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Opioid Modulation of Resting-State Anterior Cingulate Functional Connectivity

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Abstract

Evidence suggests that individuals misuse oxycodone, a widely prescribed opioid analgesic, to self-medicate physical and emotional pain. Physical and emotional pain is thought to be represented in the brain by a ‘pain matrix,’ of which the dorsal anterior cingulate cortex (ACC) plays a central role in mediating the affective dimensions of pain. The current study examined oxycodone’s effects on resting-state functional connectivity between the dorsal ACC and regions of the pain matrix (i.e., insula, thalamus, and somatosensory cortices) using functional magnetic resonance imaging (fMRI). In a within-subjects, randomized, double-blind, placebo-controlled, dose-response design, fourteen healthy subjects completed a resting-state scan following ingestion of placebo, 10mg, or 20mg of oxycodone. Functional correlations between the dorsal ACC seed region and the pain matrix were examined and compared across sessions. Results indicated that both the 10mg and 20mg doses of oxycodone reduced functional coupling between the dorsal ACC and bilateral anterior insula and putamen relative to placebo; no differences between the high and low dose of oxycodone were observed. Given that functional interactions between these regions are involved in internal awareness and affective experience of pain or other aversive states, it is possible that oxycodone’s physical and emotional ‘analgesic’ effects are mediated by the disruption of ACC-insula and ACC-putamen connectivity at rest.

Keywords

oxycodone; pain; functional connectivity; resting-state

Introduction

Oxycodone, a semi-synthetic opioid analgesic, is currently one of the most widely prescribed drugs for the management of moderate to severe pain. Over the past decade, there has been an alarming increase in non-medical oxycodone abuse and addiction, which has led to serious public health consequences including high rates of morbidity and mortality (Young, 2001). Epidemiological data suggest that nearly 10 million Americans have abused prescription opioids in the past year (Becker *et al*, 2008) and that the economic cost of this abuse is in the billions of dollars (Birnbaum *et al*, 2006). Although the motives for the misuse of prescription opioids are not fully understood, survey data indicate that self-medication of emotional and physical pain are often cited as reasons for initiation and continued use (McCabe *et al*, 2009). Thus, oxycodone's effects on pain processing contribute to the drug's abuse liability resulting in a critical need to examine the neural mechanisms which may underlie these effects.

Studies indicate that a network of neural regions is reliably activated in response to acute physical pain (Tracey and Johns, 2010). This neural network, often called the 'pain-matrix,' includes the somatosensory cortices, insula, thalamus, and anterior cingulate cortex (ACC) (Rainville, 2002), and has been shown to exhibit increased activation in response to a wide range of noxious stimuli. Prior work has shown that the somatosensory cortices are primarily responsible for sensory-discriminative functions including location and duration of pain, while the ACC and insula are associated with the affective-motivational processes and response generation (Price, 2000). For instance, manipulations that reduce subjective experience of pain specifically alter ACC activity (Wager *et al*, 2004), and ACC lesions produce a decrease in pain sensitivity (Lawson *et al*, 2009). Moreover, voluntary control over ACC activation via neuro-feedback leads to control over pain perception in chronic pain patients (DeCharms *et al*, 2005). Given this pattern of results, it has been postulated that opioid's antinociceptive effects are primarily mediated by opioidergic neurotransmission in the ACC (Sprenger *et al*, 2006).

Interestingly, emerging evidence suggests that emotional and physical pain may share common neuroanatomical substrates (Eisenberger, 2008). A seminal study by Eisenberger and colleagues (2003) demonstrated that, in humans, social exclusion during a virtual ball-tossing game was associated with greater dorsal ACC, insula, and ventral prefrontal cortex (vPFC) activation, and changes in self-reported distress during the task were positively and negatively correlated with changes in ACC and vPFC activity, respectively. Consistent with these findings, a review of studies on grief, social exclusion, and induced sadness concluded that the insula, prefrontal cortex, and ACC were similarly involved in emotional and physical pain, but that the somatosensory cortices were unique to physical pain (Mee *et al*, 2006). A more recent review, focused on recalled autobiographical studies of sad events, suggested that the ACC, posterior cingulate cortex (PCC), thalamus, cerebellum, and parahippocampal gyrus were most often involved in the processing of psychological pain/sadness (Meerwijk *et al*, 2013). Taken together, the regulation of emotional and physical pain share common neural substrates and the ACC is most often implicated across both literatures.

Opioid analgesic agents such as oxycodone have been shown to modulate pain network activity. Specifically, pharmacofunctional magnetic resonance imaging (fMRI) studies have previously demonstrated that opioid receptor agonists (e.g., remifentanyl) attenuate pain-induced neural activation in regions such as the ACC, insula, and somatosensory cortices (Wise *et al*, 2002; Wise *et al*, 2004). Recent work by Upadhyay and colleagues (2012) found that buprenorphine, a partial opioid agonist, reduces BOLD activity in the primary and secondary somatosensory cortices, middle cingulate cortex, and posterior insula in response to noxious heat. Animal studies have similarly demonstrated that opioids modulate pain-matrix neural activation (Shah *et al*, 2005). Notably, even in the absence of pain stimuli, data indicate that opioid analgesics alter neural activation of the ACC in healthy, drug-naïve volunteers (Leppa *et al*, 2006), further suggesting that the ACC is specifically involved in the subjective effects of opioids.

While the pharmacokinetic and pharmacodynamic properties of oxycodone are well-studied, relatively little is known about the neural mechanisms underlying its effects. It is possible that the broader opioid analgesics literature may apply, but studies have suggested that oxycodone differs from other opioids in clinically important ways (e.g., half-life, opioid-receptor binding characteristics) (Zacny and Lichter, 2008). One potentially useful starting point in addressing the gap in the oxycodone literature is to examine pain-network alterations at baseline using resting-state functional connectivity techniques. There are several advantages of examining the effects of oxycodone during resting-state. Most notably, pain can be conceptualized as a homeostatic emotion that has dissociable acute sensory properties and tonic affective components (Ribeiro *et al*, 2005). Data indicate that the tonic affective components of pain (e.g., distress) are associated with greater opioid analgesic efficacy and risk for opioid abuse (Compton and Volkow, 2006). Thus, there is a need to capture these internal processes in the absence of pain administration (i.e., acute sensory stimuli), with resting-state being a useful tool towards this end.

To date, few studies have examined the effects of opioid analgesics on resting-state functional connectivity. A notable exception includes a recent study by Upadhyay and colleagues (2012) which found that intravenous and sublingual efficacious doses of buprenorphine decreased resting-state functional connectivity between the putamen and the cingulate cortex, postcentral gyrus, posterior insula, and thalamus, in a sample of healthy drug-naïve males. An additional study using healthy males found that intravenous administration of morphine disrupted functional connectivity of several resting-state brain networks including the primary sensory motor network (e.g., pre- and postcentral somatosensory cortices) and the executive salience network (e.g., medial and inferior prefrontal regions) (Khalili-Mahani *et al*, 2012). Although these findings significantly extend the existing literature, no study to date has specifically examined the effects of oxycodone on resting-state functional connectivity. Moreover, Upadhyay *et al*. (2012) found that drug effects differed as a function of administration route (sublingual vs. intravenous) and thus, there is a need to test the effects of oxycodone using a more naturalistic drug administration design (i.e., oral ingestion).

The primary aim of the current study was to investigate the effects of oxycodone on pain-matrix functional connectivity patterns during resting-state. The study utilized a within-

subjects, randomized, double-blind, placebo-controlled, dose-response design. Participants completed three separate resting-state fMRI scans after ingesting either placebo, 10mg of oxycodone, or 20mg of oxycodone. Given that individuals report abusing oxycodone to dampen pain, we used the dorsal ACC as the seed region as it has been implicated in emotional and physical pain and plays a particular role in perception of pain unpleasantness (Rainville, 2002). We hypothesized that, relative to placebo, oxycodone would reduce functional coupling between the ACC and other pain-matrix neural regions such as the insula, thalamus, and somatosensory cortices. If observed, such findings would extend our understanding of the analgesic and reinforcing effects of oxycodone.

Methods

Participants

A total of seventeen subjects were enrolled in the larger study examining the effects of oxycodone on affective experience. However, three participants did not complete all three scanning sessions and thus, were excluded from the present analyses. The final sample included fourteen healthy, right-handed volunteers. Sample descriptive information including demographics and clinical characteristics are displayed in Table 1. Participants were excluded from the overall study if they met lifetime criteria for any major Axis I or Axis II psychiatric disorder according to the Structured Clinical Interview for DSM-IV (SCID-IV Patient Edition; First *et al*, 1995), were taking psychoactive medications, or had a history of a neurological or medical illness as confirmed by a medical examination. In compliance with study procedures, all urine pregnancy screens and urine drug screens were required to be negative upon arrival to the testing sessions. All individuals provided written informed consent after explanation of the protocol, as approved by the University of Michigan Institutional Review Board.

Procedure

The current study was a within-subjects, randomized, double-blind, placebo-controlled, dose-response cross-over oxycodone challenge study. In three separate fMRI sessions, participants received either placebo, 10mg of oxycodone, or 20mg of oxycodone. Sessions were separated by at least one week, but were never more than two weeks apart (average number of days between sessions = 8.5 [$SD = 2.9$]). Prior to each session, subjects were instructed to fast for at least four hours and consume only clear liquids for at least two hours before their arrival. They were additionally told not to ingest any drugs other than their usual amounts of caffeine and nicotine 24 hours before the study.

Following abstinence verification participants were provided with a small gel capsule and to minimize expectancies were told that the capsule may contain a stimulant, sedative, opioid, cannabinoid, or placebo; only after the completion of the entire experiment (i.e., all three scans) were participants debriefed and informed of the contents of the capsules for each session. The drug capsule contained the contents of either two 5mg (i.e., 10mg dose) or four 5mg (i.e., 20mg dose) oxycodone HCL immediate-release oral capsules (Purdue Pharma, Stamford, CT) placed into an opaque tablet with dextrose filler. Placebo capsules contained only dextrose. All capsules were administered to subjects under double-blind conditions,

with administration order randomized. We selected 10mg and 20mg doses of oxycodone because: 1) Prior research has shown that doses of 10mg and 20mg of oxycodone induce mood-altering effects with negligible cognitive and psychomotor impairments (Zacny and Gutierrez, 2003); 2) We sought to test both a low and high therapeutic dose for analgesia (Coluzzi and Mattia, 2005) in line with standard abuse liability assessment guidelines; 3) Administration of these doses in healthy volunteers has not been associated with adverse events (Zacny and Gutierrez, 2003).

After capsule ingestion, participants were left alone in a waiting room for approximately 40-minutes, and MRI data collection occurred approximately 90 minutes post-oxycodone or placebo ingestion. The timing was designed to ensure that participants experienced fairly strong drug effects during data collection, as Zacny and Gutierrez (2003) report that subjective ratings of drug effects tended to peak approximately 60-minutes post-oxycodone ingestion and remain relatively stable for an additional 60–90-minutes at the 10 and 20mg dose levels. While in the MRI scanner, participants completed an emotional pictures task, emotional faces task, and a visual motor task (data not presented) as part of the larger study, which were followed by a 5-minute resting scan. During the resting scan, they were instructed to lie still with their eyes open, focus on a fixation cross and to not think of anything in particular for the duration of the scan. Throughout the experiment (0, 30, 60, 120, 180, and 240-mins post-capsule ingestion) ratings of subjective drug effects were taken using the Addiction Research Center Inventory (ARCI; Haertzen and Hickey, 1987) and the Drug Effects Questionnaire (DEQ; Johanson and Uhlenhuth, 1980). To assess changes in negative affect, participants completed a modified version of the Profile of Mood States (POMS; McNair *et al*, 1971), which included a checklist of 72 adjectives commonly used to describe momentary mood states. Participants were instructed to indicate the extent to which they felt each adjective at the moment on a 5-point Likert scale (range 0–4) at baseline (0-mins) and again when they exited the scanner (120-mins post ingestion).

Brain Imaging

Functional MRI was performed on a 3T GE Signa System (Milwaukee, WI) which acquired blood oxygenated level-dependent (BOLD) images with 43 axial, 3-mm-thick slices using a T2*-sensitive gradient echo reserve spiral acquisition sequence (2 s repetition time; 30 ms echo time; 64 × 64 matrix; 22 cm field of view; 90° flip angle), optimized to minimize susceptibility artifacts (signal loss) at the medial temporal pole. This was followed by a high-resolution, T1-weighted volumetric anatomical scan (three-dimensional spoiled gradient echo) for precise anatomical localization and normalization.

Resting Functional Connectivity Data Analyses

Data from all 14 participants, across all 42 resting scans, met criteria for high quality and scan stability, particularly head movement (mean total movement across all scans was 1.1 mm [$SD = 1.3$]). Connectivity analyses were performed using the Functional Connectivity (CONN) toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012; www.nitrc.org/projects/conn) for Statistical Parametric Mapping software (SPM8: Wellcome Trust Centre for Neuroimaging, London, UK). Images were preprocessed (slice-time correction, motion realignment, normalization using a structural template, smoothing) and the effects of

nuisance covariates (time-series predictors for global signal, white matter, cerebrospinal fluid, and movement parameters, including the first derivative, obtained during realignment to account for motion-related effects in BOLD) were removed following the implemented CompCor strategy (Behzadi *et al*, 2007). The data were then band-pass filtered to 0.01Hz – 0.09Hz. Seed-based analyses were performed by calculating the temporal correlation between BOLD signals from the CONN rsREL ACC seed region (Whitfield-Gabrieli and Nieto-Castanon, 2012; MNI coordinates = 0, 6, 40) to all other voxels in the brain. First level correlations were created for all subjects. To test whether there were differences in functional connectivity across the three sessions (placebo [PBO], 10mg oxycodone [low dose], and 20mg oxycodone [high dose]), we performed a second-level repeated-measures analysis of variance (ANOVA). We considered activations that survived $p < 0.005$ (uncorrected; Lieberman and Cunningham, 2009) with a cluster extent threshold of greater than 20 contiguous voxels (volume $> 160\text{mm}^3$) as significant to balance between Type I and Type II errors consistent with prior fMRI studies of drug effects on functional connectivity (Sripada *et al*, 2013). In order to identify the direction of effects, we subsequently conducted paired sample *t*-tests between sessions (e.g., PBO $>$ low dose; PBO $>$ high dose; low dose $>$ high dose).

Results

Subjective Drug Effects

Mean DEQ and ARCI self-report ratings are displayed in Table 2. Pre-scan (i.e., 60-mins post-drug) and post-scan (i.e., 120-mins post-drug) ratings were averaged to estimate subjective drug effects during resting-state data collection (i.e., approximately 100-mins post-drug). One-way ANOVA results indicated that DEQ self-reported ratings of feeling drug effects differed by session, $F(2, 41) = 20.53$, $p < 0.001$, such that individuals reported greater feelings of drug effects during high relative to low dose ($p = 0.03$) and PBO ($p < 0.001$), and during low dose relative to PBO ($p < 0.001$) (see Figure 1). DEQ self-reported ratings of feeling high also differed across sessions, $F(2, 41) = 6.34$, $p < 0.01$, with subjects reporting feeling high to a greater extent during high relative to low dose ($p = 0.07$) and PBO ($p < 0.01$). There were no differences between low dose compared with PBO. Differences in the ARCI PCAG (i.e., pentobarbital-chlorpromazine-alcohol group) subscale, which is a measure of euphoria, were found between sessions $F(2, 41) = 4.84$, $p < 0.05$, with greater feelings of euphoria during high dose relative to PBO ($p < 0.01$), and low dose relative to PBO ($p = 0.06$). No session differences were found for the DEQ drug liking subscale or the ARCI MGB (i.e., morphine-benzedrine group) sedation subscale.

Drug Effects on Negative Affect

Mean ratings of the POMS negative affect scales are displayed in Table 2. To assess changes in negative affect as a function of session, we conducted a series of Time (baseline vs. post-drug) $\times$ Session (PBO vs. low dose vs. high dose) repeated measures ANOVAs using the individual negative affect subscales (i.e., anxiety, depression, and anger) and a composite negative arousal score (defined as [(anxiety + vigor) - (fatigue + confusion)]) as the dependent variables. One participant did not complete the self-report ratings and was excluded from the analyses. Results indicated no significant changes in ratings, as a function

of session, on the individual negative affect subscales. However, there was a significant Time $\times$ Session interaction, $F(2, 24) = 4.76$, $p = 0.02$, for changes in negative arousal. At baseline there were no session differences in negative arousal; however, after ingesting the high dose of oxycodone, participants reported significantly less negative arousal relative to PBO, $t(12) = 3.77$, $p < .01$. There were no session differences in negative arousal between low dose and PBO.

Functional Connectivity

Analyses of whole-brain seed-to-voxel connectivity patterns indicate differences between session in functional connectivity between the dorsal ACC seed region and a cluster of voxels in the right (MNI peak: [32, 12, 2], $F(2, 39) = 20.15$, $p < 0.001$) and left anterior insula/putamen (MNI peak: [-26, 20, 2], $F(2, 39) = 9.37$, $p < 0.001$). Given that the bilateral clusters were composed of two separate anatomic regions and Upadhayay et al. (2012) previously reported that the opioid buprenorphine disrupted putamen connectivity, ACC-anterior insula and ACC-putamen functional connectivity data were extracted separately, *post hoc*, by identifying each functional cluster masked by anatomic regions of interest (ROI volumes: right insula = 936 mm³; right putamen = 1432 mm³; left insula = 80 mm³; left putamen = 32 mm³).

Data indicated that ACC-right insula functional connectivity was greater during PBO relative to low ($t(13) = 4.88$, $p < 0.01$) and high doses ($t(13) = 3.76$, $p < 0.01$); however, there were no differences between low and high dose. Similarly, results revealed that ACC-left insula functional connectivity was greater during PBO relative to low dose ($t(13) = 3.10$, $p = 0.01$), and high dose at a trend level ($t(13) = 1.83$, $p = 0.07$). There were no differences in ACC-left insula connectivity during low versus high dose. Data indicated that ACC-right putamen functional connectivity was greater during PBO relative to low ($t(13) = 5.14$, $p < 0.01$) and high doses ($t(13) = 2.77$, $p = 0.02$), and there were no differences between low and high dose. Lastly, ACC-left putamen functional connectivity was greater during PBO compared with low ($t(13) = 2.53$, $p = 0.03$) and high doses ($t(13) = 3.12$, $p < 0.01$); however, there were no differences between low and high doses. ACC-anterior insula and ACC-putamen functional connectivity by session is displayed in Figure 2.

There were no session differences in functional connectivity between the dorsal ACC and other pain-matrix regions including the thalamus and somatosensory cortices. Other brain regions outside the pain-matrix that demonstrated effects of oxycodone on ACC functional connectivity are shown for completeness in Table 3. Of note, we tested whether oxycodone-induced changes in ACC-anterior insula functional connectivity were associated with oxycodone-induced changes in negative arousal using Pearson's correlations but no significant relationships were detected.

Discussion

Previous research has demonstrated that opioid analgesics attenuate emotional and physical pain by modulating neural activity of the pain-matrix, and that the ACC is involved in subjective pain unpleasantness. Given the tonic affective components of pain may be important targets for opioid-induced analgesia, the aim of the current study was to provide

data on the effects of oxycodone on functional connectivity between the dorsal ACC and the pain matrix during rest- a tonic, internal state. Results indicate that 10mg and 20mg of oxycodone reduced functional coupling between dorsal ACC and bilateral anterior insula and putamen relative to placebo.

The present findings are notable for several reasons. First, previous work suggests that the ACC-anterior insula circuit functions as a resting-state 'emotional salience network,' such that the ACC and anterior insula work together to integrate awareness of interoceptive states with emotional salience information to ultimately form a subjective evaluation of bodily states (Taylor *et al*, 2009). With respect to pain processing, the ACC-anterior insula circuit is critically involved, via functional interactions, in the internal awareness and subjective experience of unpleasant pain-related emotions, and in guiding affective and behavioral responses to perceived unpleasantness (Medford and Critchley, 2010). Consistent with this conceptualization, studies have demonstrated that the insula and ACC are activated by attention to the unpleasantness of pain (Kulkarni *et al*, 2005), and that ACC-insula co-activation in response to highly arousing images is associated with self-reported subjective emotional awareness (McRae *et al*, 2008). Moreover, a recent study found that patients with chronic pain exhibit increased functional connectivity between the ACC and anterior insula at rest and during pain processing, highlighting the role of *increased* ACC-insula connectivity in the experience of pain states (Ichesco *et al*, 2012). Given the current findings, it is plausible that by reducing functional connectivity between the ACC and anterior insula, oxycodone dampens emotional and physical pain by disrupting the typical functions of the emotional salience-network. In other words, oxycodone may inhibit neural integration or lower the subjective awareness of interoceptive information that is necessary for the affective perception of pain.

Interestingly, the current ACC-anterior insula findings are consistent with a prior study investigating group differences in resting-state functional connectivity between abstinent prescription opioid dependent patients (primarily oxycodone users) and healthy controls (Upadhyay *et al*, 2010). Data indicated that patients had both structural and functional abnormalities, including decreased functional connectivity between the anterior insula (seed region) and the anterior and middle cingulate cortices, putamen, and laterobasal amygdala. Since the present sample included non-dependent, opioid-naïve, healthy volunteers, the acute effects of oxycodone on ACC-anterior insula functional connectivity may persist beyond intoxication states and play a key role in the pathophysiology of oxycodone addiction. More specifically, repeated exposure to oxycodone may lead to neuroadaptions within the ACC-anterior insula circuit which precipitate oxycodone dependence. Future research is needed to directly test if the acute effects of oxycodone and other opioid analgesics on ACC-insula and ACC-putamen persist with ongoing and chronic exposure.

Results from the current study indicate that oxycodone also reduced functional connectivity between the ACC and putamen, which is consistent with the findings from Upadhyay et al. (2012) on the effects of buprenorphine. Although not consistently conceptualized as part of the 'pain-matrix,' previous studies have found that the putamen has a high density of μ -opioid receptors and is potentiated during pain processing (Bingel *et al*, 2004). Similar to the anterior insula, evidence indicates that the putamen is involved in integrating motor,

emotional, and cognitive responses to pain signals (Borsook *et al*, 2010), and dopaminergic neurotransmission in the putamen is associated with subjective ratings of sensory and affective qualities of pain (Scott *et al*, 2006). Therefore, oxycodone-induced ACC-putamen and ACC-anterior insula decoupling may similarly impair perception, awareness, and/or affective response to the aversiveness of pain. Importantly, these hypothesized mechanisms are in-line with numerous animal and human pharmacological studies suggesting that μ -opioid receptor mediated neurotransmission impacts the distressing, affective components of pain rather than the perception of pain itself (Ribeiro *et al*, 2005; Zubieta *et al*, 2001).

Our findings also suggest that the prefrontal cortex (PFC) may be involved in oxycodone's effects, which is consistent with emerging data implicating the PFC in pain modulation. Results indicated that there was greater connectivity between the dorsal ACC and the right medial frontal gyrus (MedFG), right superior frontal gyrus (SFG), left inferior frontal gyrus (IFG), and bilateral middle frontal gyrus (MidFG) during high doses of oxycodone relative to placebo and low dose. Previous work has suggested that the PFC exerts top-down inhibitory influences on pain perception by disrupting functional interactions between regions of the pain-matrix and dampening ACC activity (Eisenberger *et al*, 2003; Lorenz *et al*, 2003). Thus, increased ACC-PFC functional connectivity during high dose of oxycodone may reflect acutely increased cognitive control over subjective pain unpleasantness. Interestingly, however, repeated opioid exposure may actually weaken these functional interactions, and subsequently cognitive control capabilities, as studies indicate that abstinent chronic opioid users have decreased ACC-PFC resting-state functional connectivity (Ma *et al*, 2010). Given that we did not have *a priori* hypotheses about oxycodone's effects outside of the putative 'pain matrix', the functional relevance of *enhanced* dorsal ACC to MedFG, SFG, IFG and MidFG during high, but not low, dose of oxycodone remains an open question.

It is important to note that despite the generally expected pattern of subjective drug ratings, the effects of oxycodone on ACC-insula and putamen resting-state functional connectivity were not dose-dependent, as there were no differences between low (10mg) and high (20mg) doses. Although unexpected, this pattern of results is consistent with a previous study which found that 10 and 20mg of oxycodone had dose-dependent effects on subjective drug effects but not psychophysiological responding (i.e., heart rate, blood pressure, euphoria, and respiration rate; Zacny and Lichior, 2008). This implies that there may be a discrepancy between the dosing of oxycodone's subjective and physiological effects. Relatedly, although high doses of oxycodone significantly reduced self-reported negative arousal, there were no clear dose-dependent effects on subjective indices of emotional pain. However, this pattern of results is likely due to a floor effect, as the current sample of healthy controls reported extremely low levels of negative affect (e.g., anxiety, depression, anger) at baseline. Future studies would therefore benefit by using a clinical sample with baseline levels of pain to further elucidate the role of ACC-insula/putamen functional connectivity in analgesia.

It is important to note that the current study had several methodological strengths. First, the use of a within-subjects, double-blind, cross-over design allowed for a controlled test of oxycodone's effects. The inclusion of a low (10mg) and high (20mg) dose for analgesia was novel and provided relevant data for future oxycodone studies. Additionally, drug

administration was naturalistic and the confounding effects of drug expectancies to the anticipated effects of an ‘opioid’ were diminished by design. Lastly, the current sample was opioid-naïve, had no history of psychopathology, and reported extremely low levels of licit substance use.

Despite these strengths, there are a few limitations worth noting. Although a within-subjects design, the sample size was relatively small which reduced statistical power and limited our ability to conduct sub-analyses, including correlations between oxycodone-induced changes in negative affect and functional connectivity. In addition, although we assessed changes in negative affect, we did not include an assessment of the physical or affective dimensions of pain and thus, the current relations between oxycodone, ACC connectivity, and pain are unclear. Moreover, the current findings are limited to oxycodone’s effects on connectivity at resting-state and thus the findings cannot be generalized to states of acute, provoked ‘physical’ pain (e.g., pain challenge). Future research is needed to continue to link these functional connectivity effects with subjective reports of perceived and actual pain, and broader cognitive, behavioral, and affective outcomes. Lastly, functional connectivity analyses are correlational and directionality between neural regions cannot be inferred.

In sum, the results of the present study suggest that oxycodone attenuates dorsal ACC-anterior insula and putamen resting-state functional connectivity, which may serve to impair the perception and appraisal of internal pain states occurring at a tonic manner. Given that oxycodone’s ability to dampen physical and ‘emotional’ pain is a major motive for recreational and non-medical use of oxycodone and reduced resting ACC-anterior insula functional connectivity has been found in prescription opioid-dependent patients (Upadhyay *et al*, 2010), these neural pathways may underlie the pathophysiology and treatment targets for individuals with prescription opioid use disorders.

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Figure 1.

Mean DEQ “feel drug effects” self-report scores by session and across time. PBO = placebo condition; LOW = low dose of oxycodone condition; HIGH = high dose of oxycodone condition; DEQ = Drug Effects Questionnaire. Black Bar denotes timing of resting-state scan at approximately 90 minutes post-ingestion of PBO/LOW/HIGH dose.

Figure 2.

(A) Image of the 10mm sphere dorsal ACC seed region and a voxel-wise statistical F -map displayed on a canonical brain; Clusters are separated into anatomical putamen and insula regions; Color scale reflects F -score. (B) Bar graphs illustrating extracted correlations for bilateral ACC-anterior insula and ACC-putamen connectivity across all three sessions. PBO = placebo condition; LOW = low dose of oxycodone condition; HIGH = high dose of oxycodone condition.

Table 1**Participant Demographics and Clinical Characteristics**

Demographics	Mean (SD) or %
Age (years)	24.7 (6.4)
Sex (% male)	71.4%
Race (% Caucasian)	78.6%
Education (years)	15.5 (1.5)
Clinical Variables	
Alcohol drinking days per week	1.0 (0.5)
Daily smoker	0.0%
Ever used opiates	0.0%
SCL-90-R Global Severity Index	0.1 (0.1)

Note. SCL-90-R = Symptom Checklist-90-Revised (Derogatis, 1994).

Table 2

Means and standard deviations for self-reported drug effects and negative affect during each session.

Measure	Session	Time Since Capsule Ingestion					
		Baseline	30-mins	60-mins	120-mins	180-mins	240-mins
Subjective Drug Effects							
DEQ-Feel	PBO	0.0 (0.0)	0.4 (0.6)	0.6 (0.6)	0.5 (0.7)	0.1 (0.3)	0.1 (0.3)
	LOW	0.0 (0.0)	0.5 (0.7)	1.8 (1.0)	1.6 (1.0)	1.2 (1.0)	0.6 (1.0)
	HIGH	0.0 (0.0)	0.6 (0.9)	2.6 (1.0)	2.0 (0.7)	1.7 (0.6)	1.1 (0.9)
DEQ-Like	PBO	0.0 (0.0)	-0.1 (0.3)	0.0 (0.8)	-0.1 (0.9)	0.0 (0.0)	0.0 (0.0)
	LOW	0.2 (0.8)	0.1 (0.5)	0.4 (1.5)	-0.3 (1.5)	-0.4 (1.2)	-0.3 (0.7)
	HIGH	0.0 (0.0)	0.0 (0.9)	1.1 (1.7)	-0.4 (1.5)	-1.43 (1.6)	-1.29 (1.4)
DEQ-High	PBO	0.0 (0.0)	0.1 (0.4)	0.4 (0.5)	0.1 (0.4)	0.1 (0.3)	0.0 (0.0)
	LOW	0.0 (0.0)	0.1 (0.3)	0.9 (1.0)	0.6 (0.8)	0.4 (0.5)	0.2 (0.4)
	HIGH	0.0 (0.0)	0.4 (0.8)	1.6 (1.5)	0.9 (0.8)	0.6 (0.7)	0.3 (0.5)
ARCI-MBG	PBO	2.5 (3.3)	2.2 (2.8)	2.1 (2.7)	1.8 (2.6)	2.1 (2.6)	1.9 (2.5)
	LOW	3.0 (2.7)	2.1 (2.7)	2.8 (3.1)	2.9 (3.9)	2.9 (3.2)	2.0 (2.4)
	HIGH	3.4 (2.4)	2.9 (2.9)	3.6 (4.0)	2.4 (2.8)	1.8 (2.7)	1.5 (2.2)
ARCI-PCAG	PBO	3.6 (1.9)	3.7 (1.8)	3.6 (1.9)	4.0 (2.4)	2.7 (1.0)	2.7 (1.1)
	LOW	3.4 (1.2)	4.1 (1.7)	5.6 (3.5)	5.4 (2.7)	4.5 (2.7)	4.9 (1.9)
	HIGH	3.0 (1.0)	4.1 (2.0)	6.1 (2.7)	6.9 (2.3)	6.9 (3.0)	5.7 (2.4)
Negative Affect							
POMS-Anxiety	PBO	2.7 (2.5)	-	-	3.1 (2.8)	-	-
	LOW	3.2 (2.6)	-	-	2.6 (3.7)	-	-
	HIGH	2.8 (2.4)	-	-	3.5 (4.6)	-	-
POMS-Depression	PBO	0.6 (1.2)	-	-	0.9 (2.1)	-	-
	LOW	0.2 (0.6)	-	-	0.2 (0.6)	-	-
	HIGH	1.2 (3.5)	-	-	0.8 (1.7)	-	-
POMS-Anger	PBO	1.0 (1.7)	-	-	1.0 (1.8)	-	-
	LOW	1.1 (1.8)	-	-	0.7 (1.2)	-	-
	HIGH	1.1 (2.8)	-	-	0.8 (2.2)	-	-

Measure	Session	Time Since Capsule Ingestion					
		Baseline	30-mins	60-mins	120-mins	180-mins	240-mins
POMS-Negative Arousal	PBO	5.5 (12.0)	-	-	4.0 (11.0)	-	-
	LOW	8.7 (11.4)	-	-	1.4 (15.4)	-	-
	HIGH	7.8 (9.0)	-	-	-3.8 (13.2)	-	-

Note. PBO = placebo condition; LOW = low dose of oxycodone condition; HIGH = high dose of oxycodone condition; DEQ = Drug Effects Questionnaire; ARCI = Addiction Research Center Inventory; Feel = subscale assessing how much subjects feel drug effects; Like = subscale assessing how much subjects like the drug effects; High = subscale assessing how high subjects feel; MBG = morphine-benzedrine group/measure of euphoria; PCAG = pentobarbital-chlorpromazine-alcohol group/measure of sedation; POMS = Profile of Mood States questionnaire; Anxiety = subscale assessing state levels of anxiety; Depression = subscale assessing state levels of depressed mood; Anger = subscale assessing state levels of anger; Negative Arousal = composite scale assessing state negative affect.

Table 3

Significant main effects of session for resting-state functional connectivity analyses between the ACC and all other voxels in the brain.

Region Name	MNI Coordinates			Voxels	Z-score	p-value	Direction of Effects
	X	Y	Z				
R Insula/Putamen	32	12	2	448	4.76	0.000	P > L; P > H; L = H
R Occipital Lobe	36	-78	46	297	3.77	0.000	P = L; P < H; L < H
R Temporal Pole	56	8	-34	199	3.69	0.000	P = L; P < H; L < H
L Orbitofrontal Cortex	-8	64	-6	111	3.64	0.000	P = L; P < H; L < H
R Medial Frontal Gyrus	18	58	0	95	3.63	0.000	P = L; P < H; L < H
L Medial Frontal Gyrus	-8	56	24	328	3.60	0.000	P = L; P < H; L < H
L Inferior Frontal Gyrus	-56	28	2	25	3.53	0.000	P = L; P < H; L < H
R Inferior Temporal Gyrus	66	-54	-10	85	3.51	0.000	P < L; P < H; L = H
R Middle Frontal Gyrus	32	8	42	181	3.50	0.000	P = L; P < H; L < H
L Middle Frontal Gyrus	-40	18	40	106	3.49	0.000	P = L; P < H; L < H
R Cerebellum	48	-68	-46	72	3.45	0.000	P > L; P = H; L = H
L Middle Temporal Gyrus	-64	-22	-12	68	3.33	0.000	P = L; P < H; L < H
L Insula/Putamen	-26	20	2	31	3.30	0.000	P > L; P > H; L = H
L Precuneus	-16	-48	50	25	3.28	0.001	P = L; P > H; L = H
R Superior Frontal Gyrus	22	46	2	80	3.19	0.001	P = L; P < H; L < H
L Postcentral Gyrus	-42	-26	32	22	3.18	0.001	P = L; P = H; L > H

Note. MNI= Montreal Neurological Institute; results at $p < .005$, uncorrected; >20 voxel minimum; P = placebo condition; L = low dose of oxycodone condition; H = high dose of oxycodone condition.