Published in final edited form as:
Brain Res. 2023 April 15; 1805: 148268. doi:10.1016/j.brainres.2023.148268.

Pain-related opioidergic and dopaminergic neurotransmission: Dual Meta-Analyses of PET Radioligand Studies

Sergio Garcia Guerra[2,1], **Andrea Spadoni**[3,4], **Jennifer Mitchell**[2,1], **Irina A. Strigo**[1,2]

[1]Research Service, San Francisco Veterans Affairs Health Care Center, 4150 Clement Street, San Francisco, CA 94121

[2]University of California San Francisco, 505 Parnassus Ave, San Francisco, CA 94143

[3]Research Service, San Diego Veterans Affairs Health Care Center

[4]University of California San Diego, La Jolla, CA 92093

Abstract

Molecular mechanisms of the interaction between opioidergic and dopaminergic processing during pain-related experiences in the human brain are still incompletely understood. This is partially due to the invasive nature of the available techniques to visualize and measure metabolic activity. Positron Emission Tomography (PET) radioligand studies using radioactive substances are still the only available modality to date that allows for the investigation of the molecular mechanisms in the human brain. The most commonly studied PET radiotracers are [^{11}C]-carfentanil (CFN) and [^{11}C]- or [^{18}F]-diprenorphine (DPN), which bind to opioid receptors, and [^{11}C]-raclopride (RAC) and [^{18}F]-fallypride (FAL) tracers, which bind to dopamine receptors. The current meta-analysis examines pain-related studies that used aforementioned opioid and dopamine radioligands in an effort to consolidate the available data into the most likely activated regions. Our primary goal was to identify regions of shared opioid/dopamine neurotransmission during pain-related experiences using within-subject approach. Seed-based d Mapping (SDM) analysis of previously published voxel coordinate data showed that opioidergic activations were strongest in the bilateral caudate, thalamus, right putamen, cingulate gyrus, midbrain, inferior frontal gyrus, and left superior temporal gyrus. The dopaminergic studies showed that the bilateral caudate, thalamus, right putamen, cingulate gyrus, and left putamen had the highest activations. We were able to see a clear overlap between opioid and dopamine activations in a majority of the regions during pain-related experiences, though there were some unique areas of dopaminergic activation such as the left putamen. Regions unique to opioidergic activation included the midbrain, inferior frontal gyrus, and left superior temporal gyrus. Here we provide initial evidence for the functional overlap between opioidergic and dopaminergic processing during aversive states in humans.

Corresponding Author: Irina Strigo, Ph.D., Emotion and Pain Laboratory, San Francisco Veterans Affairs Health Care Center, 4150 Clement Street, San Francisco, CA 94121, Phone 415-221-4810 ext. 25138, Irina.Strigo@ucsf.edu.

CONFLICT OF INTEREST STATEMENT
All authors declare no conflicts of interest.

1. Introduction

Pain conditions are widespread, affecting around 20% of the US population, and are often treated with opioid medications (Dahlhamer et al., 2018). However, recently there has been a push to reduce opioid use, as such medications often lead to addiction (Cowan et al., 2003; Fishbain et al., 2008). Notably, consumption of exogenous opioids lead to changes within endogenous opioid and dopamine neurotransmission (Kosten and George, 2002), both of which play fundamental roles in pain processing, pain modulation, and pain relief (Fields, 2018). Investigating whether dopaminergic and opioidergic activity are released in the same regions during similar conditions may enlighten us on how it is they work together to create and process the perception of pain/relief.

Functional MRI studies have allowed us to observe how various brain regions are influenced by experimental and clinical pain conditions. Among these, the insular cortex is activated in a wide variety of pain paradigms as well as in emotional and interoceptive aspects of pain (Jensen et al., 2016). The brain stem and anterior cingulate cortex provide connectivity among brain areas related to the subjective perception and modulation of pain (Ploner et al., 2010). The ventral striatal area, specifically the nucleus accumbens (NAc) is part of the reward system that modulates dopamine signaling in response to a pain stimulus, the activation of this area occurs with both acute pain and pain relief (Baliki et al., 2010; Becerra et al., 2013). The PFC has been widely implicated in the neuromodulation of pain through its connections with areas such as the cerebral neocortex, hippocampus, periaqueductal grey (PAG), thalamus, amygdala, and basal nuclei (Ong et al., 2019).

Nevertheless, the only method by which to measure neurotransmission in the human brain is still Positron Emission Tomography (PET). The endogenous opioidergic system is normally assessed using [^{11}C]-carfentanil (CFN) and [^{11}C]- or [^{18}F]-diprenorphine (DPN) as radiotracers. CFN is a selective agonist at the μ-opioid receptor (MOR), which is thought to preferentially bind to the μ1 receptor sub-type (Eriksson and Antoni, 2015), whereas DPN is a weak partial agonist with equal affinity for the MOR, κ-opioid receptor (KOR), and δ-opioid receptor (DOR). The endogenous dopaminergic system is normally assessed by [^{11}C]-raclopride (RAC) and [^{18}F]-fallypride (FAL) tracers, which are selective antagonists on D2/D3 dopamine receptors. Information about both basal levels of receptor availability and changes in availability caused by alterations in endogenous dopamine and opioid concentrations can be evaluated, as these radioligands are sensitive to endogenous opioid and dopamine levels. PET radioligand studies have provided valuable information on the idiosyncratic concentrations and distributions of such neurochemicals across the brain, and researchers have used these data to better understand aversive processing related to physical and emotional pain (e.g. (Hsu et al., 2013; Zubieta et al., 2001), as well as addiction processes associated with opioids (Greenwald et al., 2003) and dopamine (Volkow et al., 2009). Notably, as demonstrated by prior animal studies (Benarroch, 2012), there is anatomical overlap of neurotransmitter systems. Studies demonstrating such overlap of these neurochemicals in the human brain are limited (Goldman-Rakic et al., 1990) and one of the major limitations of current PET technology is that it only allows for the imaging of a single radiotracer at a time. Recent research has provided insight into the fact that endogenous opioids are released in the ventral striatum, insula, anterior cingulate

cortex (ACC), prefrontal cortex (PFC), and brain stem during aversive experiences, though knowing whether dopamine is also released in many of the same regions during similar aversive conditions may demonstrate that the two neurotransmitter systems might be working together to create and process the perception of pain/relief. Thus, an increased understanding of the brain regions where these neurotransmitters co-localize in the human brain may further elucidate pain and aversive processing. The present dual meta-analysis specifically aims to create a map of the opioid and dopamine neurotransmitter systems in the brain through aversive ("hurt") conditions.

1.1 Neural Correlates of Opioid Receptors

The endogenous opioid system consists of 3 families of opioid peptides: β-endorphin, enkephalins, and dynorphins, and 3 families of receptors: μ (MOR), δ (DOR), and κ (KOR) (reviewed in detail elsewhere e.g. (Benarroch, 2012). Though endogenous opioids can be found extensively throughout the central and peripheral nervous system, they are particularly concentrated in circuits involved in pain modulation, pain relief, responses to stress, and autonomic control. Some of the areas with the highest opioidergic receptor concentration are the cerebral cortex, brainstem, thalamus, striatum, hypothalamus, hippocampus, and dorsal horn (Benarroch, 2012). Radioligand studies of opioidergic receptors included in this meta-analysis have reported opioid activations in a number of cortical and subcortical regions, including frontal cortices (Dougherty et al., 2008; Jones et al., 1999; Klega et al., 2010; Maarrawi et al., 2013; Mueller et al., 2010; Wey et al., 2014; Willoch et al., 2004), insula (Brown et al., 2015; Dougherty et al., 2008; Jones et al., 1999; Mueller et al., 2010; Wey et al., 2014; Willoch et al., 2004), anterior cingulate cortex (Dougherty et al., 2008; Jones et al., 1999; Maarrawi et al., 2013; Mueller et al., 2010; Sprenger et al., 2006; Wey et al., 2014; Willoch et al., 2004), thalamus (Brown et al., 2015; Dougherty et al., 2008; Jones et al., 1999; Wey et al., 2014; Willoch et al., 2004) and putamen (Brown et al., 2015; Jones et al., 1999; Wey et al., 2014).

1.2 Neural Correlates of Dopamine Receptors

Dopamine is widely involved in circuits encoding reward, aversion, salience, uncertainty, novelty (Bromberg-Martin et al., 2010), and pain modulation (Wood, 2008). The midbrain houses some of the areas with the highest dopaminergic concentrations, namely the Ventral Tegmental Area (VTA) and Substantia Nigra (SN), as well as projections that lead to the dorsal striatum, nucleus accumbens, amygdala, hippocampus, and prefrontal cortex (PFC). Radioligand studies of dopaminergic receptors have reported activations in a number of cortical and subcortical regions, including bilateral putamen (Berman et al., 2013; Scott et al., 2008; Wood et al., 2007), left putamen (Martikainen et al., 2015), left caudate (Berman et al., 2013; Martikainen et al., 2015; Scott et al., 2007; Scott et al., 2008; Wood et al., 2007), right caudate nucleus (Martikainen et al., 2015; Scott et al., 2008; Wood et al., 2007), right nucleus accumbens (Martikainen et al., 2015; Pecina et al., 2015; Scott et al., 2008), left nucleus accumbens (Scott et al., 2008), and globus pallidus (Wood et al., 2007).

1.3 Interaction between opioidergic and dopaminergic neurotransmission

In many regions, opioids are co-expressed with other neurotransmitters (Benarroch, 2012). Specifically, opioid neurotransmitter systems interact with dopamine not only in the

midbrain but also in projection areas such as the striatum, a key area implicated in pain relief (Fields, 2018). In addition to its established role in the reward system, many studies have suggested that the NAc also serves as a meeting point for multiple components of pain processing and analgesia. Some of the regions connected by the NAc include the ACC, PFC, thalamus, amygdala, somatosensory cortex, and the spinal cord, which span the reward and pain systems (Harris and Peng, 2020). Striatal medium spiny neurons express both dopamine and opioid receptors (Ambrose et al., 2004; Pollard et al., 1977). Blocking striatal opioid receptors leads to attenuated amphetamine-induced locomotion and impulsivity (Gonzalez-Nicolini et al., 2003; Wiskerke et al., 2011), whereas dopamine D2 receptor (DRD2) blockade inhibits the rewarding effects of morphine in opiate dependent rats (Laviolette et al., 2002). Likewise, activating μ-opioid receptors (MOR) modulates the mesolimbic dopamine system. As shown in rats, morphine modulates the release of dopamine by disinhibition through GABAergic interneurons in the midbrain ventral tegmental area (VTA) (Jalabert et al., 2011). In humans, alfentanil triggers dopamine release in the striatum (Hagelberg et al., 2002). Likewise, activating D2/D3 receptors modulate mesolimbic opioid system. As shown in several studies in humans, amphetamine releases endogenous opioids in the striatum, as well as in insular and anterior cingulate cortices (Colasanti et al., 2012; Mick et al., 2014), confirming the interdependence of the two systems. To date only a few studies have examined the overlap between opioidergic and dopaminergic receptor binding in the same individual, though there is data showing overlap in the ventral striatum and dorsal caudate nucleus (Tuominen et al., 2015).

From current literature it is evident that there is high variability across PET radioligand studies regarding the foci of activations. These inconsistencies may be attributed to several factors including, but not limited to, demographic characteristics of the sample such as age and sex, the presence of comorbid disorders and/or childhood adversity, differences in protocols and processing, and statistical analyses. Here we applied seed-based d mapping meta-analyses (Radua et al., 2012) that have been established as a standard tool for identifying coordinate- based convergence of voxel-based imaging data. This analysis was conducted separately for the opioidergic radioligands and for the dopaminergic radioligands and enabled us to explore overlap between the two neurotransmitter systems in aversive experiences.

2. Methods:

2.1 Article Selection

We conducted a literature search for radioligand PET studies that were published between June 1999 and March 2022 using several sources including PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Embase (https://www.embase.com) to find reports with the radioligands of interest such as “carfentanil”, “diprenorphine”, “raclopride”, “fallypride”. The study Flow Chart is depicted in Figure 1. The final article search was conducted on March 2022 and yielded 393 PET imaging studies using the radioligands of interest to be considered for further review. The studies included in our analysis mapped brain regions associated with opioidergic and dopaminergic receptors using CFN, DPN, RAC and FAL radioligands. We investigated general opioid receptors (MOR, DOR, and

KOR) via diprenorphine (DPN) while selective radioligands like carfentanil (CAR) was used to study MOR. Both fallypride (FAL) and raclopride (RAC) were used to study dopamine type-2 and type-3 (D2/D3) receptors. D1-receptor specific radioligands were considered for additional data of the dopaminergic system, though only two radioligands are used for human subjects, [11C]SCH 23390 and [11C]NNC-112. After conduction an article search, it was determined that there were no PET studies investigating pain conditions using these radioligands.

All studies of pain-related aversive processing that provided voxel-based coordinates of the observed peak activations were included. Due to the variable nature of PET radioligand studies, i.e., examining acute and chronic pain conditions as well as correlational changes, we limited our inclusion to studies only reporting within-group observations, i.e., only those studies that reported changes in endogenous dopaminergic or opioidergic transmission as a result of experimental pain/aversion or endogenous chronic pain manipulation (painful/aversive state vs. non-pain state). Studies reporting between-group observations (i.e., changes in the endogenous neurotransmission between healthy subjects and individuals with chronic pain) were excluded from the meta-analyses.

2.2 Inclusion/exclusion criteria for activation foci

Significant peak activation coordinates and corresponding intensity values for each of the articles in Table 1 were extracted for differences in experimental conditions. If studies included two separate control conditions, only foci from one of the within-subject comparisons were used to avoid using foci from the same participant twice. In these cases, the selected contrast compared a painful or unpleasant condition with a non-painful condition. If a study conducted a whole-brain and a region of interest (ROI)-based analysis, coordinates from both analyses were included separately, provided that the ROIs were not reported in the whole-brain results.

Twenty-three radioligand studies (Table 1) were included in the current investigation based on the inclusion and exclusion criteria, and produced a total of 451 subjects from which peak voxels and clusters were extracted and transformed into Montreal Neurological Institute (MNI) space if they were provided in Talairach space. Of the 393 articles found, 368 were excluded for the following reasons: 1) Radioligands of interest were not investigated (i.e. CFN, DPN, RAC or FAL), 2) study solely focused on how neurological disorders affect the neurotransmitter of interest (e.g. Parkinson’s Disease), 3) study did not investigate aversive processing; 4) study provided only correlational relationship with the baseline neurotransmitter release; and 5) studies only reported on the between-group comparisons between healthy controls and individuals with chronic pain without within-subject experimental manipulation.

2.3 Meta-analysis

We conducted a coordinate-based random-effects meta-analysis using Sdm-Psi software version 6.21 (https://www.sdmproject.com/). Coordinates reported in Talairach space were converted to MNI space using the “convert peaks” tool provided by Sdm-Psi. We also gathered the peak intensity for each coordinate in the form of t-scores, otherwise they

were converted from z-scores or p-values into t-scores using the “Convert peaks” feature of Sdm-Psi. Twelve studies were identified that examined mu-opioid receptors using CFN and 3 studies were identified that assayed all opioid receptors using DPN; these 15 studies were included in the opioidergic meta-analysis. Seven studies were used to examine D2/D3 receptors using RAC and 1 study used FAL radioligand; these 8 studies were included in the dopaminergic meta-analysis.

An anisotropic effect-size-based seed-based d mapping (AES-SDM) statistical analysis was conducted to determine the mean regions of the brain that were consistently activated. Coordinates from each of the radioligands were first analyzed separately to examine the neural regions involved across each of the neurotransmitters. In order to determine the robustness of each of the studies, a jackknife analysis available through Sdm-Psi was conducted. Analyses from opioidergic and dopaminergic radioligands were then combined to examine the spatial overlap and non-overlap between mu-opioid, general opioid, and D2/D3 receptors using AFNI function *3dcalc* (Cox, 1996).

When there were differences in the thresholding in whole-brain and ROI analyses, they were entered separately in order to correct for the threshold differences conducted by the authors. The areas of activation found in the results were shown in high consistency throughout the included studies and the z-scores indicate the likeliness of activation in these areas. Furthermore, a jack-knife analysis was also conducted to account for voxels with only a few studies contributing, this way single studies that could possibly dominate the results would not skew the meta-analysis (Cutler et al., 2018). TFCE (Threshold-free cluster enhancement) analysis was conducted to optimize for cluster-based thresholding. This method improves thresholding sensitivity and prevent smaller clusters from being unaccounted for (Smith and Nichols, 2009). False Discovery Rate (FDR) threshold was set to $p < 0.005$ in order to assess for random spatial associations between experiments. The standard AES-SDM thresholds (uncorrected voxelwise p-value of $p < 0.005$, extent threshold clusters for ≥ 10 voxels, and z values of greater than or equal to $Z \geq 1$, which are proposed to optimally balance sensitivity and specificity) were used (Lieberman and Cunningham, 2009).

3. Results

3.1 Opioid

To increase power, we combined studies that evaluated selective (μOR) and non-selective (μOR, δOR, and κOR) opioid receptor radioligands. This resulted in a total of 15 articles, with a total n = 283 subjects, yielding 121 foci. When all opioidergic activity was combined, 6 clusters (Table 2) were observed with peak activations in the ventral medial prefrontal cortex, anterior cingulate cortex, right amygdala extending to the temporal pole, right anterior insula, another cluster in the right ventral anterior insula, and a small cluster in the left insula. The largest cluster, with a maximum peak in the ventral medial prefrontal cortex, is composed of 3317 voxel activations spreading across the ventromedial prefrontal cortex and striatum, including bilateral caudate nucleus and thalamus (Figure 2, top).

Jackknife sensitivity analysis revealed that activations in the right caudate, right insula, and the midbrain, were highly robust, as they were replicated in all 15 studies. Areas in the

right putamen were highly influenced by Peciña et al., 2015. Opioidergic activations in the inferior frontal gyrus were determined to not be robust, as there was a lack of activation in 7 of the 15 studies (Table 4).

3.2 Dopamine

Eight manuscripts evaluating dopaminergic activity via RAC and FAL reported a total of 49 foci with a total n = 166. Three clusters were observed with peak activations in the right putamen, right caudate nucleus, and left insula (Table 3). The right putamen cluster included 487 voxels and spread across right insula and right globus pallidus (Figure 2, bottom).

Jackknife sensitivity analysis revealed that activations in the bilateral caudate and bilateral insulae were highly robust, as they were replicated in all eight studies. It should also be noted that activity in the thalamus was highly influenced by Peciña et al., 2014 and Scott et al., 2007. Dopaminergic activations in the cingulate gyrus were determined to not be robust as there was a lack of activation in 4 of the studies (Table 4).

3.3 Overlap

In order to explore co-localization of endogenous opioid and dopaminergic neurotransmission during pain-related aversive experiences, we created a conjunction between opioid and dopamine thresholded meta-analytical maps. The resulting map is displayed in Figure 3. We found biggest overlap within the right striatal regions (Table 5). The striatal cluster covered most of the right caudate nucleus and spread into the right thalamus (Figure 3).

4. Discussion:

The goal of this investigation was to provide the meta-analytical map of opioidergic and dopaminergic transmissions and their overlap during experiencing aversive conditions including experimental pain, endogenous clinical pain, and emotional pain in humans using the opioidergic and dopaminergic radioligands carfentanil, diprenorphine, raclopride and fallypride. Using the existing literature, we completed two comprehensive meta-analyses of PET radioligand activations using opioidergic and dopaminergic radioligands during painful/aversive experiences.

Consistent with the animal literature, we found pain-related opioidergic activation within striatum, cingulate gyrus extending to supplementary motor area and the midbrain region of the brainstem. The striatal cluster was large and spread across bilateral amygdalae, thalamus, bilateral insulae, subgenual cingulate and frontal pole regions. Our second meta-analysis of dopaminergic activation showed pain -related dopaminergic activation within striatum and cingulate gyrus. The striatal cluster was large and spread across bilateral insulae and the thalamus.

Our primary goal was to identify regions of shared opioid/dopamine neurotransmission during pain-related experiences. The motivation-decision model of pain (Fields, 2018) states that actions are influenced by decisions between whether to approach something pleasant (a reward) or avoid something unpleasant (pain/loss). In this meta-analysis, we potentially

shed light on the interaction between pain and pain relief systems in humans and how their associated neurotransmitters, dopamine and opioid respectively, are connected. Given that PET radioligand studies are only able to include one radioligand at a time, it is difficult to study these interactions in humans.

One of the biggest clusters of overlap was found within striatal regions, suggesting that both dopamine and opioid receptor-mediated mechanisms are involved in modulating the perception of aversive experiences related to sensory/emotional pain. The basal ganglia circuits contain one of the highest levels of endogenous opioids and opioid receptors on the brain (McDonald and Lambert, 2005). All opioid receptor subtypes are present in the basal ganglia circuit and their net effect depends on their presynaptic or postsynaptic localization in the different structures of this circuit (Sulzer et al., 2016). Furthermore, both the midbrain VTA and nucleus accumbens receive beta-endorphin–containing projections from the arcuate nucleus and contain enkephalinergic interneurons. Both beta-endorphin and enkephalins, acting via receptors, inhibit GABA release from local inhibitory interneurons, thus facilitating dopamine release in the nucleus accumbens. D2 striatal cells modulate the indirect dopaminergic pathway, which is activated when a stimulus is less rewarding than predicted, suggesting that this is the pathway in which avoidance to an unpleasant stimulus is encoded (Bromberg-Martin et al., 2010). A PET study showed that a single dose of the receptor agonist remifentanil elicited a decrease in the binding of the D2/D3 receptor radiotracer FAL in the ventral striatum, dorsal putamen, and amygdala, reflecting a release of endogenous opioids in both alcohol-dependent patients and controls (Spreckelmeyer et al., 2011). Our results are consistent with co-release of these neurotransmitters in these regions. Along with the existing literature (Kirkpatrick and Bryant, 2015; Reisi et al., 2014; Sulzer et al., 2016), our results suggest that aversive experiences during sensory/emotional pain conditions activates both dopamine and opioid receptors. Our results support the existing literature, in that we found the striatum to have the highest activation in both dopaminergic and opioidergic meta-analyses.

Several limitations should be noted. Our meta-analysis was intended to compare only painful or aversive experimental conditions to understand how opioidergic and dopaminergic systems interact when both hurt and relief conditions are experienced. Due to difficulty and invasive nature of radioligand studies, studies that were included in the current analysis were limited, especially considering limited literature with raclopride and aversive processing. While n=166 is large enough to conduct a meta-analysis, the findings might not be as robust as in our opioid meta-analysis of n=283. In order to increase power and understand aversive-related processing we included studies that examined aversion and hurt related to emotional pain, rather than solely physical pain. In addition to being distressing in nature, social rejection and physical pain have a similar representation in the somatosensory system of the brain (Eisenberger, 2012; Kross et al.). A significant body of research has also established that physical and social pain activate distinct neural representations that are co-localized at the gross anatomical level (Woo et al., 2014; Yarkoni et al., 2011). We are not able to detect patterns of activation in this analyses, only anatomical areas of activation, as the data collected was within-subject peak activation voxels. Given the sex differences in the neurobiology of pain, another limitation of the study involves the inability to conduct a gender analysis due to the small number of studies that provided coordinates for only male

or female participants. Finally, pleasure and reward-related processing was not the goal of this study, but should be compared in the future.

5. Conclusion:

To our knowledge, this is the first powerful, data-driven meta-analysis identifying and comparing the neural correlates of opioidergic and dopaminergic transmission in PET radioligand studies of pain. The study design enabled high validity and statistical power by including 449 subjects.

The motivation for the current meta-analysis was to examine the regions in which opioid and dopamine pathways were activated during pain-related and unpleasant conditions, and consequently create a map of the distinct localization of neurotransmitters as well as their overlap. Areas that are known to be consistently activated by pain modulation are the insula, ACC, hypothalamus, PAG, rostral ventral medulla, and spinal cord (Tracey, 2010). After performing a mean analysis of opioid and dopamine binding, we found activity in these previously identified regions, but additionally were able to determine what activity was due to opioid versus dopamine neurotransmission. The significance of the resulting conjunction map (Figure 3) indicates that pain modulation is co-managed by opioid and dopamine receptors in a number of brain regions. Understanding the anatomical arrangement of these types of receptors may help us to further understand the interplay between the neural networks involved in pain modulation and pain relief. By creating maps of opioid and dopamine receptor activation, along with a map of their co-activation during pain modulation, we hope to provide data that can be used to develop targeted pharmaceuticals for patients with pain conditions. For example, animal research on drugs targeting a combination of opioid receptors have found that when targeting δ and μ-opioid receptors, the efficacy of μ-opioid receptors increases and tolerance and dependence are attenuated (Ananthan, 2008). By mapping μ-opioid receptor (CFN) and non-specific opioid receptor (DPN) activation, we hope to provide a deeper understanding of these systems to help assist in the development of future pain treatments.

FUNDING AND DISCLOSURES

This work is supported by a VA Clinical Science Research and Development Merit Grant (I01 CX001762), and, in part, by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number U19AR076737, as well as and Painless Research Foundation.

6. References

Ambrose L, Unterwald E, Van Bockstaele E, 2004. Ultrastructural evidence for co-localization of dopamine D2 and μ-opioid receptors in the rat dorsolateral striatum. The Anatomical Record Part A: Discoveries in Molecular, Cellular, and Evolutionary Biology: An Official Publication of the American Association of Anatomists. 279, 583–591.

Ananthan S, 2008. Opioid ligands with mixed μ/δ opioid receptor interactions: an emerging approach to novel analgesics. Drug Addiction: From Basic Research to Therapy. 367–380.

Baliki MN, Geha PY, Fields HL, Apkarian AV, 2010. Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. Neuron. 66, 149–60. [PubMed: 20399736]

Becerra L, Navratilova E, Porreca F, Borsook D, 2013. Analogous responses in the nucleus accumbens and cingulate cortex to pain onset (aversion) and offset (relief) in rats and humans. J Neurophysiol. 110, 1221–6.

Benarroch EE, 2012. Endogenous opioid systems: current concepts and clinical correlations. Neurology. 79, 807–814. [PubMed: 22915176]

Berman BD, Hallett M, Herscovitch P, Simonyan K, 2013. Striatal dopaminergic dysfunction at rest and during task performance in writer's cramp. Brain. 136, 3645–3658. [PubMed: 24148273]

Bromberg-Martin ES, Matsumoto M, Hikosaka O, 2010. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron. 68, 815–834.

Brown CA, Matthews J, Fairclough M, McMahon A, Barnett E, Al-Kaysi A, El-Deredy W, Jones AK, 2015. Striatal opioid receptor availability is related to acute and chronic pain perception in arthritis: does opioid adaptation increase resilience to chronic pain? Pain. 156, 2267.

Colasanti A, Searle GE, Long CJ, Hill SP, Reiley RR, Quelch D, Erritzoe D, Tziortzi AC, Reed LJ, Lingford-Hughes AR, 2012. Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. Biological psychiatry. 72, 371–377.

Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG, 2003. A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Medicine. 4, 340–351.

Cox RW, 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput.Biomed.Res. 29, 162–173.

Cutler J, Radua J, Campbell-Meiklejohn D, 2018. Adjusting for Variable Brain Coverage in Voxel-Based fMRI Meta-Analysis. BioRxiv. 457028.

Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Von Korff M, Porter L, Helmick C, 2018. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. Morbidity and Mortality Weekly Report. 67, 1001.

Dougherty DD, Kong J, Webb M, Bonab AA, Fischman AJ, Gollub RL, 2008. A combined [11C]diprenorphine PET study and fMRI study of acupuncture analgesia. Behav Brain Res. 193, 63–8. [PubMed: 18562019]

Eisenberger NI, 2012. The pain of social disconnection: examining the shared neural underpinnings of physical and social pain. Nat Rev Neurosci. 13, 421–34.

Eriksson O, Antoni G, 2015. [11C] Carfentanil binds preferentially to μ-opioid receptor subtype 1 compared to subtype 2. Molecular imaging. 14, 7290.2015. 00019.

Fields HL, 2018. How expectations influence pain. Pain. 159 Suppl 1, S3–S10. [PubMed: 30113941]

Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS, 2008. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. Pain medicine. 9, 444–459.

Goldman-Rakic PS, Lidow M, Gallager D, 1990. Overlap of dopaminergic, adrenergic, and serotoninergic receptors and complementarity of their subtypes in primate prefrontal cortex. Journal of Neuroscience. 10, 2125–2138. [PubMed: 2165520]

Gonzalez-Nicolini M, Berglind W, Cole K, Keogh C, McGinty J, 2003. Local μ and δ opioid receptors regulate amphetamine-induced behavior and neuropeptide mRNA in the striatum. Neuroscience. 121, 387–398. [PubMed: 14521997]

Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta JK, 2003. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology. 28, 2000–9. [PubMed: 12902992]

Hagelberg N, Martikainen IK, Mansikka H, Hinkka S, Nagren K, Hietala J, Scheinin H, Pertovaara A, 2002. Dopamine D2 receptor binding in the human brain is associated with the response to painful stimulation and pain modulatory capacity. Pain. 99, 273–9. [PubMed: 12237205]

Harris HN, Peng YB, 2020. Evidence and explanation for the involvement of the nucleus accumbens in pain processing. Neural regeneration research. 15, 597. [PubMed: 31638081]

Hsu DT, Sanford BJ, Meyers KK, Love TM, Hazlett KE, Wang H, Ni L, Walker SJ, Mickey BJ, Korycinski ST, Koeppe RA, Crocker JK, Langenecker SA, Zubieta JK, 2013. Response of the

mu-opioid system to social rejection and acceptance. Mol Psychiatry. 18, 1211–7. [PubMed: 23958960]

Jalabert M, Bourdy R, Courtin J, Veinante P, Manzoni OJ, Barrot M, Georges F, 2011. Neuronal circuits underlying acute morphine action on dopamine neurons. Proceedings of the national academy of sciences. 108, 16446–16450.

Jensen KB, Regenbogen C, Ohse MC, Frasnelli J, Freiherr J, Lundström JN, 2016. Brain activations during pain: a neuroimaging meta-analysis of patients with pain and healthy controls. Pain. 157, 1279–1286.

Jones AK, Kitchen ND, Watabe H, Cunningham VJ, Jones T, Luthra SK, Thomas DG, 1999. Measurement of changes in opioid receptor binding in vivo during trigeminal neuralgic pain using [11C] diprenorphine and positron emission tomography. Journal of Cerebral Blood Flow & Metabolism. 19, 803–808. [PubMed: 10413036]

Kirkpatrick SL, Bryant CD, 2015. Behavioral architecture of opioid reward and aversion in C57BL/6 substrains. Frontiers in behavioral neuroscience. 8, 450. [PubMed: 25628547]

Klega A, Eberle T, Buchholz H-G, Maus S, Maihöfner C, Schreckenberger M, Birklein F, 2010. Central opioidergic neurotransmission in complex regional pain syndrome. Neurology. 75, 129–136. [PubMed: 20625165]

Kosten TR, George TP, 2002. The neurobiology of opioid dependence: implications for treatment. Science & practice perspectives. 1, 13. [PubMed: 18567959]

Kross E, Berman MG, Mischel W, Smith EE, Wager TD, Social rejection shares somatosensory representations with physical pain. Proc Natl Acad Sci U S A. 108, 6270–5. [PubMed: 21444827]

Laviolette SR, Nader K, van der Kooy D, 2002. Motivational state determines the functional role of the mesolimbic dopamine system in the mediation of opiate reward processes. Behavioural brain research. 129, 17–29. [PubMed: 11809491]

Lieberman MD, Cunningham WA, 2009. Type I and Type II error concerns in fMRI research: re-balancing the scale. Social cognitive and affective neuroscience. 4, 423–428. [PubMed: 20035017]

Maarrawi J, Peyron R, Mertens P, Costes N, Magnin M, Sindou M, Laurent B, Garcia-Larrea L, 2013. Brain opioid receptor density predicts motor cortex stimulation efficacy for chronic pain. PAIN®. 154, 2563–2568. [PubMed: 23900133]

Martikainen IK, Nuechterlein EB, Pecina M, Love TM, Cummiford CM, Green CR, Stohler CS, Zubieta JK, 2015. Chronic Back Pain Is Associated with Alterations in Dopamine Neurotransmission in the Ventral Striatum. J Neurosci. 35, 9957–65. [PubMed: 26156996]

McDonald J, Lambert D, 2005. Opioid receptors. Continuing education in anaesthesia, critical care & pain. 5, 22–25.

Mick I, Myers J, Stokes PR, Erritzoe D, Colasanti A, Bowden-Jones H, Clark L, Gunn RN, Rabiner EA, Searle GE, 2014. Amphetamine induced endogenous opioid release in the human brain detected with [11C] carfentanil PET: replication in an independent cohort. International Journal of Neuropsychopharmacology. 17, 2069–2074. [PubMed: 24807268]

Mueller C, Klega A, Buchholz H-G, Rolke R, Magerl W, Schirrmacher R, Schirrmacher E, Birklein F, Treede R-D, Schreckenberger M, 2010. Basal opioid receptor binding is associated with differences in sensory perception in healthy human subjects: a [18F] diprenorphine PET study. NeuroImage. 49, 731–737. [PubMed: 19703571]

Ong W-Y, Stohler CS, Herr DR, 2019. Role of the prefrontal cortex in pain processing. Molecular neurobiology. 56, 1137–1166. [PubMed: 29876878]

Pecina M, Love T, Stohler CS, Goldman D, Zubieta J-K, 2015. Effects of the Mu opioid receptor polymorphism (OPRM1 A118G) on pain regulation, placebo effects and associated personality trait measures. Neuropsychopharmacology. 40, 957–965. [PubMed: 25308352]

Ploner M, Lee MC, Wiech K, Bingel U, Tracey I, 2010. Prestimulus functional connectivity determines pain perception in humans. Proceedings of the National Academy of Sciences. 107, 355.

Pollard H, Llorens-Cortes C, Schwartz J, 1977. Enkephalin receptors on dopaminergic neurones in rat striatum. Nature. 268, 745–747. [PubMed: 197427]

Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus D, Cardoner N, Surguladze S, 2012. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. European psychiatry. 27, 605–611. [PubMed: 21658917]

Reisi Z, Haghparast A, Pahlevani P, Shamsizadeh A, Haghparast A, 2014. Interaction between the dopaminergic and opioidergic systems in dorsal hippocampus in modulation of formalin-induced orofacial pain in rats. Pharmacology Biochemistry and Behavior. 124, 220–225. [PubMed: 24955867]

Scott DJ, Stohler CS, Koeppe RA, Zubieta JK, 2007. Time-course of change in [11C]carfentanil and [11C]raclopride binding potential after a nonpharmacological challenge. Synapse. 61, 707–14.

Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK, 2008. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Arch Gen Psychiatry. 65, 220–31. [PubMed: 18250260]

Smith SM, Nichols TE, 2009. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage. 44, 83–98. [PubMed: 18501637]

Spreckelmeyer KN, Paulzen M, Raptis M, Baltus T, Schaffrath S, Van Waesberghe J, Zalewski MM, Rösch F, Vernaleken I, Schäfer WM, 2011. Opiate-induced dopamine release is modulated by severity of alcohol dependence: an [18F] fallypride positron emission tomography study. Biological psychiatry. 70, 770–776. [PubMed: 21802658]

Sprenger T, Valet M, Boecker H, Henriksen G, Spilker ME, Willoch F, Wagner KJ, Wester HJ, Tolle TR, 2006. Opioidergic activation in the medial pain system after heat pain. Pain. 122, 63–7.

Sulzer D, Cragg SJ, Rice ME, 2016. Striatal dopamine neurotransmission: regulation of release and uptake. Basal ganglia. 6, 123–148. [PubMed: 27141430]

Tracey I, 2010. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. Nat Med. 16, 1277–83. [PubMed: 20948533]

Tuominen L, Tuulari J, Karlsson H, Hirvonen J, Helin S, Salminen P, Parkkola R, Hietala J, Nuutila P, Nummenmaa L, 2015. Aberrant mesolimbic dopamine–opiate interaction in obesity. NeuroImage. 122, 80–86. [PubMed: 26260431]

Volkow ND, Fowler J, Wang G, Baler R, Telang F, 2009. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology. 56, 3–8. [PubMed: 18617195]

Wey HY, Catana C, Hooker JM, Dougherty DD, Knudsen GM, Wang DJ, Chonde DB, Rosen BR, Gollub RL, Kong J, 2014. Simultaneous fMRI-PET of the opioidergic pain system in human brain. Neuroimage. 102 Pt 2, 275–82.

Willoch F, Schindler F, Wester HJ, Empl M, Straube A, Schwaiger M, Conrad B, Tolle TR, 2004. Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [11C]diprenorphine PET study. Pain. 108, 213–20. [PubMed: 15030940]

Wiskerke J, Schetters D, van Es IE, van Mourik Y, den Hollander BR, Schoffelmeer AN, Pattij T, 2011. μ-Opioid receptors in the nucleus accumbens shell region mediate the effects of amphetamine on inhibitory control but not impulsive choice. Journal of Neuroscience. 31, 262–272.

Woo CW, Koban L, Kross E, Lindquist MA, Banich MT, Ruzic L, Andrews-Hanna JR, Wager TD, 2014. Separate neural representations for physical pain and social rejection. Nat Commun. 5, 5380. [PubMed: 25400102]

Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA, 2007. Fibromyalgia patients show an abnormal dopamine response to pain. Eur J Neurosci. 25, 3576–82. [PubMed: 17610577]

Wood PB, 2008. Role of central dopamine in pain and analgesia. Expert Rev Neurother. 8, 781–97. [PubMed: 18457535]

Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD, 2011. Large-scale automated synthesis of human functional neuroimaging data. Nat Methods. 8, 665–70. [PubMed: 21706013]

Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS, 2001. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science. 293, 311–5.

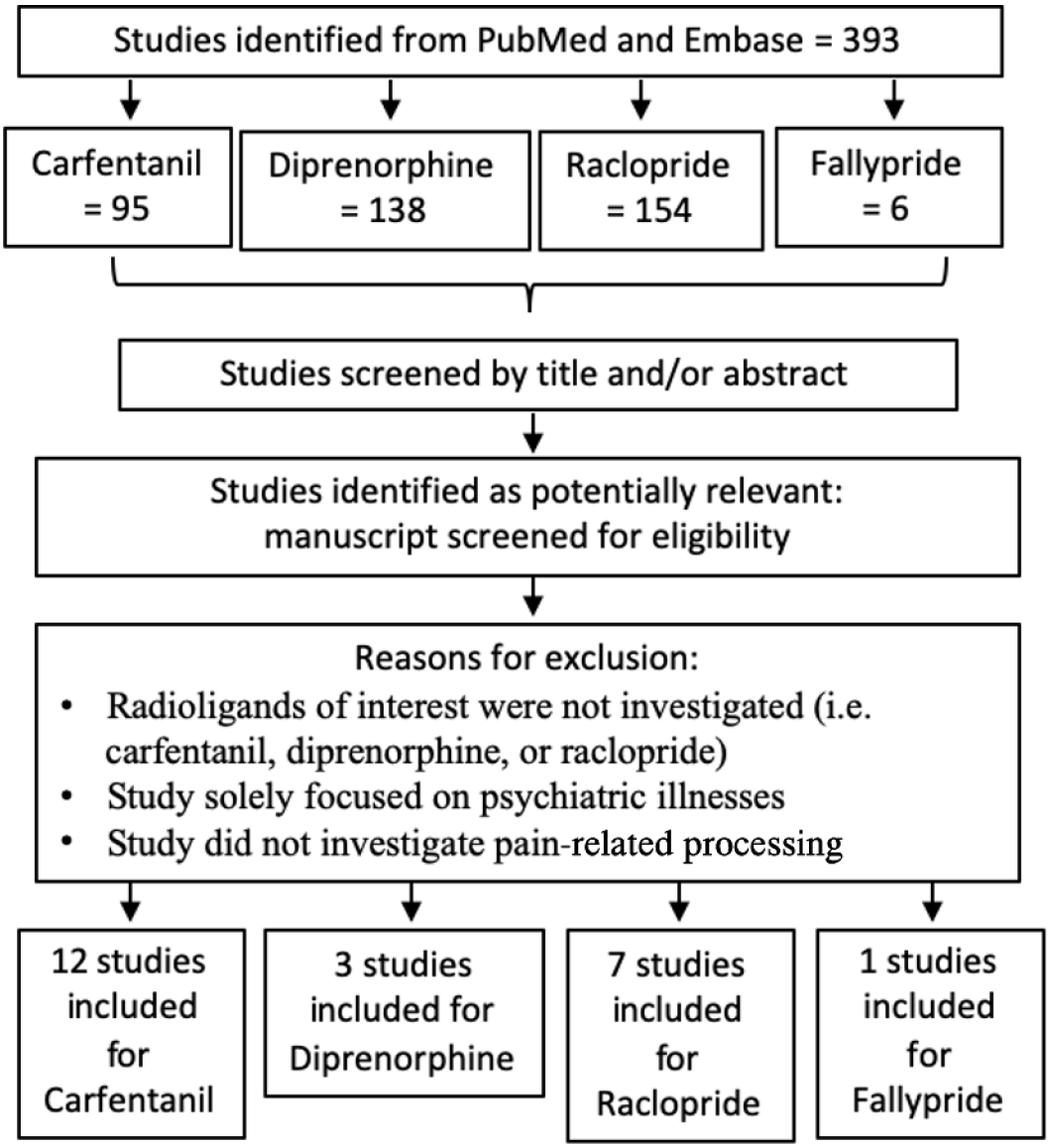

Fig. 1.

Flow chart of search strategy and study selectin for meta-analyes Study search and screening procedures repeated for Pub med and Science Direct.

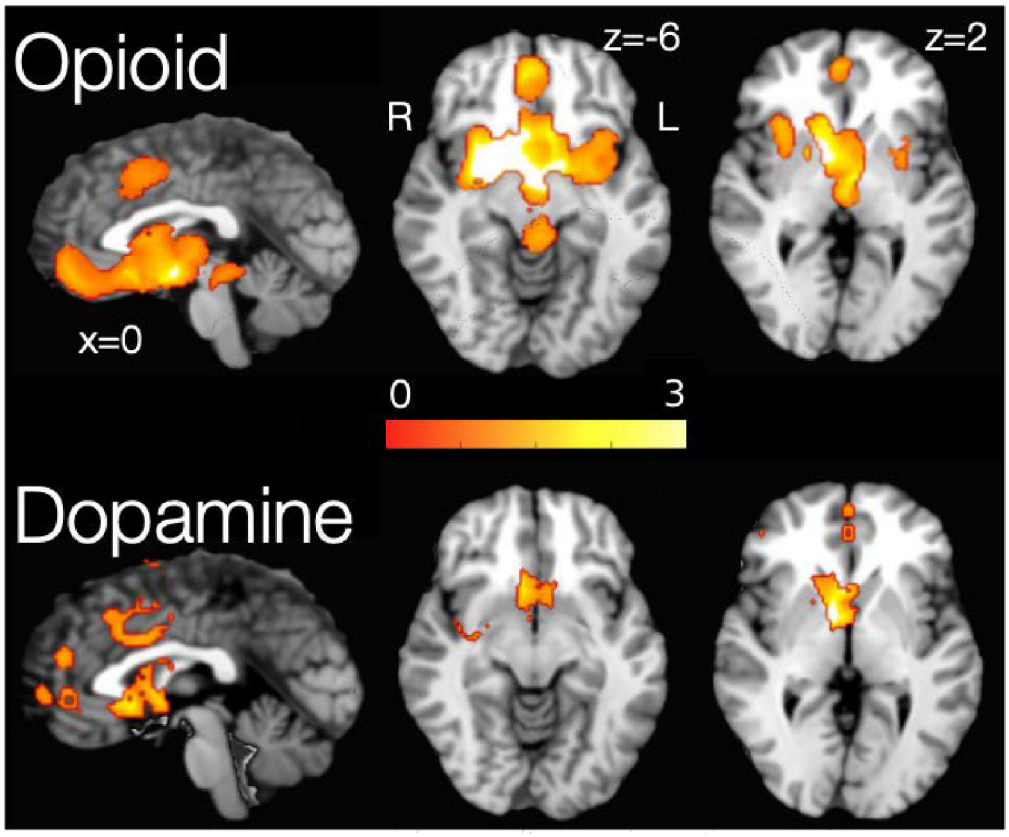

Figure 2:
Areas of significant change in the endogenous opioid (top) and dopamine (bottom) transmission during pain-related experiences. Gradient bar represents SDM value.

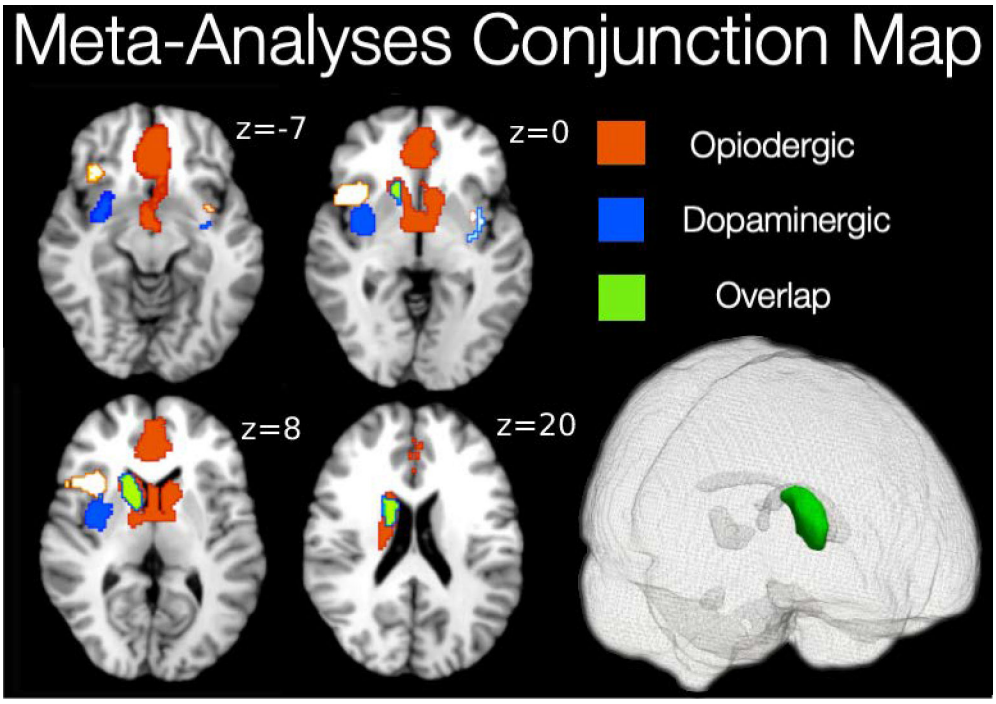

Figure 3:
Areas of overlap (green) between endogenous opioid (red) an dopamine (blue) transmission during pain-related experiences.

Table 1:

Characteristics of studies included in the meta-analysis

Study	Sample	Condition	Stimulation	Method of stimulation	Sex (M,F)	N	Age	Type	Significance
Opioid									
Carfentanil									
Prossin, 2015	Healthy controls	Pain Increase	Masseter muscle pain	Hypertonic Saline	12, 22	34	22±11	WBA	p<0.001
Zubieta, 2001	Healthy controls	Pain Increase	Masseter muscle pain	Hypertonic Saline	13,7	20	24±2	WB	p<0.05
Scott, 2007	Healthy controls	Pain Increase	Masseter muscle pain	Hypertonic Saline	14,0	15	27±5	WBA & ROI	p < 0.01
Wager, 2007	Healthy controls	Pain Increase	Thermal Pain	Thermode	n/a	15	25±5	ROI	p < 0.001
Scott, 2008	Healthy controls	Pain Increase	Masseter muscle pain	Hypertonic Saline	9, 11	20	24±3	WBA	p < 0.0001
DaSilva, 2014	Migraine	Pain Increase	Headache pain	During headache	3,4	12	n/a	WBA	n/a
Nascimento, 2014	Migraine	Pain Increase	Thermal Pain	Thermode	3, 3	6	26	WBA	p < 0.0001
Pecina, 2015	Healthy controls	Pain Increase	Masseter muscle pain	Hypertonic Saline	21, 29	50	26±0.7	WBA	p < 0.0001
Zubieta, 2003	Healthy controls	Pain Increae	Sad mood induction	Autobiographical memory	0, 14	14	36±9	WBA	P < 0.001
Hsu, 2013	Healthy controls	Pain Increase	Rejection Pain	Social feedback task	5, 13	18	32±12	VOI	p < 0.05; p < 0.01
Harris, 2009	Fibromyalgia	Pain Releif	Fibromyalgia pain	Accupuncture	0, 20	20	44.3±13.6	WBA & ROI	P < 0.001
Pecina, 2013	Healthy controls	Pain Relief	Masseter muscle pain	Placebo	19, 18	37	30±10	WBA & ROI	p < 0.001; p < 0.05
Diprenorphine									
Maarrawi, 2007	Neuropathic pain	Pain Increae	Chronic pain	Contralateral pain	4, 4	8	55.2±11	ROI	p < 0.0005
Wey, 2014	Healthy controls	Pain Increase	Pressure pain	Pressure cuff	4, 4	8	24	ROI	p < 0.05
Jones, 1999	Trigeminal Neralgia	Pain relief	Neuralgia pain	Surgery	6,0	6	61.5 ± 19.5	ROI	p < 0.01
Dopamine									
Radopride									
Berman, 2013	Writer's cramp	Pain Increae	Writer's cramp pain	Tapping Task	10, 5	15	52.41 ± 9	WBA & ROI	p < 0.05
Martikainen, 2015	CNBP patients	Pain Increae	Masseter muscle pain	Hypertonc saline	18, 14	16	35 ± 11	WBA & ROI	p < 0.05; p < 0.005
Pecina, 2015	Healthy controls	Pain Increae	Masseter muscle pain	Hypertonc saline	21, 29	50	26±0.7	WBA	p<0.05; p < 0.0001

Study	Sample	Condition	Stimulation	Method of stimulation	Sex (M,F)	N	Age	Type	Significance
Opioid									
Carfentanil									
Scott, 2006	Healthy controls	Pain Increae	Masseter muscle pain	Hypertonc saline	18, 7	25	27±5	WBA	p<0.0001; p<0.01
Scott, 2007	Healthy controls	Pain Increae	Masseter muscle pain	Hypertonc saline	14, 0	14	27±5	ROI	P < 0.01
Scott, 2008	Healthy controls	Pain Increae	Masseter muscle pain	Hypertonc saline	9, 11	20	24±3	WBA & ROI	p = 0.05, p<0.0001
Wood, 2007	FM patients	Pain Increae	Tibialis muscle pain	Hypertonc saline	0, 22	11	n/a	ROI	p < 0.05
Fally pride									
Jarcho, 2015	Healthy controls	Pain Increase	Thermal Pain	Thermode	0, 15	15	24±3.11	WBA	p = 0.001

FM = Fibromyalgia; WBA =Whole brain analysis; VOI = Volume of interest; ROI = Region of interest; CNBP = Chronic non-neuropathic back pain

Table 2

MNI center of cluster coordinates in each cluster in opioid activations

x	y	z	Cluster Size	Brain Region, Brodmann Area
6	18	4	3317	Ventralmedial PFC, Striatum, Thalamus
0	−6	42	1315	Anterior Cingulate Cortex
22	2	−32	962	Right Amygdala, Right Temporal Pole
40	16	4	394	Right Insula, Right Inferior Frontal Gyrus
36	24	−10	53	Right Ventral Anterior Insula
−34	4	−4	18	Left Insula, Left Putamen

Threshold Voxel threshold; $p < 0.005$. Extent threshold; cluster size ≥ 10 voxels.

Table 3

MNI center of cluster coordinates for brain regions in D2/D3 activations

MNI coordinate						
x	**y**	**z**	***SDM-Z***	***P value***	**Cluster Size**	**Brain Region**
34	0	0	4.504	0.0010	487	Right Putamen, Right Insula
14	10	12	3.958	0.0010	443	Right Caudate Nucleus
−36	2	2	3.523	0.0040	55	Left Insula, Left Putamen

Threshold Voxel threshold: $p < 0.005$. Peak height threshold: peak SDM-Z > 3.128. Extent threshold: cluster size ≥ 55 voxels.

Table 4 Jack

Knife sensitivity analysis for each significant cluster

Studies	Right Caudate	Left Caudate	Thalamus	Right Insula	Cingulate Gyrus	Left Insula/STG	Midbrain	Inferior frontal gyrus
Opioid								
DaSilva, 2014	y	y	y	y	y	y	y	y
Harris, 2009	y	y	y	y	n	y	y	y
Hsu, 2015	y	y	y	y	y	y	y	y
Jones, 1999	y	y	y	y	y	y	y	y
Maarrawi, 2007	y	y	y	y	y	n	y	y
Nascimento, 2014	y	y	y	y	y	y	y	y
Pecina, 2012	y	y	n	y	y	n	y	n
Pecina, 2014	y	y	y	y	y	n	y	n
Prossin, 2015	y	n	y	y	y	y	y	y
Scott, 2007	y	y	y	y	y	y	y	y
Scott, 2008	y	y	y	y	y	y	y	y
Wager, 2007	y	y	y	y	y	y	y	y
Wey, 2014	y	y	y	y	y	y	y	y
Zubieta, 2001	y	y	y	y	y	y	y	y
Zubieta, 2003	y	n	y	y	n	y	y	y

	Right Caudate	Left Caudate	Thalamus	Right Insula	Cingulate Gyrus	Left Insula
Dopamine						
Berman, 2013	y	y	y	y	y	y
Jarcho, 2015	y	y	y	y	n	y
Martikainen, 2015	y	y	y	y	y	y
Pecina, 2014	y	y	n	y	n	y
Scott, 2007	y	y	n	y	n	y
Scott, 2008	y	y	y	y	y	y
Scott, 2006	y	y	y	y	y	y
Wood, 2007	y	y	y	y	n	y

Table 5

Peak MNI coordinates for overlap brain regions of opioid and D2/D3 activations

Peak MNI coordinate			***Center of Mass***			**Cluster Size**	**Brain Region**
x	**y**	**z**	***CM x***	***CM y***	***CM z***		
14	14	0	13.6	9.8	11.6	420	Right Dorsal Striatum

Extent threshold: cluster size ≥ 10 voxels