996). The individual with MDD at the food court may have ruminated considerably in the past while waiting in line ups and not at all about the pleasant experience of enjoying the result of that action, i.e., delicious food. Therefore, this individual may easily recall how unpleasant it is to wait in a line and only vaguely recall the pleasantness of a meal (updating priors regarding how much each experience was ‘liked’ or ‘disliked’).

Outcome sensitivity would also be expected to bias the updating of priors for the recall of past actions and their outcomes, where associations between actions and consequent failure may be more likely to be strongly encoded and consolidated in MDD, leading to failed instrumental actions being recalled as occurring more frequently in general and more easily when the failed instrumental action occurred recently (affecting estimations of reinforcement history). Individuals with MDD have been shown to have greater sensitivity to negative feedback (Ruchow et al., 2006), which is consistent with findings from the instrumental conditioning studies reviewed above that individuals with MDD are more likely to guide their actions based on recent negative feedback as opposed to the overall reinforcement history (Murphy et al., 2003; Tavares et al., 2008).

Lastly, outcome sensitivity would influence the updating of priors for Pavlovian CSs, including conditioned associations between environmental stimuli and (1) their outcomes alone (affecting future motivational salience of these stimuli) and (2) stimuli and a representation of the action alone or a representation of both the action and its outcome (affecting future action selection; Dayan & Berridge, 2014), which in MDD would likely entail enhanced encoding and consolidation of cues in the environment that predict failure and blunted encoding and

consolidation of cues when outcomes are positive (i.e., successful instrumental actions). For example, if an individual with MDD attempts to engage a colleague at work in casual conversation and is told by the colleague that it is not a good time, they may attend to the person's body language and facial expression and these cues may be associated with a failure to connect with co-workers, even if these cues do not predict failure to engage with co-workers in the future.

To summarize, the updating of priors in the MELD framework involves updating future estimations of how pleasant or unpleasant an outcome is, the estimated reinforcement history for that particular action, and the environmental cues and context that predict that outcome. Each of these updates are influenced by outcome sensitivity, where greater sensitivity to negative outcomes in MDD may facilitate the updating of priors for disliking negative outcomes, actions that produce negative outcomes, and Pavlovian CSs that predict negative outcomes. Alternatively, in MDD, less sensitivity to positive outcomes would inhibit updating of priors for liking positive outcomes, actions that lead to positive outcomes, and Pavlovian CSs that predict those outcomes.

Representation of PIT in the MELD framework

In our framework, we propose two ways altered PIT may be a barrier to obtaining positive reinforcement for individuals with MDD. The first is exaggerated influence of aversive and blunted influence of appetitive Pavlovian CSs on motivational salience. Enhanced aversive salience would be expected to increase the value of undesirable instrumental outcomes and lower the value of desirable instrumental outcomes. We further propose that blunted appetitive salience would result in limited influence of appetitive Pavlovian CSs on the value of both desirable and undesirable outcomes. The second way PIT is proposed to operate in MDD according to our

framework is the influence of Pavlovian CSs on action selection (Berridge et al., 2009). Specifically, attentional biases towards aversive Pavlovian CSs are proposed to bias the recall of ineffective as opposed to effective instrumental actions, as well as strong associations between aversive Pavlovian CSs and ineffective instrumental actions. Therefore, consistent with current conceptualizations of PIT (Balleine & Ostlund, 2007; Dorfman & Gershman, 2019), we propose that individuals with MDD are disadvantaged in terms of the general motivating properties of Pavlovian CSs on instrumental actions and their influence on action selection.

Comparing frameworks

The ACDM framework, which characterizes unique alterations in decision-making in anxiety and depression, was influential in the formulation of the MELD framework (Bishop & Gagne, 2018). Although our framework is applied only to MDD here, many aspects of our framework overlap with those included in the ACDM framework applied to depression. The primary psychological components of the ACDM framework, including the value of instrumental outcomes, the probability that an outcome will be obtained following various actions, and the estimation of effort required for particular actions, are broadly reflected in the MELD (instrumental outcome value, action selection, and effort tolerance versus estimated effort cost, respectively). Another important component of the ACDM framework applied to depressed mood is the suggestion that depressed individuals may have a reduced ability to recall actions that were associated with a desirable outcome, a feature that is also included in our framework. What distinguishes the two frameworks is our incorporation of additional cognitive processes that may contribute to instrumental actions in MDD, most notably the influences of Pavlovian CSs on instrumental behaviour. Our framework also complements estimated effort cost with the concept of effort tolerance, reflecting the amount of effort an individual is willing to produce to

1089 obtain the desired outcome. Here we separate the estimation of effort required from willingness
1090 to expend effort because both may affect whether an individual (successfully or unsuccessfully)
1091 exerts effort towards a desired outcome (Chong et al., 2016; Chong et al., 2015; Cléry-Melin et
1092 al., 2011). Thus, while these two frameworks are complementary, the MELD framework aims to
1093 provide broader account of emotional learning in MDD.

1094 **Future directions**

1095 The proposed framework, developed to aid in the characterization of emotional learning
1096 in MDD, offers a simplified account of how Pavlovian cues may influence instrumental
1097 behaviour. It does not address how the acquisition and extinction of Pavlovian associations may
1098 interact with instrumental behaviours in MDD. Due to the inconsistent findings in past studies
1099 examining aversive Pavlovian conditioning in MDD and paucity of studies investigating
1100 appetitive Pavlovian conditioning in MDD, further investigation is needed to address this gap.
1101 Furthermore, while an abundance of research has investigated incentive salience and its clinical
1102 importance for problems like addiction (Berridge & Robinson, 2016), research and theory
1103 regarding aversive or fear salience is lacking despite its probable relevance to mental health
1104 conditions like MDD. Aversive Pavlovian influence over instrumental conditioning is proposed
1105 in our framework to play a critical role in maladaptive instrumental behaviours in MDD. A
1106 promising future direction for research on motivational salience and its clinical application
1107 would be the conceptualization and investigation of aversive salience and the role it may play in
1108 MDD. PIT is a paradigm that may be well-suited to such research, especially when primary
1109 aversive stimuli and socially relevant aversive stimuli are used as the US for Pavlovian training
1110 phases of PIT paradigms.

A notable omission from this article is the potential role of PIT in the propensity for, and onset of, MDD. Although research to date has not investigated this topic, we speculate that attentional and memory biases would facilitate exaggerated aversive Pavlovian control and blunted appetitive Pavlovian control over behaviours for individuals susceptible to depression. As a consequence, individuals who are susceptible to depression would be expected to experience fewer positively reinforcing experiences overall, leading to bouts of depression. Longitudinal studies examining how performance on PIT tasks relates to depression risk and the onset of MDD are needed to explore these hypotheses.

Conclusion

Emotional learning is considered to be an evolutionarily adaptive psychological process required for reflexively responding to anticipated significant events and performing actions that can promote desirable experiences and prevent or escape undesirable ones. Individual differences in emotional learning, including Pavlovian and instrumental conditioning and interactions between the two, can inform the emotional processes that contribute to and maintain MDD as well as potential treatments. Since, in real-world contexts, Pavlovian and instrumental conditioning are always under mutual influence, examining PIT in the context of depression is important for acquiring a more complete picture of the pattern of cognitive processes that contribute to and maintain depressive symptomology. To date, research on these topics is relatively limited considering the central role that behavioural theories of depression (which rely heavily on emotional learning principles) have played in understanding and treating MDD. Further investigating MDD using emotional learning paradigms is essential for advancing our understanding of MDD from a behavioural perspective. Furthermore, informing future work with

1133 a theoretical framework such as the one proposed here will aid in developing and refining a
1134 comprehensive characterization of emotional learning in MDD.

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