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Exploring the potential role of mesocorticolimbic circuitry in motivation for and adherence to chronic pain self-management interventions

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ABSTRACT

Adherence to pain self-management strategies is associated with favorable psychobehavioral outcomes among individuals with chronic pain. Substantive adherence to treatments teaching these adaptive skills often proves challenging, resulting in poor individual and societal outcomes. Evidence demonstrates motivation for behavior change as a key predictor of treatment adherence. Despite behavioral techniques that target motivation, however, nonadherence persists as a barrier to positive clinical outcomes in chronic pain. Understanding the neurobiological mechanisms underlying treatment motivation might highlight novel avenues for augmentative therapies. The purpose of this review is to present theory and evidence that the mesocorticolimbic system (i.e., brain circuitry associated with reward processing and motivation) contributes to treatment motivation among chronic pain patients, ultimately influencing adherence. We review evidence for motivation as a key adherence determinant, detail neuroimaging findings relating mesocorticolimbic circuitry and motivation, and discuss data supporting mesocorticolimbic dysfunction among chronic pain patients. We propose a neurobehavioral model for adherence to pain self-management interventions, listing testable hypotheses. Finally, we discuss potential research and intervention implications from the proposed model.

1. Introduction

Acute pain is an important signal of potential bodily harm that triggers protective cognitive, emotional, and behavioral reactions (Cordier and Diers, 2018). Over time, an individual learns to implement responses that minimize the deleterious effects of acute pain, such as avoiding touching a hot stove. In the context of pain that is chronic and does not act as a warning signal, however, these learned responses can actually become maladaptive habits that inadvertently exacerbate symptoms (Flor, 2012). For example, avoiding exercise due to fear of aggravated pain can contribute to muscle weakness and increased pain intensity (Larsson et al., 2017). For this reason, chronic pain management has increasingly centered on interventions that replace maladaptive learned responses with adaptive strategies.

Self-management interventions are nonpharmacological approaches to pain management that teach adaptive strategies through a combination of medical education, behavioral adaptations, interpersonal problem-solving, and/or emotion management (Lorig and Holman, 2003). Pain self-management involves a patient's active and daily implementation of adaptive health practices that help control distressing symptoms (Grady and Gough, 2014). Understandably, adopting and consistently practicing positive health behaviors to replace ingrained pain responses can be incredibly challenging (King et al., 2009). Estimates suggest that over half of patients engaged in self-management interventions are considered nonadherent (Reis and Brown, 1999). Given that the Center for Disease Control now recommends nonpharmacologic therapies as one of the first lines of chronic pain treatment (Dowell et al., 2016; Leider et al., 2011), establishing factors that influence adherence to pain self-management practices is imperative to improve the efficaciousness of such therapies.

The central premise of this review is that dysfunction of the mesocorticolimbic system (i.e., brain circuitry associated with hedonic appraisal, reinforcement, and motivated behavior) is associated with attenuated motivation in chronic pain patients, potentially resulting in difficulty adhering to symptom self-management strategies. To support this thesis, we discuss evidence showing that 1) motivation is a strong predictor of adherence to self-management strategies (Ng et al., 2012; Kähkönen et al., 2015; Kerns et al., 1999; Kim et al., 2015; Heider et al., 2017), 2) motivation is subserved by the mesocorticolimbic system (Salamone et al., 2015; Bailey et al., 2016), and 3) mesocorticolimbic

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dysfunction is present in some individuals with chronic pain (Apkarian et al., 2013; Cordier and Diers, 2018; Flor, 2012; Larsson et al., 2017; Lorig and Holman, 2003; Grady and Gough, 2014; King et al., 2009; Reis and Brown, 1999; Dowell et al., 2016; Leider et al., 2011; Ng et al., 2012; Kähkönen et al., 2015; Kerns et al., 1999; Kim et al., 2015; Heider et al., 2017; Salamone et al., 2015; Salamone and Correa, 2012; Schwartz et al., 2014; Bromberg-Martin et al., 2010; Bailey et al., 2016; Apkarian et al., 2013; Porreca and Navratilova, 2017; Navratilova and Porreca, 2014; Navratilova et al., 2016; Moulton et al., 2011; Taylor et al., 2016).

Although research in this area is somewhat nascent, compelling evidence for mesocorticolimbic dysfunction in chronic pain patients suggests that these individuals might have poor response to pain self-management interventions (via low motivation and adherence), as well as current strategies to improve motivation for treatment (via neural deficiencies limiting motivated behaviors; e.g., motivational interviewing). We appreciate that treatment motivation and adherence are complex phenomena and encourage future research to explore additional biopsychosocial factors that might further predict adherence rates (e.g., social support, socioeconomic limitations); however, the scope of this review will be limited to discussion of the above-described factors.

Using the theoretical framework and evidence from the Motivational Model for Pain Self-Management (Jensen et al., 2003a) (MMPSM), we posit that mesocorticolimbic circuitry presents a target neurobiological mechanism for treatment motivation, ultimately impacting adherence to pain self-management strategies. There are numerous frameworks of health behavior change (Rosenstock et al., 1988; Hochbaum et al., 1952; Fishbein, 1979; Ajzen, 1985), with a common thread that patients' attitudes, beliefs, motivational state, and demographic characteristics shape adherence to self-management strategies. Despite our understanding of the psychosocial components of short- and long-term engagement in these skills, the problem of nonadherence widely persists. We propose that a neurobiologically-informed framework more robustly captures the problem of nonadherence by highlighting mechanisms underlying certain psychological phenomena discussed in these models (Jensen, 2010).

The impetus for the present review is *not* to propose a biomarker of treatment motivation in individuals with chronic pain. Previous studies have provided neuroimaging evidence of questionnaires/tasks related to mesocorticolimbic function (Angelides et al., 2017; Mortensen et al., 2015; Wacker et al., 2009; Keller et al., 2013; Simon et al., 2010), which can help clinicians feasibly probe dysfunction of this system (i.e., patients potentially at-risk for poor treatment motivation/engagement). Because the US National Pain Strategy calls for improvements in pain self-management programs (Von Korff et al., 2016), the rationale for this review is to encourage research efforts establishing a mechanistic link between mesocorticolimbic dysfunction and motivation for engagement in and adherence to pain self-management strategies. This evidence will support the development of novel, augmentative therapies that target deficient neural systems underlying motivation in order to promote greater benefit from pain self-management strategies (discussed at the end of this review).

2. Adherence to pain self-management strategies and clinical outcomes

Self-management interventions vary in the use of specific strategies but share common features. The Stanford model of self-management emphasizes positive patient-provider rapport in order to 1) promote the patient's role in problem-solving barriers to skills practice, 2) empower him/her to decide when strategies should be implemented, 3) teach how resources can be effectively used, and 4) make an action plan for accomplishing intervention goals (Lorig and Holman, 2003). Similarly, cognitive-behavioral therapies are self-management interventions that teach cognitive and behavioral strategies to reduce emotional distress associated with pain and improve quality of life (Johnston et al., 2010; Thomas et al., 1998). A common theme among these interventions is the goal to teach transferable skills that improve the patient's self-efficacy in managing symptoms long-term (Mann et al., 2013). Further, they fundamentally assume that patients will adhere to strategies discussed during intervention sessions in order to develop long-term lifestyle changes.

The term "adherence" implies that the patient is an active, volitional participant in his/her healthcare decision-making and takes the initiative to implement positive health behaviors. This term differs from "compliance," which implies a passive involvement in care characterized by following providers' orders (Brawley and Culos-Reed, 2000). Not surprisingly, adherence to prescribed treatment regimens requires motivation and effort, especially when the treatment involves alteration of lifelong habits.

Adherence to pain self-management interventions is less frequently studied than medication compliance. However, estimates suggest that adherence rates for nonpharmacological modalities are generally lower than those for medications (Butow and Sharpe, 2013). For example, in a large study of over 500 chronic pain patients completing a 3-week pain self-management intervention, only 30% of patients endorsed regularly using all instructed strategies (Nicholas et al., 2012). Premature dropout rates for cognitive-behavioral pain interventions range from approximately 27% (Busch et al., 2008) to 60% (Reis and Brown, 1999; Kerns and Haythornthwaite, 1988), and failure of long-term maintenance is estimated upwards of 39% (Cinciripini and Floreen, 1982). Finally, findings from home physical exercise programs similarly demonstrate moderate adherence, with poor long-term maintenance of home exercise practice (Medina-Mirapeix et al., 2009; Kolt and McEvoy, 2003).

Nonadherence consistently serves as a barrier to positive pain treatment outcomes (Timmerman et al., 2016; Turk and Rudy, 1991; Jordan et al., 2006). Low engagement specifically leads to poorer health outcomes (Martin et al., 2005), adds wasteful healthcare costs (Iuga and McGuire, 2014), and negatively impacts patient/provider rapport (DiMatteo et al., 2002). Alternatively, strong adherence predicts favorable clinical outcomes, such as reduced emotional distress and improved quality of life (Kerns et al., 1999; Nicholas et al., 2012; DiMatteo et al., 2002; Nicholas et al., 2014; Cecchi et al., 2014; Turk and Okifuji, 2002; Turk et al., 2003; Kerns et al., 2014). For these reasons, the World Health Organization cites adherence as a critical, modifiable component of health system effectiveness, with poor individual health outcomes and high societal healthcare costs as the main consequences of poor long-term adherence (Sabaté, 2003).

Nonadherence can occur for multiple reasons specific to the patient or the environment (e.g., provider traits, sociodemographic barriers). Examples of patient factors include low expectations for treatment efficacy, perceived barriers to treatment, personality factors, and lack of support (Rosenstock et al., 1988; Hochbaum et al., 1952; DiMatteo et al., 2002; Anderson et al., 2016; Green and Murphy, 2014) (for an in-depth review of such components, please refer to Mathes et al., 2014). These variables operate in tandem to yield an individual's readiness for change, or motivation for treatment. In this regard, motivation refers to the likelihood that a person will initiate therapy, actively participate in treatment, and maintain changes implemented over the course of therapy (Bennett et al., 1991). Motivation is one of the most important predictors of adherence to pain management skills (Kerns et al., 1999; Biller et al., 2000; Dorflinger et al., 2013), as well as adherence to other positive health behaviors (Ng et al., 2012; Kähkönen et al., 2015; Kim et al., 2015; Mata et al., 2011). It is also predictive of favorable clinical outcomes following treatment (Heider et al., 2017; Stewart et al., 2017).

3. The Motivational Model for Pain Self-Management

The MMPSM proposes that adherence to pain self-management

strategies is a result of an individual's motivation to engage in treatment (Jensen et al., 2003a). Examples of self-management strategies described in the MMPSM include exercise, activity pacing, relaxation exercises, avoiding catastrophizing, and assertiveness in interpersonal relationships. In this framework, motivation is malleable and influenced by a variety of factors that play into 1) perceived importance of engaging in or refraining from treatment and 2) the individual's beliefs that adherence to behavior change is possible. First, perceived importance results from patients' mental cost/benefit analysis of engaging in pain self-management strategies, learning history with previous behavior change attempts, and appreciation of contingencies surrounding strategy engagement. Second, perceived self-efficacy can be influenced by experience in successfully applying self-management skills, modeling of others who sufficiently implement similar strategies, verbal persuasion in the form of self-talk and encouragement from others, and perceived barriers to engaging in self-management strategies.

Evidence demonstrates the applicability of the MMPSM in describing motivation and adherence to behavioral pain treatments in individuals with chronic pain from multiple sclerosis (Kratz et al., 2011) and spinal cord injury (Molton et al., 2008). Other research groups have also found associations among perceived importance of treatment, perceived self-efficacy in engaging in strategies, treatment motivation, and adherence to pain self-management strategies (Anderson et al., 2016; Biller et al., 2000; Guite et al., 2014). Importantly, a community-based pilot study demonstrated that addressing individuals' beliefs about the importance of self-management strategies, expectations for engagement in these strategies, and self-efficacy for applying skills prior to intervention resulted in significantly higher rates of adherence to treatment (Habib et al., 2005). These findings collectively highlight the value of the MMPSM in explaining adherence to pain self-management strategies and suggest that some factors, such as self-efficacy, both promote adherence and contribute to pain-related treatment outcomes.

4. Mesocorticolimbic function and motivated behaviors

Neuroimaging studies describe the mesolimbic system and its cortical projections (i.e., mesocorticolimbic system) as circuitry that is activated during motivation to approach and avoid appetitive and aversive stimuli, respectively (Salamone and Correa, 2012; Salamone, 1994). This system includes neurons in the ventral tegmental area (VTA) that project to the nucleus accumbens (NAc), thalamus, hippocampus, and amygdala. Further, there are dense afferent projections to corticolimbic regions associated with emotion and memory, such as the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (vmPFC) (Cardinal et al., 2002), as well as indirect connections to paralimbic structures (e.g., anterior insula) (Naqvi and Bechara, 2009; Jarcho et al., 2012). Fig. 1 depicts consistently activated regions identified through a Neurosynth (Yarkoni et al., 2011) meta-analysis of 135 functional neuroimaging studies that highly load on the key term "motivation." Most prominently highlighted are mesolimbic regions, including bilateral NAc and VTA, as well as corticolimbic OFC, ACC, and mPFC. Dopaminergic receptors densely populate the NAc, and dopamine is released during the regulation of motivated behavior, attention, and hedonic processes (Salamone et al., 2015; Jarcho et al., 2012; du Hoffmann and Nicola, 2016).

Various neuroimaging techniques can be used to quantify mesocorticolimbic function in humans. Functional connectivity (FC), or correlated activity among spatially remote regions (Friston, 1994), is increasingly recognized as an informative technique for assessing network-level dysfunction across clinical populations (Fox and Greicius, 2010; Greicius, 2008). In this regard, "dysfunction" can refer to *hyperconnectivity* within a given neural network or regions outside of the network compared to healthy individuals. Hyperconnectivity is thought to represent an increase in communication among brain regions resultant from nonlinear interactions between situational demands, neurological challenge, and resource availability (Hillary et al., 2015). Alternatively, *hypoconnectivity* compared to healthy individuals is thought to represent loss of communication among regions within a neural network (Schultz et al., 2017).

In healthy individuals, unique FC patterns among mesocorticolimbic regions have been reported in the context of appetitive and aversive stimuli processing (Camara et al., 2009; Ikemoto, 2010; Kringelbach, 2005). Initiation of motivated behaviors is associated with connectivity among VTA, NAc, and the dorsolateral PFC (Ballard et al., 2011). Stimulus-dependent FC between hippocampus and OFC is related to motivated behaviors for appetitive vs neutral cues (Zweynert et al., 2011). Further, decision-making based on behaviors requiring greater effort are associated with intranetwork FC among NAc, VTA, ventral pallidum, ACC, and amygdala (Bailey et al., 2016). These results support the use of FC in understanding the role of mesocorticolimbic circuitry in motivated behaviors.

Hypoconnectivity among mesocorticolimbic regions has been demonstrated in individuals with low motivation resultant from unipolar and bipolar depression (Satterthwaite et al., 2015; Furman et al., 2011; Trost et al., 2014). Additionally, preliminary evidence from the substance abuse literature demonstrates an association between treatment motivation/adherence and mesocorticolimbic activity (Prisciandaro et al., 2014) or gray matter volume (Moreno-Lopez et al., 2014; Le Berre et al., 2013). Reductions in gray matter volume reported in these studies might result from atrophy via excitotoxicity and inflammation (Apkarian et al., 2004; Kuchinad et al., 2007; Puiu et al., 2016), which could alter functional communication among regions given diminished neural resources. Collectively, these findings suggest that structure and function of mesocorticolimbic regions are associated with motivated behavior, and individuals with mesocorticolimbic dysfunction might have attenuated motivation for treatment adherence.

5. Mesocorticolimbic dysfunction in chronic pain

The findings reviewed thus far support a mechanistic link between

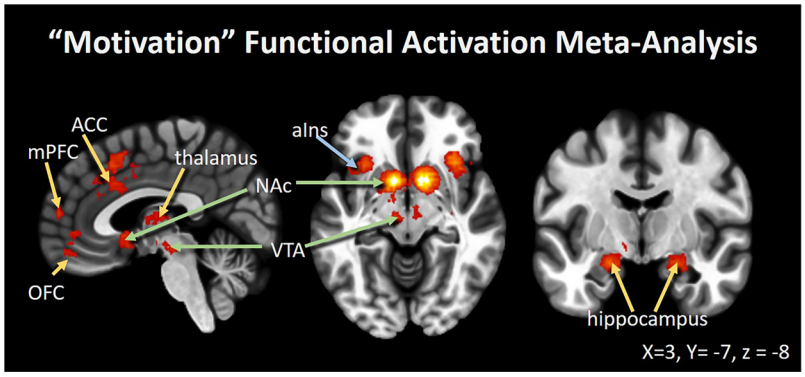

Fig. 1. Motivation Circuitry: A forward-inference functional activation statistical map of regions consistently activated across 135 neuroimaging studies that load highly on the key term "motivation" (Neurosynth: http://neurosynth.org/). Results indicate that areas include mesolimbic (green arrows), corticolimbic (yellow arrows), and paralimbic (blue arrow) structures. This meta-analysis emphasizes mesocorticolimbic circuitry's involvement in motivated behaviors across studies. *Abbreviations: medial prefrontal cortex (mPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), ventral tegmental area (VTA), anterior insula (aIns), and nucleus accumbens (NAc).*

motivation and mesocorticolimbic circuitry. Accordingly, mesocorticolimbic dysfunction is associated with impairments in motivated behaviors. Emerging evidence highlights alterations in mesocorticolimbic function and associated reward processing in individuals with chronic pain. Although specific patterns of mesocorticolimbic response to acute pain and dysfunction in chronic pain are still being established (Bauch et al., 2014; Leknes et al., 2011; Jensen et al., 2003b; Loggia et al., 2014), combined results highlight the vulnerability of this patient population to poor motivation for symptom self-management.

Previous studies demonstrated a higher likelihood of transitioning from subacute to chronic low back pain in individuals with hyperconnectivity between NAc-mPFC (Baliki et al., 2012; Petre et al., 2015) and hippocampus-mPFC (Mutso et al., 2014). Once in a chronic pain state, patients show slower rates of extinction for reinforced pain behaviors (Flor et al., 2002), blunted operant learning slope for pain habituation (Becker, Kleinböhl, Baus, & Hölzl, 2011), and poorer reward responsiveness (Elvemo et al., 2015). It is possible that chronically-taxed mesolimbic structures work less efficiently over time, contributing to poorer motivation and concomitant treatment adherence. These findings are supported by studies showing that baseline dopamine metabolism is reduced in patients with fibromyalgia (Wood et al., 2007; Ledermann et al., 2016; Albrecht et al., 2016), burning mouth syndrome (Hagelberg et al., 2003), and chronic back pain (Martikainen et al., 2015) compared to pain-free controls. Individuals with chronic pain also tend to have clinical comorbidities that are commonly associated with abnormal reward processing, such as depression (Tremblay et al., 2005; Redlich et al., 2015), substance abuse (Volkow et al., 2009; Beck et al., 2009; Garland et al., 2017), obesity (Nummenmaa et al., 2012), and sleep disturbance (Gujar et al., 2011; Hasler et al., 2012).

Because pain is an aversive stimulus, individuals are motivated to seek removal of this stimulus. In fact, analgesia is described as a type of negative reinforcement. If pain relief is not substantively rewarding, however, motivation to engage in pain self-management strategies might be attenuated in individuals with chronic pain. Supporting this notion are studies demonstrating increased NAc, ACC, and vmPFC activity at the offset of a noxious thermal stimulus in healthy individuals (Leknes et al., 2011; Becerra and Borsook, 2008; Becerra et al., 2013; Wanigasekera et al., 2012). Humans and animals with chronic pain, however, show a reduction in NAc activity during pain offset (Baliki et al., 2010; Kato et al., 2016), suggesting attenuated reward from relief. As a result of diminished negative reinforcement from relief, it is possible that individuals with chronic pain experience reduced motivation to engage in pain relief behaviors, negatively influencing adherence.

6. Testable hypotheses for the neurobiologically-informed Motivational Model for Pain Self-Management

Stemming from the reviewed extant literature, we propose testable hypotheses for an updated version of the MMPSM that incorporates putative neurobiological mechanisms contributing to motivation for pain self-management (Fig. 2). Given that the problem of nonadherence continues to exist among patients with chronic pain, the goal of our updated model is to determine whether potential neurobiological deficiencies contributing to poor motivation feed into observed nonadherence. If supported, this line of research will ideally inform development of novel, adjunctive therapies correcting mesocorticolimbic deficiencies, with the hope that administration during critical treatment timepoints will promote long-term practice of effective pain self-management strategies.

The MMPSM broadly states that in order for individuals with chronic pain to adhere to pain self-management techniques, adequate motivation for change is necessary (Jensen et al., 2003a). Motivation is influenced by the perceived importance of engaging in a target behavior, as well as self-efficacy for the ability to effectively engage in the therapy. The literature reviewed above strongly supports this model, and demonstrates that the mesocorticolimbic system tracks effectual and aberrant motivational states (Salamone et al., 2015; Salamone and Correa, 2012; Schwartz et al., 2014), including chronic pain (Loggia et al., 2014; Wood et al., 2007; Martikainen et al., 2015; Baliki et al., 2010; Jääskeläinen et al., 2001; Berger et al., 2014).

Mesocorticolimbic function contributes to two important constructs of motivation for treatment adherence: perceived importance of self-management strategies and perceived self-efficacy (Fig. 2.a.). Previous findings also show aberrant learning history with pain and processing of contingencies (i.e., reinforcers and punishers) in chronic pain patients (Flor et al., 2002; Becker et al., 2011), contributing to low perceived importance of engaging in pain self-management strategies (Fig. 2.b.1). Second, individuals' personality characteristics or mindset significantly influences their perceived self-efficacy for self-management of pain (Guite et al., 2014; Gracely et al., 2004; Burgmer et al., 2011; Campbell and Edwards, 2009; Samwel et al., 2006; Jensen et al., 1991) (Fig. 2.b.2.). We hypothesize that:

H1. Mesocorticolimbic function subserves treatment-related learning history, contingency processing, and cost/benefit analysis. Individuals with mesocorticolimbic dysfunction will have lower perceived importance of symptom self-management.

H2. Mesocorticolimbic function subserves appraisal of behavior change adeptness. Individuals with mesocorticolimbic dysfunction will have poorer self-efficacy for symptom self-management.

As a result of altered perceptions for treatment importance and self-efficacy, motivation for behavior change is affected (Fig. 2.c.). The MMPSM describes motivation as graded along five stages originally described by (Prochaska and DiClemente., 1992): 1) "precontemplation" occurs when individuals have scant interest in changing behavior, 2) "contemplation" occurs when individuals have considered behavior change for the distant future, 3) "preparation" occurs when individuals actively consider attempting behavior change, 4) "action" occurs when individuals engage in behavior change, and finally, 5) "maintenance" occurs when individuals sustain already changed behaviors over a long period. We hypothesize that:

H3. Magnitude of mesocorticolimbic dysfunction will correlate with reported treatment motivation, so that greater dysfunction is associated with poorer readiness for change.

H4. Self-reported treatment motivation moderates the relationship between pre-treatment mesocorticolimbic function and adherence. Individuals with higher treatment motivation demonstrate a stronger relationship between mesocorticolimbic function and adherence.

As the individual moves through these stages of motivation, behavioral and mesocorticolimbic processes can influence the slope and plateau of changes in motivation. If the patient enters the preparation and action phase, then initiation in treatment is achieved (Fig. 2.d.1.). If the individual's treatment-induced analgesia is adequately reinforcing, then motivation for adherence increases, leading to maintenance over time (Fig. 2.d.2.). In individuals with chronic pain, attenuated reinforcement from analgesia, which is associated with altered mesocorticolimbic functioning, might result in poorer self-efficacy and perceived importance of the therapy, increasing the likelihood of treatment nonadherence (Fig. 2.e.).

H5. Practice of a pain management strategy will be associated with mesocorticolimbic activity via reinforcement. Individuals with high reinforcement from this practice (optimal mesocorticolimbic function) will have greater motivation for future strategy practice, leading to better adherence. Individuals with poor reinforcement from strategy practice (attenuated mesocorticolimbic function) will have lower motivation for future strategy practice, leading to poorer adherence.

An alternative pathway to treatment nonadherence may also emerge if competing reinforcers (e.g., social attention or escape from

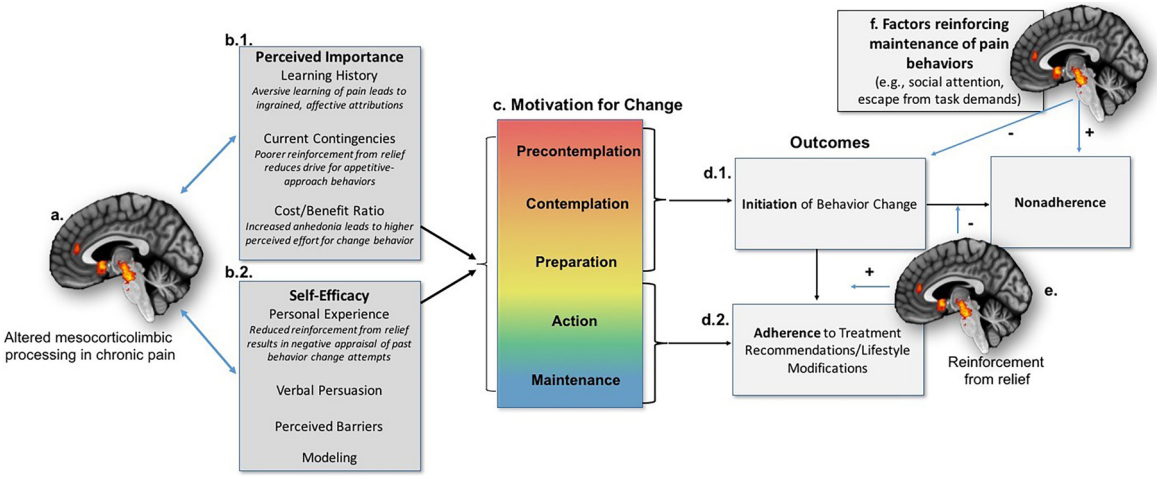

Fig. 2. A Neurobehavioral Model of Pain, Mesocorticolimbic Circuitry, and Treatment Adherence: The present model demonstrates how neurobiological factors might contribute to the Motivational Model for Pain Self-Management. First, previous evidence has demonstrated altered function among brain circuitry related to hedonic processing and motivation (i.e., mesocorticolimbic system), reflecting changes in reward and motivational processes in a chronic pain state (a.). As a result, pain self-management strategies might seem less important (b.1.) or the individual might have poorer self-efficacy to implement such strategies (b.2.). Motivation for behavior change/treatment adherence occurs across a gradient based on these factors (c.), and movement through these stages ultimately leads to initiation of self-management strategies (d.1.). If enough reinforcement from pain relief is processed via mesocorticolimbic circuitry (e.), initiation and subsequent adherence are increased. However, if reinforcement from relief is not sufficient, or if competing reinforcers maintain pain behaviors (f), then nonadherence is the primary outcome.

task demands) (Bastian et al., 2014) are in place and elicit greater unconscious reinforcement than treatment-related analgesia (Fig. 2.f.). We hypothesize that:

H6. Factors that maintain pain behaviors (e.g., social attention or escape from task demands) will moderate the relationship between therapy-related reinforcement and adherence, so that individuals with high reinforcement from pain-maintaining factors will have a weaker relationship between therapy-related reinforcement and adherence.

7. Implications for future research and intervention

The goal of pain self management interventions is to teach patients strategies that they will practice over the course of treatment and continue to regularly implement as adopted lifestyle habits. However, nonadherence to these skills during the initiation/course of intervention and following treatment is prevalent. Current interventions to improve adherence fall short. A meta-analysis of adherence interventions demonstrated that only 18 of the 42 trials examined yielded significantly improved adherence across patients (Jordan et al., 2010). Additional predictors and potentially modifiable factors should be explored to set patients up for optimal benefit from pain self management interventions.

If supported by substantial evidence, this neurobiologically-informed MMPSM presents translational avenues to refine existing or develop novel adherence interventions. Specifically, we envision these *adjunctive* interventions to be very brief and targeted to patients at-risk for poor adherence. Further, the adjunctive intervention would only be administered at key points during treatment. At-risk patients can be identified through well-validated questionnaires probing mesocorticolimbic function. Rather than spend several pain intervention sessions troubleshooting adherence from a solely behavioral standpoint, individuals at-risk for poor mesocorticolimbic function would be referred for adjunctive interventions at the initiation of treatment to promote optimal reward processing during engagement of intervention skills. Improved mesocorticolimbic function could potentially then promote an individual's perceived importance of treatment and self-efficacy of applying skills in a feedforward loop.

If effective, the initial costs to apply these adjunctive therapies would likely outweigh the long-term costs and patient/provider frustration associated with nonadherence. Although research is still needed to address this topic, potential avenues for such therapies include neurofeedback, pharmacological interventions, behavioral retraining, and neurostimulation [e.g., repetitive transcranial magnetic stimulation (rTMS), transcranial direct-current stimulation (tDCS), and - for cases of extreme anhedonia - deep brain stimulation (DBS)]. Studies have shown modest efficacy of such methods in improving motivation via mesocorticolimbic targeting in healthy participants (Chib et al., 2013; Soutschek et al., 2017; Su et al., 2017), as well as individuals with intractable depression and anxiety spectrum disorders (Holtzheimer et al., 2001; Gaynes et al., 2014; Leggett et al., 2015; Xie et al., 2015; Malone et al., 2009; Bewernick et al., 2012; Schlaepfer et al., 2013; Bewernick et al., 2010; Schlaepfer et al., 2008).

In considering this model, certain limitations should also be weighed. To the best of our knowledge, no study has experimentally tested the specificity of the mesocorticolimbic system in treatment motivation and adherence in individuals with chronic pain. However, the testable hypotheses listed above provide avenues for research on this topic. Second, there are limitations in the measurement of motivation and adherence, such as bias in questionnaire wording and inconsistency in adherence endpoints (Jordan et al., 2006; Stirratt et al., 2015). We encourage future research to better characterize these aspects of treatment motivation and adherence.

Third, fMRI reliability has been documented as fair to good in the general neuroimaging literature (Braun et al., 2012; Birn et al., 2013; Bennett and Miller, 2010) and pain neuroimaging (Letzen et al., 2014, 2015; Upadhyay et al., 2015; Quiton et al., 2014). Future efforts should examine the reliability of neuroimaging findings over time in understanding this potential mechanistic link. Fourth, our model does not comprehensively include non-patient factors that can influence treatment motivation and adherence, such as provider characteristics or sociodemographic barriers. If the testable hypotheses in our model are supported, we encourage future work to incorporate this information into a larger framework that describes the influence of all these variables to explain as much variance as possible in treatment adherence. Finally, there is no clear evidence to dictate which set of self-management strategies most effectively improves symptoms. Future adaptive trials might help provide a clearer set of guidelines for which self-management strategies might be most effective with optimal adherence for a given population.

8. Conclusions

Motivation and associated adherence are critical for successful symptom management in individuals with chronic pain. Given that mesocorticolimbic circuitry is linked with motivation and demonstrates aberrant function among chronic pain patients, perceived importance of treatment and self-efficacy might be skewed in these individuals. Mesocorticolimbic dysfunction might lead to poorer reinforcement from analgesia, further decreasing patients' treatment motivation in a feedforward loop. As such, mesocorticolimbic circuitry presents a possible target to improve patient clinical outcomes via motivation and adherence to symptom self-management strategies.

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Declarations of Interest

None.

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