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Prescription opioid misusing chronic pain patients exhibit dysregulated context-dependent associations: Investigating associative learning in addiction with the cue-primed reactivity task

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ABSTRACT

Background: Associative learning undergirds the development of addiction, such that drug-related cues serve as conditioned stimuli to elicit drug-seeking responses. Plausibly, among opioid misusing chronic pain patients, pain-related information may serve as a conditioned stimulus to magnify opioid cue-elicited autonomic and craving responses through a process of second-order conditioning.

Methods: We utilized a novel psychophysiological probe of pain-opioid conditioned associations, the Cue-Primed Reactivity (CPR) task. In this task, participants were presented with images as primes (200 ms) and cues (6000 ms) in pairs organized in four task blocks: "control-opioid," "pain-opioid," "control-pain," and "opioid-pain." Opioid-treated chronic pain patients (N = 30) recruited from an Army base in the Western United States were classified as opioid misusers (n = 17) or non-misusers (n = 13) via a validated cutpoint on the Prescription Drug Use Questionnaire (PDUQ; Compton et al., 2008). Opioid misuse status was examined as a predictor of HRV, craving, and mood responses on the CPR task.

Results: HRV increased to a greater extent during the pain-opioid block compared to the control-opioid block for non-misusers compared to misusers ($p = .003$, $\eta^2_{partial} = 0.27$). In contrast, craving increased to a greater extent from baseline to the pain-opioid block for misusers than for non-misusers ($p = .03$, $\eta^2_{partial} = .16$).

Conclusions: Findings suggest that opioid-treated chronic pain patients exhibit Pavlovian conditioned responses to opioid cues strengthened by an associative learning process of second-order conditioning when primed by pain-related images. This pain-opioid contingency appears to become disrupted among individuals who engage in opioid misuse, such that opioid-related stimuli elicit motivational responses irrespective of pain-related contextual stimuli.

1. Introduction

Associative learning is key to the development of addiction. Unlike goal-directed drug seeking, which is determined by the predicted incentive value of the drug, habitual drug seeking is elicited by conditioned stimuli that have come to be associated with the drug seeking response (Hogarth et al., 2013). Via a goal-directed learning process, the drug user first comes to realize that drug seeking produces a valued outcome (e.g., euphoria or amelioration of an aversive state). As drug use recurs over time, a habit-learning process occurs in which the drug user forms an association between drug-related stimuli and drug seeking motivational responses (e.g., craving, physiological activation) based on the co-occurrence of these events and subsequent drug-induced reinforcement. This process results in the conditioned drug-related stimulus (e.g., the sight of the drug or paraphernalia) eliciting habitual drug-seeking, irrespective of the outcome. Second-order

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Table 1
Demographic and Clinical Characteristics of the Opioid-Treated Chronic Pain Sample of Soldiers (N = 30).

Measure	Non-Misusers (n = 13)	Misusers (n = 17)	Difference Tests
Male, N (%)	12 (92%)	16 (94%)	$X^2 = 0.04$, $p = .84$
Age	34.6 ± 9.2	32.8 ± 6.7	$t = 0.64$, $p = .53$
Years of Military Service	11.6 ± 7.2	10.1 ± 6.4	$t = 0.59$, $p = .56$
Number of Deployments	2.2 ± 1.9	2.8 ± 2.3	$t = 0.78$, $p = .45$
Racial/Ethnic Background, N (%)			$X^2 = 0.14$, $p = .99$
White	8 (62%)	11 (65%)	
Latino	2 (15%)	3 (18%)	
Black	2 (15%)	2 (12%)	
No response	1 (8%)	1 (6%)	
Primary Pain Type, N (%)			$X^2 = 3.12$, $p = .37$
Low Back Pain	8 (62%)	11 (65%)	
Joint Pain	3 (23%)	2 (12%)	
Cervical Pain	1 (8%)	4 (24%)	
Other	1 (8%)	0 (0%)	
Pain (0–10)	4.9 ± 2.3	3.7 ± 2.1	$t = 1.5$, $p = .12$
Prescription Drug Use Questionnaire	6.5 ± 1.8	14.5 (5.1)	$t = 6.01$, $p < .001$
Morphine equivalent daily dose (in mg)[†]	47.3 ± 16.9	40.6 ± 18.6	$t = 1.0$, $p = .31$
Primary opioid type, N (%)[†]			$X^2 = 2.34$, $p = .31$
Hydrocodone/oxycodone	6 (46%)	5 (29%)	
Tramadol	6 (46%)	7 (42%)	
Buprenorphine	1 (8%)	5 (29%)	
Psychiatric Disorder Diagnosis			
Major depressive disorder	4 (31%)	3 (18%)	$X^2 = 0.71$, $p = .40$
Generalized anxiety disorder	1 (1%)	2 (12%)_	$X^2 = 0.14$, $p = .60$
Post-traumatic stress disorder	6 (46%)	6 (35%)	$X^2 = 0.36$, $p = .55$
Alcohol dependence	0 (0%)	1 (< 1%)	$X^2 = 0.79$, $p = .57$
Other substance dependence	0 (0%)	1 (< 1%)	$X^2 = 0.79$, $p = .57$

[†] Morphine equivalent daily dose in milligrams was summed across all opioid medications prescribed. Though Table 1 lists only the self-reported "primary" opioid prescription, multiple participants reported taking more than one opioid medication.

conditioning occurs when another stimulus (e.g., an affective state for which the drug user sought relief through drug use) is associated with a first-order conditioned drug-related stimulus and thereby comes to elicit a conditioned motivational response like that evoked by the drug-related stimulus. However, second-order conditioning can also magnify the strength of the original conditioned response when the second-order conditioned stimulus (e.g., negative affect) co-occurs with the original first-order conditioned stimulus (e.g., drug cues), thereby having an excitatory association (Rashotte et al., 1977; Rescorla, 1988).

This associative learning process may be particularly salient among chronic pain patients who misuse prescription opioids. When an individual with chronic pain first experiences pain relief after initiating opioid analgesic use, goal-directed learning occurs such that the individual comes to intentionally seek opioids in order to obtain the valued outcome of reduced pain levels. Pain eventually comes to serve as a conditioned stimulus that elicits the conditioned response of opioid use. As opioid use becomes chronic, habit learning occurs such that opioid cues like the sight of the pill, pill bottle, medicine cabinet, or pharmacy become associated with the drive to seek opioids. When paired with the experience of elevated pain levels, opioid cues may produce an especially potent conditioned drug seeking response. In the normative associative learning sequence, pain stimuli precede opioid use and thus may prime drug seeking elicited by opioid cues. When opioid users misuse opioids for their euphorigenic effects, this associative learning process may evolve such that opioid cues elicit drug seeking, irrespective of the need to obtain pain relief. Thus, as a chronic pain patient who misuses opioids progresses towards opioid addiction, the normative, context-dependent associative learning process that had paired pain and opioid use becomes dysregulated such that the motivation to seek opioids is largely decoupled from pain and driven by opioid cues that have acquired incentive salience through habit learning (Garland et al., 2013).

This associative learning process has not been investigated among opioid-treated chronic pain patients. In the current study, we utilized a novel psychophysiological probe of pain-opioid associations, the Cue-Primed Reactivity (CPR) task. In this task, participants are presented with opioid-related cues that are primed by either pain-related or neutral (i.e., control) stimuli. During the CPR task, heart rate variability (HRV) was assessed. HRV is the beat-to-beat, parasympathetic modulation of heart rate by the vagus nerve (Berntson et al., 1997) that is stimulated during attentional processing of rewarding or emotionally-salient cues by central nervous system structures (e.g., prefrontal cortex [PFC], anterior cingulate cortex [ACC], amygdala, striatum) involved in neurovisceral integration (Thayer and Lane, 2000, 2009). Though attenuated resting HRV is associated with substance dependence and craving (Quintana et al., 2013a,b), increased phasic HRV can also be elicited as a classically conditioned response to presentation of conditioned appetitive stimuli (Inagaki et al., 2005) and during expectation of natural reward receipt (Inagaki et al., 2013). Studies have identified drug cue-elicited increases in HRV (Culbertson et al., 2010; Erblich et al., 2011; Garland et al., 2012a,b; Ingjaldsson et al., 2003; Rajan et al., 1998), and increased HRV during food cue-exposure (Spitoni et al., 2017; Udo et al., 2014) that attenuates when food is consumed (Nederkoorn et al., 2000). Phasic HRV increases have been observed when opioid-treated chronic pain patients attend to images of prescription opioids (Garland et al., 2015). Thus, HRV may be a useful autonomic index of conditioned responses elicited by drug-related stimuli among prescription opioid misusing chronic pain patients and thereby provide a means of assessing associative learning processes linking pain and opioid-related cues.

The present study aimed to determine whether (a) priming opioid cues with pain-related images would elicit more potent autonomic and subjective responses relative to trials when opioid cues are primed by control images or when pain-related images are primed by opioid cues and (b) prescription opioid misusers with chronic pain evidence dysregulated context-dependent associations such that opioid cues elicit a more potent autonomic and subjective response irrespective of the presence of pain primes. To examine these questions in the present study, a sample of opioid-misusing chronic pain patients (opioid misusers) and chronic pain patients who did not misuse opioids (non-misusers) completed the CPR task while HRV was measured concurrently. We had two hypotheses: 1) pain-primed opioid cues would