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Allostatic dysregulation of natural reward processing in prescription opioid misuse: Autonomic and attentional evidence

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ABSTRACT

Chronic pain patients who misuse prescription opioids may suffer from allostatic dysregulation of natural reward processing. Hence, this study examined whether prescription opioid misusers with chronic pain ($n = 72$) evidenced decreased natural reward responsiveness relative to non-misusers with chronic pain ($n = 26$). Subjects completed a dot probe task containing pain-related, opioid-related, and natural reward stimuli while attentional bias (AB) scores and heart rate variability (HRV) responses were assessed. Compared to non-misusers, misusers evidenced significantly more attenuated HRV responses to opioid, pain, and natural reward cues presented during the dot probe task. These significant between-groups differences in HRV were largest during attention to natural reward cues, but became non-significant in a sensitivity analysis controlling for opioid dosing. In addition, non-misusers evidenced an AB toward natural reward cues, whereas misusers did not. Findings suggest that opioid misusers exhibit attentional and autonomic deficits during reward processing.

1. Introduction

Chronic exposure to prescription opioid analgesics may result in opioid misuse and addiction due to the pharmacologic actions of opioids on the mesocorticolimbic dopamine system—the common neural circuitry underlying a broad range of addictive behaviors (Koob & Volkow, 2009). Chronic pain patients prescribed long-term opioid analgesic pharmacotherapy are at risk for developing prescription opioid use disorder; approximately 10% of such individuals exhibit opioid misuse behaviors such as unauthorized dose escalation or self-medication of negative affect with opioids (Fishbain, Cole, Lewis, Rosomoff, & Rosomoff, 2007). A recent survey of treatment-seeking opioid dependent persons found rates of opioid self-medication of negative affective states as high as 90% (Garland et al., in press). Thus, prescription opioid misusers may seek and consume opioids as a means of regulating dysphoria and maintaining a positive hedonic tone.

Maintenance of hedonic homeostasis may be undermined by increasing tolerance to the effects of opioids coupled with recurrent episodes of chronic pain and coincident negative emotions. The individual may thereby be impelled to use increasingly higher doses of opioids to allay emotional and somatic distress (Shurman, Koob, & Gutstein, 2010). However, this attempt to achieve an equilibrium is costly: chronic opioid use may shift the hedonic set point, rendering the individual increasingly insensitive to rewards in the natural environment and tipping the hedonic balance further toward negative affectivity (Koob & Le Moal, 2008). In turn, the effort to preserve dwindling hedonic tone may fuel a cycle of escalating dependence on opioids (Garland, Froeliger, Zeidan, Partin, & Howard, 2013a).

Pre-clinical and clinical studies suggest that addiction to a wide range of substances is undergirded by changes in dopaminergically-mediated reward function Augustus Diggs, Froeliger, Michael Carlson, & George Gilbert, 2013; Gipson et al., 2013; Heinz et al., 2004; Kalivas & Volkow, 2005; Lintas et al., 2012) including attenuated neurobehavioral reactivity to natural rewards and heightened reactivity to drug-related cues (Koob & Volkow, 2009; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). In contradistinction to healthy, non-addicted individuals who exhibit an attentional bias (AB) toward images representing positive, naturally rewarding stimuli (Wadlinger & Isaacowitz, 2010), opiate dependent individuals evidence an AB to opiate-related visual cues presented for 500 ms on dot probe tasks, as evidenced by faster responses to probes replacing opiate photographs than to probes replacing neutral probes (Lubman, Peters, Mogg, Bradley, & Deakin, 2000). Similarly, prescription opioid dependent chronic pain patients exhibit an AB to prescription opioid cues presented for 200 ms (Garland, Froeliger, Passik, & Howard, 2013b). AB for a cue presented for ≤200 ms is believed to index biases in initial attentional orienting, whereas AB for longer duration stimuli (>500 ms) is believed to index delayed disengagement of attention from an emotionally salient cue (Field & Cox, 2008). Moreover, opiate dependent individuals exhibit enhanced event-related brain potentials (e.g., P300) to opiate cues coupled with attenuated electrophysiological brain responses to images depicting natural rewards (Lubman, Allen, Peters, & Deakin, 2007; Lubman, Allen, Peters, & Deakin, 2008). Such decreased responsiveness to natural rewards is a robust predictor of future opiate use (Lubman et al., 2009). Although the studies by Lubman and colleagues support the presence of decreased responsiveness to natural rewards among individuals addicted to illicit opiates (e.g., heroin), to our knowledge no study has identified reward dysfunction among chronic pain patients who misuse prescription opioids. If research demonstrates the presence of deficits in natural reward processing among such patients, such a finding would provide a potentially crucial treatment target and help to further elucidate the risk chain leading from chronic pain to opioid misuse and addiction (for a review, see Garland et al., 2013a).

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Attentional and emotional processing of rewarding or emotionally-salient cues is thought to elicit reactivity in a network of central (e.g., prefrontal cortex [PFC], anterior cingulate cortex [ACC]) and autonomic nervous system structures with downstream effects on visceral and peripheral parameters, including the beat-to-beat modulation of heart rate by the vagus nerve, known as high-frequency heart rate variability (HRV) (Thayer & Lane, 2000, 2009). HRV is mediated by parasympathetic influences on the sinoatrial node of the heart (Berntson et al., 1997). Elevated HRV may reflect self-regulatory effort or efficacy (Segerstrom & Nes, 2007), and individuals with impairments in regulation of attention, emotion, and appetitive urges exhibit attenuated HRV at rest (Ingjaldsson, Laberg, & Thayer, 2003a; Thayer & Lane, 2009) and when attempting to suppress craving in response to addiction-related cues (Garland, Carter, Ropes, & Howard, 2012a). Yet, increased HRV can also be elicited as a classically conditioned response to conditioned appetitive stimuli (Inagaki, Kuwahara, & Tsubone, 2005; Stockhorst, Huenig, Ziegler, & Scherbaum, 2011). Studies have identified cue-elicited increases in HRV associated with craving for addictive substances such as methamphetamines, nicotine, and alcohol (Culbertson et al., 2010; Erblich, Bovbjerg, & Sloan, 2011; Garland, Franken, & Howard, 2012b; Garland, Franken, Sheetz, & Howard, 2012c; Ingjaldsson, Laberg, & Thayer, 2003b; Rajan, Murthy, Ramakrishnan, Gangadhar, & Janakiramaiah, 1998), and increased HRV during exposure to food cues (Udo et al., 2013) which abates upon consumption of a meal (Nederkoorn, Smulders, & Jansen, 2000). Thus, HRV may be a useful index of self-regulation and reward responsiveness among prescription opioid misusing chronic pain patients, though no study has examined this measure in this clinical population to date.

To address the dearth of findings in this potentially important research area, the present study aimed (a) to establish whether prescription opioid misusers with chronic pain evidence decreased natural reward responsiveness (as indicated by HRV responses) relative to chronic pain patients who take opioids as medically prescribed and (b) to determine whether prescription opioid misusers with chronic pain exhibit comparatively attenuated cardiac-autonomic control during attention to a range of emotionally-salient cues. As converging evidence of reward dysregulation, we sought to determine if opioid misuse was associated with reduced AB to natural reward cues.

To examine these questions in the present study, a sample of opioid-misusing chronic pain patients (opioid misusers) and chronic pain patients who took but did not misuse opioids (non-misusers) completed a dot probe task in which opioid-related, pain-related, and natural-reward images were presented while HRV was measured concurrently. We had three hypotheses: (1) as an index of impaired cardiac-autonomic control during regulation of attention to emotional information, opioid misusers would exhibit significantly less phasic cue-elicited HRV during the dot probe task than non-misusers, but would not show differences in resting state HRV at baseline; (2) given that deficits in natural reward processing are a hallmark of addiction, these phasic HRV differences would be most pronounced for natural reward-related cues; and (3) as further evidence of deficient reward processing, we also hypothesized that the non-misuser group would exhibit a significant positive AB toward natural reward cues, whereas the opioid misuser group would not exhibit this normative positive AB—indicative of their underlying reward deficit.

2. Methods

2.1. Participants

Participants met eligibility criteria if they had a diagnosable chronic pain condition, had been prescribed long-term analgesic pharmacotherapy (for at least 90 days, see clinical guidelines presented in Chou et al., 2009), and had taken opioids daily or nearly every day (≥5 days/week) for >3 months. Participants were recruited from primary care clinics, pain clinics, and neurology clinics in Tallahassee, FL via flyers and online classified ads. Advertisements sought to recruit participants who "suffer from and are prescribed medicine for chronic pain" for a study focused on improving ways to address problems with chronic pain and prescription pain medication. Prescription opioid misuse was determined by scores on the self-reported Current Opioid Misuse Measure (COMM; $\alpha = .83$) (Butler et al., 2007). The original COMM validation study conducted with patients treated in specialty pain management clinics found that a score of ≥9 was suggestive of prescription opioid misuse. However, according to a study of a broad sample of chronic pain patients from a variety of primary care settings who took prescription opioids but not necessarily on a daily basis, receiver–operator characteristic curve analyses revealed that a score of 13 or higher on the COMM had maximum sensitivity and specificity to identify prescription opioid misuse among chronic pain patients in primary care settings (Meltzer et al., 2011). We chose this more conservative COMM threshold value to minimize false positives and because, similar to Meltzer et al. (2011), our sample was broad and not confined to patients from specialty pain clinics.

Based on this cutoff score, participants were grouped into one of two groups: a group of chronic pain patients who took prescription opioids daily/nearly every day and reportedly engaged in opioid misuse behaviors (*misusers*, $n = 72$), and a group of chronic pain patients who took prescription opioids daily/nearly every day without engaging in opioid misuse (*non-misusers*, $n = 26$). Table 1 describes participant demographics and prevalence of various chronic pain conditions in the sample.

Table 1
Sample characteristics of opioid misusers ($n = 72$) and non-misusers ($n = 26$) in the study.

	Opioid misusers ($n = 72$)	Non-misusers ($n = 26$)
Age (years)	46.6 (SD = 13.4)	47.3 (SD = 11.6)
Gender (women, %)	49 (69.2%)	18 (68.1%)
Chronic pain conditions[a]		
Lumbago	43 (59.7%)	13 (50.0%)
Fibromyalgia	13 (18.0%)	7 (26.9%)
Arthritis	5 (6.9%)	2 (7.7%)
Cervicalgia	5 (6.9%)	0 (.0%)
Other	6 (8.3%)	4 (15.3%)
Duration of chronic pain (years)	10.7 (11.0)	12.7 (9.5)
Opioid misuse score (COMM)	21.9 (9.2)	8.5 (3.1)

[a] *Note*: participants could report more than one chronic pain condition.

2.2. Data collection

2.2.1. Current opioid misuse measure

The Current Opioid Misuse Measure (COMM; $\alpha = .83$) (Butler et al., 2007) assessed self-reported aberrant drug-related behavior. Participants responded to 17 items rated on a Likert scale (0 = never, 4 = very often) regarding how often in the past 30 days they had engaged in behaviors potentially reflective of opioid misuse or took opioid medication in excessive doses or in nonprescribed ways, tapped by items such as "In the past 30 days, how often have you taken your medications differently from how they are prescribed?", "In the past 30 days, how often have you used your pain medicine for symptoms other than for pain (e.g., to help you sleep, improve your mood, or relieve stress)?"

2.2.2. Dot probe task

A dot probe task was used to measure AB to opioid-related, pain-related, and natural reward cues. Each trial began with a fixation cross (i.e., crosshair) presented for 500 ms. Next, two images matched for visual complexity, composition, and figure-ground relationships appeared side by side on the computer screen for either 200 or 2000 ms. Pairs of photos containing one emotionally-salient image and one neutral image were presented. Three blocks of cues (opioid-related, pain-related, and pleasure-related) were presented in randomized, counterbalanced order across participants. Specific picture cues were presented in a randomized order within each block and blocks were counterbalanced across participants.

Three sets of 12 photographs, each set representing one type of cue, were selected from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1997) and media libraries on the Internet. *Opioid-related cues* included images of pills and pill bottles. *Pain-related cues* included images of severe injuries, painful medical procedures, and human faces grimacing in pain. *Natural reward cues* included images of romantic couples, athletic victories, and food. A set of 36 neutral images was selected from the IAPS and each neutral image was paired with an emotionally-salient image matched for visual features such as color, figure-ground relationships, and presence of human faces.

Presentation duration and left/right position of the images were randomized and counterbalanced within each block of 64 trials. Half ($n = 32$) of the trials for each cue type were presented in each visual field (VF: left VF, right VF), and within each VF, half of the trials were presented at each presentation duration (200 ms, $n = 16$; 2000 ms, $n = 16$). The image pairs disappeared, and a target probe replaced one of the images after a 50 ms inter-stimulus interval (ISI). Probes appeared for 100 ms, and probe location (left VF, right VF) was counterbalanced. Each block was presented 1 time, and the order of blocks over the timecourse of the task was counterbalanced across participants. Participants indicated the location of the target by responding with a left/right button press, and the reaction time (RT) was recorded.

2.2.3. HRV measurement

Disposable Ag–AgCl electrodes were attached to participants' right and left pectoral muscles. Electrocardiogram (ECG) data were sampled at 1000 Hz and recorded continuously throughout the protocol on a Biopac MP150 (Biopac Systems, Goleta, CA). Respiration rate was concomitantly assessed with a breathing belt and also recorded on the Biopac MP150 system.

2.3. Procedures

Participants were instructed to take their prescribed opioid medication as usual on the day they completed study measures. In a single session, participants first