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Article

Accepted Version

Rizvi, S. J., Gandhi, W. and Salomons, T. (2021) Reward processing as a common diathesis for chronic pain and depression. *Neuroscience and Biobehavioral Reviews*, 127. pp. 749-760. ISSN 0149-7634 doi: <https://doi.org/10.1016/j.neubiorev.2021.04.033> Available at <https://centaur.reading.ac.uk/98700/>

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To link to this article DOI: <http://dx.doi.org/10.1016/j.neubiorev.2021.04.033>

Publisher: Elsevier

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Reward processing as a common diathesis for chronic pain and depression

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Abstract

Pain disorders and psychiatric illness are strongly comorbid, particularly in the context of Major Depressive Disorder (MDD). While these disorders account for a significant amount of global disability, the mechanisms of their overlap remain unclear. Understanding these mechanisms is of vital importance to developing prevention strategies and interventions that target both disorders. Of note, brain reward processing may be relevant to explaining how the comorbidity arises, given pain disorders and MDD can result in maladaptive reward responsivity that limits reward learning, appetitive approach behaviours and consummatory response. In this review, we discuss this research and explore the possibility of reward processing deficits as a common diathesis to explain the manifestation of pain disorders and MDD. Specifically, we hypothesize that contextual physical or psychological events (e.g. surgery, divorce) in the presence of a reward impairment diathesis worsens symptoms and results in a negative feedback loop that increases the chronicity and probability of developing the other disorder. We also highlight the implications for treatment and provide a framework for future research.

Keywords: Major depression; chronic pain; reward processing; diathesis; comorbidity

1. Introduction

Pain disorders and psychiatric illness comprise approximately 11% of global disability, causing immense impairment individually, socially and economically (Kyu et al, 2018). The prevalence of pain and mental disorders speaks to their impact with approximately 20% of the population experiencing a psychiatric diagnosis or a diagnosis of a chronic pain disorder within the last year (Breivik et al., 2006; Schopflocher et al., 2011; Steel et al., 2014). Notably, there is also a high level of comorbidity among chronic pain and mental illness. A mood disorder, particularly depression, may be present in 40-50% of chronic pain patients (Radat, Margot-Duclot, & Attal, 2013; Demettynaere et al, 2007; Von Korff et al, 2005). Conversely, over 60% of depressed patients report a chronic pain condition (Ohayon & Schatzberg, 2010). Clinically, the comorbidity between these disorders is of particular importance, since they are more treatment resistant when presenting in combination (Fishbain et al, 1997).

Theory regarding the mechanisms of the high comorbidity between pain disorders and mental illness relates to overlapping neural networks in pain processing and emotion regulation (Koechlin & Kossowsky, 2018; Wiech & Tracey, 2009; Nekovarova, 2014). More recently, however, maladaptive brain reward processing as a common nexus has been suggested (Borsook et al, 2007; Nees & Becker, 2018). There are consistent data demonstrating reduced reward responsivity in Major Depressive Disorder (MDD), and similarly, there is emerging research detailing alterations of the reward system associated with chronic pain (Navratilova et al., 2015; Rizvi et al., 2016; Taylor et al., 2016). A review of the overlap between altered reward processing and pain across all psychiatric illnesses is beyond the scope of this review, but given the centrality of reward processing to depression symptomatology and the high comorbidity between chronic pain and depression, the aim of this review will be to critically assess the existing evidence supporting alterations of reward processing in depressed and chronic pain patients, and to explore the role of altered reward processing as a pathophysiological factor common to both disorders and, potentially, as the cause for their high comorbidity rate.

2. Depression and Chronic Pain Comorbidity

In approaching the high rate of comorbidity between pain and depression from a clinical standpoint, it is necessary to better understand the causal structure of this relationship and the mechanisms that may give rise to it. One model is the “antecedent hypothesis”, which posits that chronic pain is caused by some (usually unspecified) psychopathology (Blackburn-Munro, 2001). This model has been widely influential since Freud’s conjecture about “hysterical” disorders and Engel’s profile of the “pain prone patient”, which attributed vulnerability to chronic pain from unresolved

guilt and other psychological states (Breuer & Freud, 1895; Engel, 1959). These explanations were at the root of pain disorders in earlier versions of the Diagnostic and Statistical Manual (DSM) which presumed a role for psychological factors in the etiology of reported pain (e.g. “Psychogenic” pain disorders). Diagnoses that presume a psychological origin have been expunged from the most recent DSM, due to unreliability and lack of empirically supported mechanistic explanations for how a psychological state might cause physical pain¹ (Katz, Rosenbloom, & Fashler, 2015). These diagnoses were replaced by “Somatic Symptoms Disorder”, which takes an agnostic view of the relationship between pain and psychological distress, simply noting that distress is occurring within the context of pain. Nevertheless, the belief that unexplained pain must be caused by psychopathology remains a default for many clinicians, with patients frequently told the pain is “all in your head” and sent to mental health providers with the presumption that once mental health issues are resolved, pain will disappear as miraculously as it arose. Criticism of this default presumption does not preclude the possibility that pain might in some cases be caused by negative emotions (such as when psychological tension causes a head or neck ache, or when a panic attack causes chest pains), or that psychological states play no part in facilitating pain. It is merely to say that the lack of a clear explanation for pain does not automatically mean such pain is caused by psychological factors, and such presumptions should only be made when there is clear, falsifiable evidence for a mechanism.

Although there is evidence for depression (and cognitive processes associated with depression) increasing vulnerability to pain (e.g. Gupta et al., 2007), there is not strong evidence, nor a viable mechanistic model for how depression might cause pain in the absence of peripheral pathology, limiting the power of antecedent models as causal (rather than facilitatory) explanations of the development of pain. There is more abundant evidence for depression developing as a consequence of pain (Banks & Kerns, 1996). Ongoing, poorly managed pain is a chronic stressor that disrupts normal social and occupational functioning, supporting the plausibility of this model. Nevertheless, models where pain causes depression are clearly insufficient as they do not account for comorbidity in cases where pain does not precede mental health symptoms, nor do they fully explain the cycle of pain and negative affect that makes these disorders more treatment resistant in combination (Fishbain et al, 1997).

A third possibility, and one that will be explored further in this review is that this relationship could, in many cases, be due to a third factor, a vulnerability that puts an individual at increased risk of both depression and chronic pain. Such an explanation could be viewed as a diathesis-stress model, with the manifestation of the latent shared vulnerability dependent on the nature of the

¹ For the duration of this article the term “pain” will be used as defined by IASP “.....” to denote phenomenological states resembling injury, rather than in its broader sense to denote any emotionally distressing state (i.e. “emotional or social pain”)

stressors experienced by the individual. For a person with the diathesis, psychosocial stressors (e.g. loss of a close interpersonal relationship) might lead to depression or some other mental health disorder, while somatic stressors (e.g. surgery or a workplace injury) might lead to chronic pain under conditions where others heal quickly and live without pain. It should be noted that such a model is not mutually exclusive from the two models mentioned above. For example, an individual with the vulnerability might develop chronic pain following a workplace injury. The stress of living with pain (including not only the pain, but the accompanying disability and social isolation), when combined with the pre-existing vulnerability might then lead to a major depressive episode which in turn facilitates further pain. As such, the diathesis would not only represent a vulnerability, but a mutual maintenance factor, a mechanism through which pain and depression facilitate each other. In what follows, we will make a case for how maladaptive reward learning processes might represent one such diathesis, making some individuals particularly vulnerable to developing both chronic pain and depression.

3. Impaired Reward Processing as a Potential Shared Vulnerability

Decreased interest and pleasure in response to positive stimuli (i.e. anhedonia) is a core diagnostic feature of depression, so the notion that maladaptive reward processing might be a key etiological factor is intuitive. This is less the case for pain, so understanding reward processing as a vulnerability factor for pain will be the focus of the discussion below. One reason for this may be that prototypical examples of pain such as “touching a hot stove” emphasize a conceptualization of pain that highlight the reactive nature of pain (“pain caused me to pull away from the stove”) and its aversive quality (“touching that stove sucked!”). While this captures highly salient aspects of pain, focus on these aspects obscures learning and inferential processes related to pain and how these processes can be shaped by appetitive reinforcement. To continue with the example above, while the pain of touching a stove is highly aversive, the relief gained from withdrawing (and perhaps running our hand under cold water) reinforces those behaviours, teaching us to use them again in similar situations. Furthermore, the memory of pain helps to reinforce any behaviours that allow us to avoid touching the stove in the future. As such, reward processes play a key role in how we learn about, experience and respond to pain, and understanding the role of reward processes in pain requires explicit consideration of inferential processes that contribute to pain and the role that appetitive reinforcement might play in them. For example, extant models of pain (eg. Imperative [Klein, 2015] and homeostatic [Craig, 2003] models) stress its role in motivating actions that will return the organism to an optimal state of health. As pointed out by Fields (Fields, 2018), these actions are most adaptive when they can be initiated proactively in response to cues signalling

imminent pain. An adaptive system also requires that these actions be evaluated and altered if they don't have their desired effect in avoiding or reducing pain. As such, pain is increasingly being viewed as an inferential process, whereby the individual forms an expectation ("prior"), which is then updated if that expectation is violated (Büchel, Geuter, Sprenger, & Eippert, 2014; Fields, 2018; Seymour, 2019; Wiech, 2016). A critical feature of these models is that the expectation biases perception towards it, such that a highly negative expectation will make the resulting pain percept more negative ("nocebo effect") while a highly positive expectation will result in a less aversive pain percept ("placebo effect"). Any difficulty in updating the expectation of pain would result in a system poorly attuned to physical threats in the environment. In some cases this might manifest as a sustained perceptual bias towards pain.

A chronic bias towards negative states (including depression and anxiety) involves two closely-related processes: an attentional bias towards negative outcomes and a deficit in reward learning, the latter which will be the primary focus of this review. With respect to attentional bias, individuals with chronic pain are more likely to interpret ambiguous stimuli as pain or illness related (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013; Pincus & Morley, 2001; Schoth & Lioffi, 2016). It has also been shown that a pain related negative cognitive bias, pain catastrophizing, is predictive of the development of chronic pain following physical trauma (Theunissen, Peters, Bruce, Gramke, & Marcus, 2012), indicating that cognitive biases may not only exacerbate pain but act as a predisposing factor. Similarly, there is a vast literature documenting attentional biases towards negative interpretations in depression, and these cognitive biases have been shown to be a risk factor for the development of depression (Everaert, Koster, & Derakshan, 2012). In the absence of information about a cue of potential danger or the appropriate behavioural response to that cue, presumption of threat might be adaptive, as a "better safe than sorry" strategy that helps the organism avoid potential dangers in uncertain situations. What sets vulnerable individuals apart is the imperviousness of these negative expectations to contradictory information. Individuals with a negative cognitive bias keep expecting aversive outcomes, despite information which would cause others to update their expectations to reflect a greater sense of safety.

As mentioned, the inability to update negative expectations involves a second learning-based process: a deficit in reward learning. For example, within a predictive processing framework, this would be formalized as an inability to update expectations based on better than predicted outcomes (e.g. when pain is less than anticipated). Reward learning can take two forms in the context of pain: avoidance and relief. Avoidance is where an action results in an expected pain not being delivered. Relief is the alleviation of a tonic pain (Seymour & Dolan, 2013). Successful adaptation to the environment requires learning which actions will have positive outcomes. A deficit

in the ability to update expectations based on positive outcomes would prevent beneficial approach-related actions and future learning of ways to avoid expected negative outcomes.

There is increasing evidence that reward-related processes might serve as such a vulnerability/mutual maintenance factor for prolonged maladaptive pain (Finan & Smith, 2013). There has also been a great deal of research demonstrating deficits in reward function in depression, which is also associated with greater likelihood of treatment resistance (McMakin et al, 2012, Spijker et al., 2001; Vrieze et al., 2014; Uher et al, 2012). As such, we will review the mechanisms that might predispose some individuals to maladaptive reward processing, both in the context of nociceptive input and psychosocial stressors that might predicate depression.

4. Reward and its interactions with pain and depression

Reward is defined as “any pleasant event that follows a response and therefore increases the likelihood of the response recurring in the future” (Collins English Dictionary – Complete and Unabridged, 12th Edition 2014 © Harper-Collins Publishers). In this definition, ‘pleasant events’ refer to anything that shifts the individual on their hedonic spectrum towards desired, pleasant states and, hence, away from aversive states. The definition thus highlights the hedonic aspect of reward and its purpose to facilitate learning in order to maximize approach-behaviour for pleasant events, or to minimize negative events, in the future. Pursuing reward is crucial for survival and therefore one of our strongest motivators. In the following sections, we will portray reward and its interactions with pain and depression accordingly, breaking it down into its different facets; specifically, reward-dependent learning (reinforcement-based changes in expectations and behaviours), wanting (incentive salience, craving, anticipation, the motivation to work for reward), and liking (the hedonic response to reward, consummatory pleasure). In brief, in order to engage with a reward, one must first learn that a stimulus-reward association is present. A prediction error signal within the brain’s reward circuits encodes the presence of unexpected rewards, unexpectedly high rewards, as well as the absence of anticipated rewards (Bray and O’Doherty 2007; Contreras-Vidal and Schultz 1999; Delgado 2007; O’Doherty 2004). Via prediction errors, the individual learns to predict the consequences of their actions and will use this knowledge to (1) maximize the likelihood of rewards and to (2) minimize punishment in the future. If the comparison of one’s expectation, and the actual outcome yield a difference (i.e. prediction error) the knowledge can be updated, and the future prediction will be more accurate (Niv and Schoenbaum 2008). ‘Wanting’ describes the shift of an individual’s orientation towards an environmental stimulus that represents more than mere sensory input but becomes a desired (‘wanted’) stimulus – a process referred to as *incentive salience* (Berridge 2007). When reward is now being anticipated, goal-directed actions need to be

consequently initiated and be sustained to obtain the reward, including for instance the motivation to work for it. Once reward seeking has been successful and the individual is finally consuming the reward, pleasure is typically felt. In accordance with the literature, we will refer to the hedonic response to reward as 'liking' or 'consummatory pleasure'. For a more elaborate overview of these reward processes and their neural underpinnings we refer the reader to previously published review articles (Berridge, Robinson, & Aldridge, 2009; Pool, Sennwald, Delplanque, Brosch, & Sander, 2016; Robinson, Fischer, Ahuja, Lesser, & Maniates, 2016). Traditionally, the clinical symptom of anhedonia was considered to primarily reflect a decrease in interest and consummatory pleasure. However, it is now clear that anhedonia reflects the spectrum of impaired reward experience that includes deficits across learning, wanting and liking (Rizvi et al., 2016).

4.1. Pain and reward interactions

Anhedonia is commonly described in chronic pain patients (Marbach and Lund 1981; Garland et al, 2019), with greater pain severity being associated with higher consummatory anhedonia and a general lack of motivation (Barendregt et al., 1998; Carpinelli et al, 2019; Fishbain et al., 2004). Numerous brain regions, including the ventral and dorsal striatum, rostral ACC, and insular cortex are involved in pain and reward processing, offering a neural substrate for the two systems to interact (Becker et al., 2012; Leknes and Tracey 2008; Navratilova et al., 2015). See Figure 2 for an overlap of the brain regions involved in reward processing, pain and depression.

The ventral striatum is imperative to develop expectations of reward and predict when it will and will not occur via specific dopamine-mediated activity patterns, which in turn represents a key process underlying reward-dependent learning (e.g. Gottfried et al., 2003; McClure et al., 2004; Pagnoni et al., 2002; Schultz 2007). The key neural element of reward-dependent learning is the prediction error signal of the ventral striatum (Bray and O'Doherty 2007; Contreras-Vidal and Schultz 1999; Delgado 2007; O'Doherty 2004). As discussed above, reward prediction has important implications for predicting pain relief as well as perpetuating a negative cognitive bias.

Patients suffering from chronic pain, such as fibromyalgia and complex regional pain syndrome, have deficits in improving their performance on reward-dependent learning tasks (Apkarian et al., 2004a; Becker et al., 2011; Verdejo-Garcia et al., 2009; Walteros et al., 2011), typically showing more random choice behavior and a slower or no increase in their learning curve based on past rewards or punishments. Similarly, chronic back pain patients were found to show altered loss aversion in a monetary gambling task than healthy control participants – patients chose disadvantageous high reward/high loss options, thus accepting the risk of loss to a greater extent than healthy controls (Berger et al., 2014). The observed behavioural alterations do not seem to be dependent on a general decrease in cognitive function in patients or on concurrent pain levels

(Berger et al., 2014; Walteros et al., 2011), suggesting the effects to be specific to altered reward functioning associated with chronic pain. The findings in patients have been supported by rodent studies, showing slower learning curves for rats with neuropathic pain compared to sham-operated and naïve animals in a choice task after reinforcement contingencies were changed compared to a previous task (Cowen et al., 2018). Thus, rodents with chronic pain seem to show less profitable behavior. Taken together, the results in humans and animals suggest that individuals with chronic pain lack the ability to learn based on previous reward or punishment because of an abnormal prediction error signal, and thus fail to improve their behavior. A deficit in the ability to update information based on new cues could have several effects that would serve to facilitate further pain, first by increasing the expectation of pain (resulting in placebo effects), second by limiting reinforcement of adaptive actions (making them less likely to be repeated), and finally by reducing the mitigating effects of external rewards (e.g. food, pleasurable activities).

Mitigating pain by means of external rewards has been observed in healthy people who were exposed to a longer-lasting heat stimulus (1 hour). The study revealed that healthy individuals show increased motivation to obtain high rewards when simultaneously having to endure a tonic heat stimulus compared to when being in a pain-free state (Gandhi et al., 2013). The increase in motivation in this study was associated with changes in unpleasantness – the more unpleasant participants perceived their painful state the harder they tried to obtain high rewards. Gandhi et al. (2013) concluded from these results that pain as an unpleasant state shifts the individual negatively on the homeostatic spectrum, motivating them to seek external rewards. Since the pain itself cannot be escaped in this situation, reaching out for positive means – in this case obtaining monetary reward – can serve as an attempt to reestablish homeostasis at least to some degree. However, this state of increased motivation for reward seeking is not observed in patients with chronic pain. In fact, a general lack of motivation is typically described in chronic pain patients (Barendregt et al., 1998; Fishbain et al., 2004). A reduced motivation to show goal-directed approach behaviour when in pain may be an adaptive response on the short-term, within a setting of acute pain. For instance, rest can help the process of recovery in this circumstance (Gandhi et al. 2017). However, lacking the motivation for goal-directed actions – the pursuit of pleasurable activities and experiences, for example, becomes maladaptive as pain becomes chronic. Based on the knowledge that positive experiences (consuming reward) decrease the perception of concurrent pain (Becker et al., 2013; Becker et al., 2015), pursuing rewards would be an adaptive coping mechanism for inescapable pain (as it is typically the case in chronic pain conditions).

Neurochemically, dopamine appears to play a central role in situations where different motivators compete with each other – such as a pain that we desperately want to end and the

presence of an external reward that we desire. Dopamine has been proposed to mediate the relative salience of painful and positive potentially rewarding stimuli in the environment when we find ourselves in the conflict to attend to one stimulus or the other (Taylor et al., 2016). It seems to facilitate the decision to either endure pain (and be able to focus on other, more relevant contextual stimuli) or show a fight/flight action to avoid/escape pain (Taylor et al., 2016; Gandhi et al., 2017). Thus, dopamine appears to underlie (pain) coping mechanisms, helping to make a sensible decision in the presence of conflicting motivators, as described within the motivation-decision model (Fields et al. 2006). Abnormalities within this system could therefore be assumed to leave an individual at an increased risk of being unable to cope when pain is being encountered, thus impairing an individual's ability to learn adaptive responses to incoming nociceptive input and leaving them more vulnerable to pain chronification.

Impairments of dopamine signalling within mesolimbic circuits around the ventral striatum have, indeed, been described in animals and humans with chronic pain (*reviewed in* Taylor et al., 2016). Human studies revealed that dopamine release in response to experimental pain is reduced in patients with chronic widespread pain (Martikainen et al., 2015; Wood et al., 2007), and VTA activity diminished in response to reward in patients with fibromyalgia (Loggia et al., 2014). Importantly, rather than being a mere consequence of living with pain, abnormalities within the mesolimbic system appear to contribute to the development of chronic pain (Borsook et al., 2013). Specifically, reward-associated circuits around the NAc seem to mediate the experience of acute pain in healthy people (Scott et al, 2006, Baliki et al, 2010), as well as the transition from acute to chronic back pain (Baliki et al., 2012). However, longitudinal behavioral studies investigating how reward processing interacts with emerging pain are still sparse, so the exact role of reward-related processes in the chronification of pain need to be elucidated.

Very closely linked to the hypothesis that motivational processes and prediction error signalling might be deficient in individuals with chronic pain, is the possibility that patients simply do not perceive pleasure when being rewarded. This would mean that there is *per se* no rewarding signal to help improve future behavior. Neurochemically, pleasure felt when being rewarded is associated with the endogenous opioid system – a system that also plays a key role in descending pain modulation (e.g. Zubieta et al, 2001, Navratilova et al, 2015) and pain-induced affect (Massalay et al. 2019). Opioid signalling in the rostral ACC, for instance, seems to mediate placebo analgesia (Petrovic 2005, Wager et al, 2004) and is associated with pain relief when given as a reward (Leknes et al, 2011) in healthy participants. Using opioid receptor PET, studies identified decreased binding potentials in chronic pain patients with neuropathic pain (Maarrawi et al., 2007) and fibromyalgia (Harris et al., 2007). These findings are supported by a recent rodent study showing reduced mu-

opioid receptor availability in the dorsal striatum (caudate and putamen), insular cortex, and motor cortex after the induction of chronic neuropathic pain (Thompson et al., 2018). Reduced opioid receptor availability of the dorsal striatum was associated with anhedonia in these animals. Strikingly, a recent fMRI study in teenagers demonstrated that activation of the dorsal striatum during reward consumption significantly predicted the clinical pain magnitude participants would report 2 years after the scan (Nees et al 2017). The results thus suggest that alterations of the neural processing underlying hedonic responses to reward may not only alter as a consequence of living with pain but can precede and predict the development of chronic pain.

Taken together, these results demonstrate deficits in reward processing in individuals with chronic pain, including deficits in learning, wanting, and liking. Critically, work in both animal and human populations suggests that these deficits might not be a simple result of living with intractable pain but may, in fact, play a facilitatory role in the development of chronic pain.

4.2. Depression and reward interactions

Given anhedonia is a cardinal symptom of MDD, it follows that reward processing deficits have been consistently observed across all facets of reward learning, liking and wanting (Rizvi et al, 2016; Pizzagalli, 2014). Impairments in learning are evidenced through response bias tasks that determine an individual's implicit ability to identify stimuli that are more frequently rewarded (i.e. evaluation of whether reward is perceived through a stimulus-reward association). In these studies, MDD patients consistently do not learn this as well as healthy controls and have a lower response bias to more rewarded stimuli (Pizzagalli et al, 2008; Pizzagalli, 2014; Henriques & Davidson, 2000). Such an impairment at the outset of reward processing could yield notable difficulties in appetitive approach behaviours and consummatory responses, which consequently do not provide accurate information to update reward learning associations.

Learning through experiences of probability for reward are imperative to keep expectations in line with one's environment. As discussed above, failure to do so via impairments in prediction error signalling can significantly impact a person's appetitive responses. Indeed, MDD research on the prediction error signal from unexpected reward outcomes has mostly demonstrated blunted brain activity compared to healthy controls (Ubl et al, 2015; Kumar et al, 2008; Kumar et al, 2018; Gradin et al, 2011) and an association between a reduced reward-expectancy relationship to prediction error in the ventral striatum and increased levels of anhedonia (Greenberg et al, 2015). Interestingly, in one study depressed patients did not exhibit prediction error signals coding for unexpected reward but did show signals coding for less reward than expected in the ventral striatum (Ubl et al, 2015). This is consistent with the negative cognitive bias observed in MDD, where there is

greater attentional focus to negative stimuli. For example, Rouhani and Niv (2019) recently demonstrated enhancement of episodic memory with negative prediction errors but not positive prediction errors. Early evidence also suggests that a greater number of depressive episodes is correlated with blunted prediction error signal in the striatum (Kumar et al, 2018), suggesting that chronicity can have additive effects on reward processing capabilities.

Challenges in integrating feedback can also hamper reward learning in MDD through an inability to update stimulus-reward associations with context. This may be particularly relevant to the receipt of negative reward stimulus feedback, where task performance is not optimized due to hypersensitivity to negative feedback (Elliott et al, 1997; Murphy et al, 2003). Notably, Bakic and colleagues (2017) observed that relative to controls, MDD patients exhibited specific impairment in negative feedback signals rather than negative prediction error signals.

Decreases in facets of wanting have consistently been demonstrated in MDD. The monetary incentive delay task has been frequently used to evaluate brain responses to anticipation and outcome of reward (Rizvi et al, 2016). While there is some conflicting evidence for striatal activity during anticipation in depressed patients compared to healthy controls (Knutson et al, 2008; Dichter et al, 2012; Stoy et al, 2012), a recent meta-analysis provided evidence for an overall decrease in striatal anticipatory activity in the context of depression (Keren et al, 2018). Studies suggest that reward motivation and effort are also decreased in depression. More specifically, MDD patients are less motivated to expend effort for reward (Hershenberg et al, 2016; Treadway et al, 2012; Park et al, 2017). This effect may be evident even in subsyndromal depression (Yang et al, 2014). These data, taken together, point to reduced reward approach behaviours in MDD that ultimately limit the quantity of reward and positive reinforcement that an individual can receive.

Reward liking is also consistently reduced in MDD. Clinical scales reflecting loss of consummatory pleasure demonstrate significant impairment in depressed patients compared to healthy controls (reviewed in Rizvi et al, 2016). Task data also demonstrate reduced nucleus accumbens and caudate activity during reward receipt (Pizzagalli et al, 2009). A meta-analysis of fMRI and electroencephalography data also reported reduced neural activity in the caudate during consummatory phases of reward (Keren et al, 2016). Notably, tasks evaluating consummatory response to sucrose in MDD compared to healthy controls have not yielded significant findings on self-report ratings (Berlin et al, 1998; Dichter et al, 2010; McCabe et al, 2009). However, between-group differences in ventral striatal activity during consumption of chocolate were significant in one trial (2009) irrespective of insignificant differences on clinical ratings of pleasure. These data suggest the possibility that decreases in neural activation during consummatory reward in depression may occur without comparable self-report ratings.

The degree to which a reward is valued can also indicate the extent of reward liking. In particular, studies of preference for immediate small or delayed larger rewards (delayed discounting) have demonstrated that compared to healthy controls, depressed patients exhibit a preference for smaller immediate reward (Pulcu et al, 2014; Dombrovski et al, 2012; Takahashi et al, 2008). A recent meta-analysis of delayed discounting studies supports these findings, demonstrating that in depression there is increased discounting of larger delayed rewards, an effect that can be observed across other psychiatric disorders as well (Amlung et al, 2019).

Notably, varied evidence exists with respect to how reward deficits persist into remission. In particular, some data suggest impaired reward response bias learning and brain activity during anticipation and response to reward is maintained in remitted MDD patients (Dichter et al, 2012; Pechtel et al, 2013). In contrast, other studies suggest that motivation and effort to obtain rewards and reward valuation is improved in remission and not significantly different from healthy controls (Yang et al, 2014; Pulcu et al, 2014). The idea that different aspects of reward may endure in depression reflects that these processes may occur, at least in part, independently of each other. In support of this theory, Sherdell and colleagues (2012) reported a disassociation between motivation to view cartoons and liking them in depressed patients, while they remained associated among healthy controls. Further research is needed to determine the differential impact of remission on reward function, however these preliminary data indicate the potential that deficits in reward response may reflect an enduring trait that is not dependently linked to depression severity. An alternative interpretation for these findings is that current antidepressants may not effectively target reward networks.

The discussed evidence suggests that the reward system in chronic pain patients and patients suffering from MDD functions differently from healthy controls (Mlost et al. 2019; Rizvi et al, 2016; Taylor et al. 2016; Whitton et al, 2015), potentially leading to a diminished ability to utilize the reward system to cope with and learn from aversive, emotional events (Gandhi et al. 2017; Pulcu and Elliot, 2015). As much of the work examined has been cross-sectional, it is difficult to rule out the possibility that these deficits are secondary to symptomatology, although some of the literature reviewed suggests that reward processing differences might facilitate the development of these disease states, possibly playing a developmental role in their etiology. Given the described overlap in neurocircuitry and reward system impairments among depression and chronic pain (see Figure 2), the extent to which treatment strategies for both disorders overlap will be explored in the following section.

5. Implications for Treatment Targeting of Reward Systems in Depression and Chronic Pain

The key neurotransmitter systems involved in reward function are catecholamines (dopamine and norepinephrine), glutamate, gamma amino-butyric acid (GABA), and opioids (Volkow et al, 2008; Shirayama et al, 2006; Barbano et al, 2007; van Zessen et al, 2012). Treatments for depression and pain disparately affect these systems and so may affect reward processing differently. Notably, antidepressant medications, tricyclics and serotonin and norepinephrine reuptake inhibitors (SNRIs) are frequently used for chronic pain management (Belinskaia et al., 2019; Mease et al., 2011; Lunn et al., 2014; Riediger et al., 2017). Although these drugs likely affect depression and pain through different mechanisms, their widespread use to treat both disorders have the potential to impact reward processing, which could in turn represent a common modulatory mechanism of both types of symptoms.

Pro-dopaminergic drugs like methylphenidate can have a positive effect on anhedonia in depressed patients compared to placebo (Rizvi et al., 2014), which follows from its effects on nucleus accumbens and prefrontal cortex dopamine (Ramaekers et al., 2013) as well as brain reward-motivation networks (Ivanov et al., 2014). Given that dopamine is considered to be depleted in depression, one study supported this notion through demonstrating a hypersensitivity to dextroamphetamine in MDD patients compared to healthy controls, which was associated with striatal, ventrolateral and orbitofrontal cortex activation (Tremblay et al., 2005). Bupropion with its action on dopamine and norepinephrine reuptake inhibitors (Costa et al., 2019), positively impacts effort-related reward (Yohn et al., 2016), and increases reward anticipation (Dean et al., 2016; Ikeda et al, 2019). In contrast to dopaminergic medications, emotional blunting has been reported with SSRIs, which manifests as reduced emotional responses to aversive and rewarding stimuli (McCabe et al., 2010). In 2010, McCabe and colleagues treated healthy volunteers with citalopram and showed decreased neural activation to aversive stimuli and decreased response to rewarding stimuli. In contrast, reboxetine, a noradrenergic drug, showed enhanced neural activation to rewarding stimuli and decreased activation to aversive stimuli. Furthermore, when the effect of neural activation to erotic stimuli was evaluated in healthy controls treated with the SSRI paroxetine or bupropion, paroxetine reduced striatal activation when viewing positive stimuli, while bupropion did not (Abler et al, 2012). These findings support the hypothesis that catecholamine systems are responsible for moderating positive affect/reward response, while potentiating serotonin can cause emotional constraint and decreased primary reward response (Pringle et al, 2013). However, the effects of serotonin on various aspects of reward processing requires further investigation as there may be aspects of reward processing that can be improved through serotonergic mechanisms.

The effect of serotonin and norepinephrine reuptake inhibitors (SNRIs) on reward function is even less clear and it is not established whether the norepinephrine action has a protective effect over the emotional blunting that can occur with SSRIs. There is a paucity of data of SNRI effects on reward processing. In one of the few studies, increased striatal activation was observed during anticipation following a two-week course of duloxetine in healthy controls (Ossewarde et al., 2011). However, a resting state functional connectivity study following 8 weeks of duloxetine in MDD patients demonstrated decreased functional connectivity between the ventral striatum and dorsolateral prefrontal cortex, which in turn was associated with greater symptom improvement (Wang et al., 2019). Notably, the authors point out the relevance of this circuitry to anhedonia severity and reward processing. Cui and colleagues (2018) recently demonstrated that during an open field test in rats, duloxetine, and the norepinephrine reuptake inhibitor, reboxetine, impacted reward valuation, whereas potentiation of serotonin only did not. With respect to the SNRI venlafaxine, one small study in MDD evaluated the effects of the SSRI fluoxetine or venlafaxine on brain activity while viewing/imagining positive and negative scenes (Heller et al., 2013). The authors reported an overall improvement in positive affect across both antidepressants that was correlated with sustained increases in NAc activity. While this increased activity was also correlated with improvements in anhedonia, this effect may have been more mediated by changes in positive affect. Another preclinical study demonstrated that delayed gratification in healthy rats increased with pro-adrenergic drugs, decreased with SSRIs and did not change with the SNRI venlafaxine (Dekeyne et al., 2002). These findings suggest it is possible that SNRIs have a more favourable impact on reward processing, potentially due to the noradrenergic action. This idea is supported by a study demonstrating that 8 weeks of levomilnacipran extended release improved energy/motivation and improvements in life functioning were strongly mediated by levels of energy/motivation (Thase et al, 2016).

Psychotherapy interventions have also been shown to impact anhedonia and reward processing. Cognitive behavioural therapy (CBT), behavioural activation, and mindfulness-based therapies demonstrate reductions in depressive symptoms including anhedonia (Farrabaugh et al, 2015; Hoffman and Gomez, 2017; Walsh et al, 2019). Behavioural activation, in particular, is purported to exert at least some of its effects through ameliorating reward system impairment: behaviourally it increases goal-directed behaviour and the frequency of positively reinforcing activities (Furukawa et al., 2018; Nagy et al., 2018), while neurally it can increase brain response to reward selection, anticipation and outcome in the striatum, anterior cingulate cortex and prefrontal cortex regions (Carl et al., 2016; Dichter et al, 2009). A recent behavioural activation study among MDD patients reported decreased connectivity between frontal regions and temporoparietal areas

in response to positive emotion, which predicted a reduction of anhedonia following 15 sessions of therapy (Walsh et al., 2019). Of note, both CBT and mindfulness therapies have been used with some success to treat chronic pain (Bawa et al., 2015; Urits et al., 2019). For example, following CBT treatment in chronic pain, studies have demonstrated improved prefrontal and somatosensory cortex connectivity, as well as frontolimbic connectivity (Shpaner et al., 2015; Yoshino et al., 2018). Mindfulness-based therapies focus on being in the here-and-now, and have received extensive support for reducing depressive symptoms (Hoffman and Gomez, 2017; MacKenzie et al, 2018). Notably, there is early evidence of reductions in chronic pain and depression among patients with comorbid MDD (de Jong et al., 2016, 2018). Interestingly, Thomas and Garland (2017) demonstrated a decrease in anhedonia in chronic patients with greater trait mindfulness even after controlling for depression severity. Despite the potential utility of psychotherapy for treating depression and chronic pain as well as treatment-emergent improvements in reward responsivity, further investigation is required to confirm the mechanism of therapy improvements. Consequently, we are unable to confirm whether the improvements in depression and pain from psychotherapy occur primarily through reward system adaptations, as there are other theoretically feasible mechanisms.

With respect to pain medication, opioid agonists have a long history of use and abuse (Finan et al., 2018) and preliminary evidence for use in depression (Kamajian et al, 2016; Falcon et al, 2016). While a comprehensive review of the literature covering the influence of opioid treatment on the reward system would be beyond the scope of this article, we will briefly summarize some of the findings that are key to this article. Recent evidence shows that pain patients who misuse opioids report even greater anhedonia than non-misusers (Gerland et al., 2019). This might be of particular relevance, considering the current opioid crisis, with a high number of opioid misusers among pain patients (Finan et al., 2018). The reported increase in anhedonia, in turn, is likely to contribute to the maintenance of chronic pain and to increase the risk to develop co-morbid depression (Fig. 1). Interestingly, trait reward responsiveness - i.e. an individual's sensitivity to rewarding environmental stimuli (Carver and White, 1994) - predicts the behavioral analgesic response to exogenous opioids (Wanigasekera et al, 2012). Further, the authors reported that the response within the reward circuitries (including OFC, ventral striatum, and amygdala) to painful stimuli before starting the opioid infusion was positively correlated to the magnitude of opioid analgesia (Wanigasekera et al, 2012). Both results clearly link the responsiveness of the reward system to the treatment success of exogenous opioids. The findings of this study may imply a weaker treatment effect of opioids (potentially leading to a less-than-expected pain relief and negative affect) in patients with a diminished response to reward and punishment and, thus, increasing the risk of pain chronification

and maintenance in these patients. We refer the reader to a more comprehensive review on the effect of opioid use on the brain reward system by Finan et al. (2018) who discuss this link nicely.

Low dose ketamine, which inhibits glutamate receptors, is used as a treatment in both pain and depression (Malhi et al., 2016; Niesters et al., 2014). Although not a first-line therapy, there is consistent research on the antidepressant effects of ketamine in depression (Caddy et al., 2015; Kryst et al., 2020). There are also reports of ketamine's potential efficacy in chronic pain (Michelet et al., 2018; Orhuro, Orhuro, Bhattia, and Cohen, 2019). However, it is unclear whether the effects of ketamine on chronic pain are more related to its modulation of affective states related to pain and depression (Humo et al., 2020; Wang et al., 2011; Yang, Maher, & Cohen, 2020). While the effect of ketamine on various aspects of the reward pathway is in its infancy, early studies suggest possible positive effects on anhedonia (Thomas et al., 2018), and increased neural activity in reward processing regions (Ionescu et al., 2018). In contrast, one study demonstrated attenuation of reward anticipation signals in the ventral striatum in healthy controls (Francois et al., 2016).

In summary, there are common treatments for depression and pain, which affect reward circuitry. The impact of these therapies on reward processing and associated improvement in symptoms speak to a potential mechanism of action and also provide further support for a common diathesis between the disorders. The overlap across systems and treatments suggests a strong rationale for treating depression and chronic pain in a more integrated manner. In the following section we will discuss the possibility that maladaptive reward processing may be a common factor underlying the development of chronic pain and depression – describing a malfunctioning of the reward system as a vulnerability to develop either or both of these conditions depending on environmental factors and individual experiences.

6. Moving forward: a framework for testing the etiological role of reward processing in comorbid Chronic Pain and Depression

The previous sections demonstrated a series of abnormalities in reward processing at both the behavioural and neural level. At the behavioural level we have divided these processes into abnormalities in learning, liking and wanting. At the neural level we have identified a series of structures involved in these processes, including the dorsal striatum, ventral striatum, orbitofrontal cortex and anterior cingulate cortex. Much of the evidence presented, however, is cross-sectional and doesn't lend itself to clear etiological inferences. In order to gain a clearer, more clinically and scientifically tractable picture of the role of reward related processes in chronic pain, depression and their comorbidity, we identify two critical questions: 1) Are altered reward processes merely a result

of chronic pain/depression, or do they represent a common diathesis?; and, if so, 2) What are the specific reward related processes that are altered and/or represent a shared diathesis?

6.1. Independent Altered Reward Processes in Chronic Pain/Depression versus Common Diathesis

While the data presented thus far is primarily cross sectional, several key pieces of evidence support our speculation that altered reward related processes might reflect a diathesis that could make a particular individual more vulnerable to both chronic pain and depression in the wake of a psychological or somatic trauma. First, a large sample has demonstrated that patient expectations are a key predictor of treatment response for individuals in chronic pain (Cormier, 2016). A key component of accurate expectation formation is the ability to update expectations on the basis of better-than-anticipated outcomes, so maladaptive reward processing could be a key contributor to the expectation-based chronification of pain. This is supported by some key pieces of evidence. First, activation of the nucleus accumbens predicts placebo analgesia (Zubieta et al, 2009), suggesting a key role for neural reward circuitry in expectation-based pain modulation. Second, in a large sample of individuals with first episode low-back pain, resting state connectivity between nucleus accumbens and medial prefrontal cortex predicted the development of chronic low back pain a year later, demonstrating a role for this circuit in pain chronification. Finally, striatal response to a monetary incentive delay task in teens was shown to predict pain two years later (Nees et al., 2017), supporting an account whereby maladaptive reward processing predisposes individuals to the development of chronic pain.

With respect to depression, findings that certain reward deficits including learning about a stimulus-reward association and reward anticipation persist into remission (Dichter et al, 2012; Pechtel et al, 2013) provides some evidence to suggest that specific reward processing deficits may be more trait based. Moreover, preliminary studies in high-risk for depression individuals (i.e. no psychiatric diagnosis, and parent with MDD) also indicate the potential presence of prodromal impairments in reward processing (Gotlib et al, 2010; Morgan et al, 2019; Olino et al, 2014), which may be predictive of a future MDD diagnosis (Rawal et al. 2013). In support of the idea that such reward deficits may precede MDD and, in fact, have a unique developmental etiology, DelDonno and colleagues (2019) found that the presence of childhood adversity accounted for a greater amount of variance in explaining reward deficits than a diagnosis of MDD. This has important implications for the comorbidity that can arise between MDD and chronic pain, namely that an early life trauma can act as a diathesis for both disorders, possibly mediated by subsequent deficits in reward processing.

Figure 1 outlines a model in which maladaptive reward learning serves as a predisposing factor for the development of either depression or chronic pain. This model remains agnostic with

respect to which specific component of reward processing might be maladaptive (see further discussion below). Abnormalities in either learning about new reward related contingencies, the desire and motivation to pursue rewards (wanting), or in the hedonic response to appetitive stimuli (liking) would influence each other (e.g. a blunted hedonic response would result in lower motivation to seek reward, and failure to learn new contingencies to obtain further reward; similarly learning that one's actions have no bearing on positive outcomes could result in both reduced motivation and an anhedonic state). Together, an individual's characteristic pattern of reward processing would predispose them to maladaptive response to stress, whether that stress be nociceptive or psychosocial. To provide an example in the case of pain, an individual undergoing a painful but necessary surgical procedure may have difficulty learning contingencies for reducing pain, a lack of motivation to pursue relief, and a blunted emotional response to pain reduction (or to pleasurable activities that might distract from pain). As such, they might heal more slowly and be more likely to have responses (pain provocation: continued pain, negative affect, enhanced expectation of pain) that would lead to sensitisation and potentially to chronification. In the case of psychosocial stress, an individual with reward processing deficits might experience a divorce but feel under-motivated to seek new social contacts, feel less pleasure in any contacts they make, and relatedly be limited in their ability to learn new ways to initiate and maintain social contacts. Together, these maladaptive responses would result in social isolation and a higher likelihood of developing depression.

In both of the above cited cases, the pathological state resulting from the diathesis-stress combination (chronic pain in the post-surgical case, depression following divorce) would, in turn, enhance reward deficits and make the individual vulnerable to the other state. As an example, intractable pain might yield emotional distress that, when combined with the pre-existing reward deficits would predispose them to developing co-morbid depression, which would further reduce motivation and increase anhedonia. Intractable pain and/or depression would in turn amplify the original stimulus (the post-surgical pain) and would further amplify maladaptive reward processing (e.g. by further reducing motivation to take action, or by inducing a helpless state whereby actions are perceived to be irrelevant to outcomes). As such, a negative feedback loop is created, with co-morbid pain and depression becoming increasingly chronic.

6.2 Specific reward related processes that are altered and/or represent a shared diathesis

The data reviewed above do not unambiguously point towards one specific reward process as the key abnormality/diathesis. In part this is due to the fact that the framework used for discussing these processes divides them into categories (learning, wanting, and liking) that are by no

means orthogonal to each other. For example, a deficit in the ability to experience the phenomenological states of euphoria or satisfaction when consuming a reward will inevitably alter that reward's reinforcement value. As outlined in Figure 1, these processes are likely bi-directionally related and mutually reinforcing. As such, while the etiological model outlined below clearly calls for longitudinal work to establish temporal precedence, it does not make strong recommendations on the particular reward-related processes that might be most fruitful. We have largely focused, however, on learning processes due to extant models of their contribution to both depression and chronic pain.

6.2.1. Research Considerations

Pain and negative affective states both have a presumed evolutionary function of helping us to avoid situations that cause harm or place us under damaging levels of stress. As such, a well-tuned system guides adaptive action by translating contextual cues into appetitive motivational states. Deficits in motivation, or in the ability to correctly assess probabilities of obtaining positive outcomes within a particular context can result in maladaptive action and facilitatory expectations. As such, adaptively coping with stressors (including injury/nociception) requires the ability to fine tune our reading of contextual cues and adjust emotional and behavioural responses accordingly. Recent models of pain (Buchel et al, 2014; Fields, 2018; Seymour, 2018) and depression (Kube et al, 2019) formally model this inferential process in a way that facilitates direct examination of how adaptive coping takes place.

The hypothesis suggested here, namely that maladaptive reward learning processes might predispose some individuals towards the development of both chronic pain and depression, suggests that longitudinal work employing formal predictive models could elucidate the mechanisms that make some individuals particularly vulnerable. Animal (Chang et al., 2014; Ren et al., 2016) and human (Baliki et al., 2012; Hashmi et al., 2013) models have pointed to a role for emotion and reward circuitry (particularly nucleus accumbens) in the maladaptive facilitation of pain from an acute to chronic state, consistent with the idea of a shared vulnerability to disorders of pain and disordered mood (see Reckziegel et al., 2019 for review). In terms of endogenous modulation of pain and negative affective states such as depression, we would not expect complete mechanistic overlap, but it is clear from the discussion above that there is important overlap in the affective, motivational, and learning processes relevant to their ability to adaptively control behaviour. Better understanding the contribution of these processes over the developmental trajectory of pain and affective disorders allows the possibility of early intervention before the cycle of pain and negative emotion has become treatment resistant.

6.2.2. Clinical Considerations

From a clinical standpoint, an advantage of a model like the one outlined in Figure 1 where different processes influence and maintain each other is that it doesn't matter at which stage we intervene, an efficacious intervention at any point in the cycle would have a positive effect on the others. Given the material reviewed above about the efficacy of cognitive therapies like CBT for reward processes related to both pain and depression, a focus on learning new reward contingencies in the context of pain and depression is promising. Testing helpless cognitions that obscure the relationship between behaviours and outcomes (e.g. pain relief, decreased disability) represents a top-down mechanism for updating priors, potentially overriding bottom up vulnerabilities that have prevented the development of adaptive updating of priors. From a behavioural standpoint, establishing a system of exogenous rewards for adaptive behaviours (e.g. allowing a valued food or purchase for completion of a physiotherapy regimen or increase in social contact) would reinforce these behaviours where a deficit exists in endogenous reward systems (e.g. where a dysregulation of tonic and phasic dopaminergic or opioidergic activity might result in the individual feeling the adaptive behaviours are lacking in intrinsic motivation). Such clinical actions are based on basic reinforcement principles that can be translated into clear and measurable clinical targets.

7. Conclusions

In summary, the high comorbidity between MDD and chronic pain disorders warrant a more fulsome understanding of the mechanisms that result in their strong overlap. In particular, we have proposed that deficits in the brain reward processing network could yield a greater probability of developing either disorder, and could serve as a mutual maintenance factor for symptoms. This assertion is based on demonstrated impairments in reward learning, wanting and liking based on behavioural and neuroimaging studies across both disorders, and early evidence also suggests that some of these deficits may precede onset of diagnosis. Our framework to evaluate reward processing as a diathesis for chronic pain and MDD comorbidity proposes that patterns of reward processing predispose an individual to respond to nociceptive or psychosocial stress maladaptively. This maladaptive response would result in reductions of accurate reinforcement information in order to adaptively guide appetitive approach behaviours. Future research should evaluate reward impairments in comorbid pain and MDD longitudinally and rigorously test the various facets of reward processing (i.e. anticipation, prediction error) that may contribute to a common diathesis.

Acknowledgments: The authors would like to thank Kristen Tse and Shijing Wang for playing a supportive role (literature searches, formatting) in the preparation of this manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Interest: SJR had received research funding or honoraria from Pfizer Canada, Quintiles, Janssen, Takeda and Allergan. TS and WG have no declarations to report.

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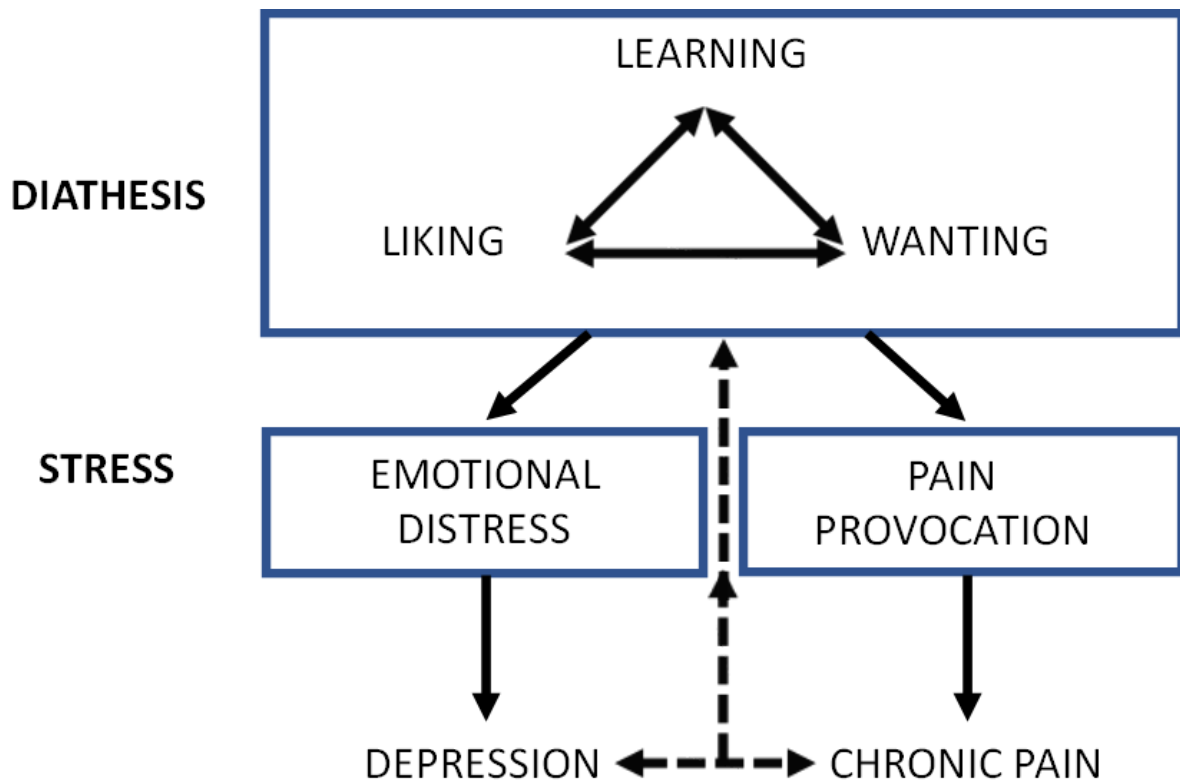


FIGURE 1. A Diathesis-Stress Model for Co-Morbid Depression and Chronic Pain: Abnormalities in processes related to learning, liking and wanting are viewed as vulnerability factors for both chronic pain and depression, which can in turn can exacerbate those abnormalities, maintaining the disorders

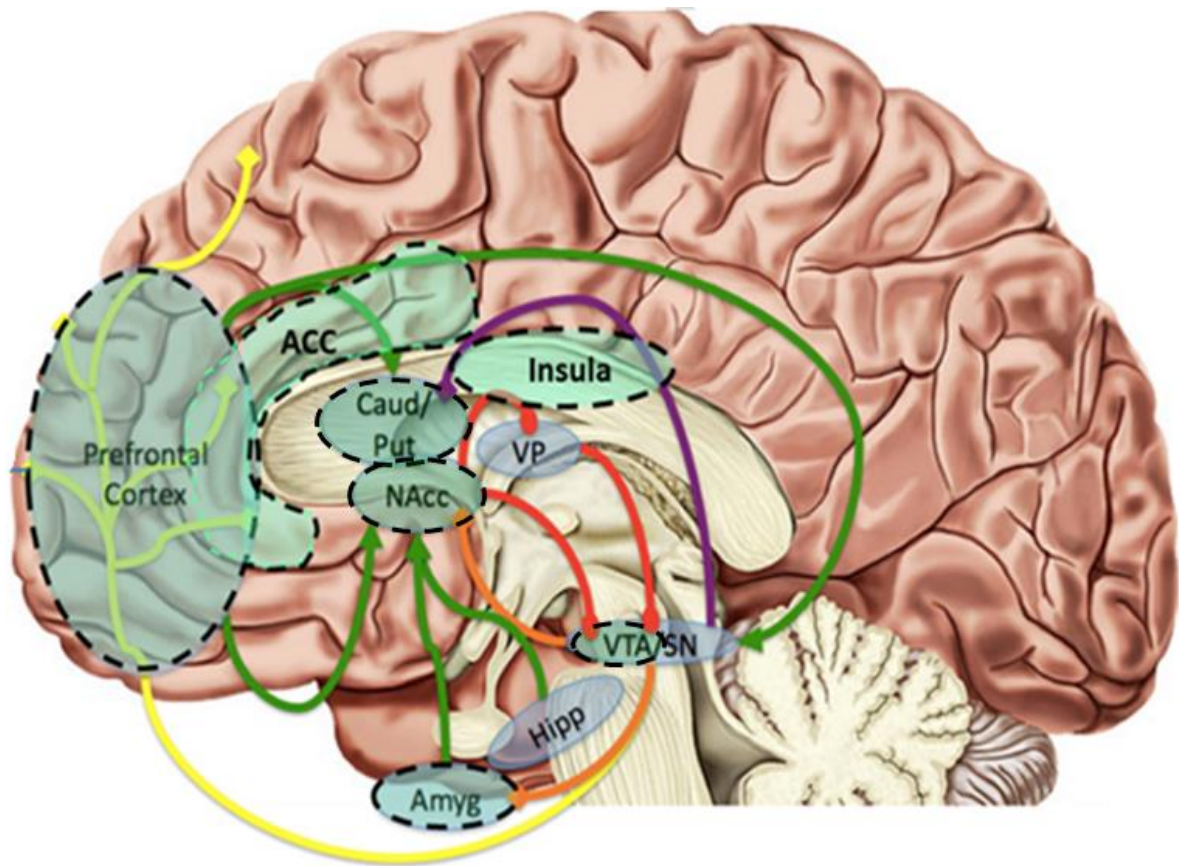


FIGURE 2. Overlap of key brain regions involved in reward processing, pain, and Major Depressive Disorder (modified from Treadway & Zald, 2011)