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REVIEW ARTICLE

Can neuroimaging help combat the opioid epidemic? A systematic review of clinical and pharmacological challenge fMRI studies with recommendations for future research

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The current opioid epidemic is an urgent public health problem, with enormous individual, societal, and healthcare costs. Despite effective, evidence-based treatments, there is significant individual variability in treatment responses and relapse rates are high. In addition, the neurobiology of opioid-use disorder (OUD) and its treatment is not well understood. This review synthesizes published fMRI literature relevant to OUD, with an emphasis on findings related to opioid medications and treatment, and proposes areas for further research. We conducted a systematic literature review of Medline and Psychinfo to identify (i) fMRI studies comparing OUD and control participants; (ii) studies related to medication, treatment, abstinence or withdrawal effects in OUD; and (iii) studies involving manipulation of the opioid system in healthy individuals. Following application of exclusionary criteria (e.g., insufficient sample size), 45 studies were retained comprising data from ~1400 individuals. We found convergent evidence that individuals with OUD display widespread heightened neural activation to heroin cues. This pattern is potentiated by heroin, attenuated by medication-assisted treatments for opioids, predicts treatment response, and is reduced following extended abstinence. Nonetheless, there is a paucity of literature examining neural characteristics of OUD and its treatment. We discuss limitations of extant research and identify critical areas for future neuroimaging studies, including the urgent need for studies examining prescription opioid users, assessing sex differences and utilizing a wider range of clinically relevant task-based fMRI paradigms across different stages of addiction.

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INTRODUCTION

Nonmedical opioid use is a major public health problem in the United States, with rates of opioid-use disorder (OUD), treatment admissions, and opioid-associated overdoses and deaths rising dramatically in recent years [1–3]. Both behavioral and pharmacological approaches have shown promise for treating OUD. In particular, methadone, buprenorphine, and naltrexone are recommended (NIDA/SAMHSA Blending Initiative [4]; [5]) widely used [6] forms of medication-assisted treatment [7, 8]. However, there is substantial individual variability in treatment response, and data indicate high rates of relapse even over the short term [9–13]. Therefore, further research is urgently needed to identify both novel treatment targets and individual difference factors conferring vulnerability for relapse.

Functional magnetic resonance imaging (fMRI) allows for indirect assessment of brain function and has been used extensively to study addictions and their treatment. Extant data indicate that multiple brain regions interact in a dynamic manner to influence a range of complex cognitive processes relevant to drug addictions. In particular, prefrontal cortical (PFC) brain regions involved in cognitive-control and executive-functioning processes [14–17] are reciprocally connected with subcortical limbic neurocircuitry (e.g., striatum, amygdala) involved in reward and incentive-salience encoding [18–21]. These networks are altered among individuals with drug addictions [16, 22, 23], and emerging data suggest that both short-term treatment efficacy [24–27] and longer-term recovery [28–30] may depend on appropriate engagement of these systems [31–33]. However, these processes are incompletely understood, particularly within the context of OUD.

Similarly, while the neurochemical/pharmacologic effects of medication assisted treatments for OUD are relatively well characterized [34], less is known about the down-stream effects of these medications on functional responses in the brain. fMRI has the potential to provide invaluable insights into these processes. Despite this potential, effective translation of research findings into the clinical realm remains elusive [35]. To synthesize existing knowledge and facilitate effective translation of findings to real-world clinical settings, we aim to build upon recent reviews focused more broadly on fMRI findings across different substance use disorders [36, 37] and others focused more narrowly on resting-state fMRI in OUD [38–40] by examining published fMRI literature (both task-based and resting-state) relevant to OUD, with an emphasis on findings related to opioid medications and treatment outcomes, as well as proposing areas for further research. By delineating common and distinct neural mechanisms of OUD pathophysiology and treatment response, it may be possible to identify which individuals are most likely to benefit from different treatments, optimize existing therapeutic approaches to target neural and clinical features of OUD, and

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unveil novel neuroscience-informed interventions to combat the nationwide opioid epidemic [32, 35, 41].

METHODS

A systematic literature search of Medline and Psychinfo was conducted on September 18th, 2017 using the following parameters: "fmri" and "heroin" or "opioid" or "opiate" or "buprenorphine" or "methadone" or "fentanyl". Our initial search yielded 157 studies. For simplicity, we categorized studies based on clinical relevance, as follows: (a) fMRI studies comparing OUD and control participants; (b) studies related to medication, treatment, abstinence or withdrawal effects in OUD (no control group required); and (c) studies involving manipulation of the opioid system in healthy individuals (no OUD group required Fig. 1). Studies not falling into one of these four categories (e.g., studies involving manipulation of the opioid system in alcohol-use disorder) were excluded.

Following exclusion of duplicate citations, manuscripts judged not to be relevant given the above criteria (based on titles and abstracts as necessary), or not to contain original, peer-reviewed research (e.g., reviews, book chapters), 69 studies were retained for full-text review. For between-group studies, we required a sample size of $n \geq 15$ per group. However, given this review's focus on clinical translation, a more liberal threshold of $n \geq 10$ was used for studies employing a within-subjects design (e.g., before and after daily methadone) or directly investigating treatment/recovery mechanisms (e.g., comparison of OUD individuals with and without subsequent relapse). Following full text inspection, an additional eight studies were judged ineligible (e.g., studies of OUD patients not related to treatment and not including a control group) and twenty were excluded due to insufficient or not specified sample sizes. Four additional studies were identified from other sources (e.g., references in other manuscripts) resulting in a total of 45 studies included in the present review. Further details on study inclusion are shown in Supplemental Fig. 1 (CONSORT diagram).

Results and sample characteristics

Using the above criteria, we identified 32 fMRI studies including opioid-dependent individuals and 13 studies involving manipulation of the opioid system in healthy controls, together comprising data from just over 1400 individuals (769 OUD; 646 controls). Neuroimaging methodologies (types of task, analysis approach) and clinical characteristics (e.g., abstinence duration, medication status) varied widely across studies. For studies including individuals with OUD ($n = 32$), this included 18 task-based studies and 14 resting state studies. The primary opioid of abuse was heroin in all but one study. No studies compared OUD individuals based on type of opioid (e.g., prescription vs. non-prescription opioid use). Seventeen (37.7%) of the 45 above-reviewed studies included solely male participants, yet no study was comprised solely of women. Across all studies, only 208 (14.7%) of participants were female; Fig. 1). None of the studies identified in our systematic review (including those excluded for sample size limitations) included sex comparisons. Tables 1–4 summarize primary study characteristics (sample size, sex, primary drug, study design) and findings. Table 5 summarizes clinical characteristics of OUD individuals included in these studies (medication status, length of heroin abstinence prior to the study, and the duration heroin use/dependence). To facilitate comparison of findings across studies, we have organized our review based on methodological similarity (i.e., type of fMRI task). Below, we review primary findings with an emphasis on those from studies related to treatment or abstinence.

Drug cue reactivity

Predominant theories regarding the neurobiological basis of addiction assert that extended substance use is associated with neuroadaptations linked to overvaluation of drug-related stimuli relative to natural rewards [23, 42]. A number of task-based fMRI studies have therefore focused on neural response to heroin-related stimuli among individuals with OUD [43–52] (Table 1). As expected, studies examining brain activation to heroin-related cues converge in reporting greater neural response among OUD participants [48, 49, 53], although the scope of this finding varies across reports. Findings generally indicate widespread increases in neural activation to heroin cues in OUD, extending throughout parietal, limbic (e.g., amygdala, striatum, hippocampus, thalamus), frontal cortical (e.g., anterior cingulate, dorsolateral prefrontal cortex, orbitofrontal cortex) and midbrain regions [45, 48, 49]. As a whole, findings from cue reactivity studies of OUD are therefore largely consistent with those from the larger addiction literature.

Neural responses to drug cues further appear sensitive to manipulation of the opioid system. Using a within-subjects, cross-over design, Walter and colleagues [43] demonstrated increased orbitofrontal activity (ROI-based analysis only) in response to drug cues following acute heroin (vs. saline) administration in individuals receiving heroin maintenance therapy. In contrast, findings of decreased activity within orbitofrontal, insular, amygdalar and hippocampal regions have been reported following daily methadone administration [46]. Similarly, existing data indicate that acute administration of both naltrexone (opioid antagonist) and buprenorphine (partial agonist) are associated with decreased subcortical activity (e.g., amygdala, striatum, hippocampus) to drug cues [47, 52].

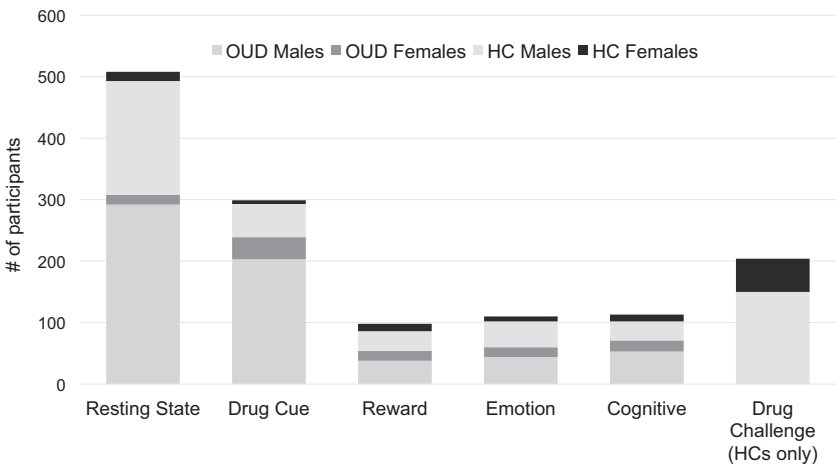

Fig. 1 Prevalence of male and female participants across reviewed fMRI studies. Across all studies, 208 (14.7%) of participants were female

Table 1. Primary findings from fMRI studies using drug cue paradigms in individuals with OUD

Ref.	OUD (N, F_n)	HC (N, F_n)	Drug	Status	Acute drug?	Design	Findings
Langleben et al. [46]	25, 12F	—	H	MMT	MMT	Pre and post	Pre-dose > Post-dose (heroin vs. neutral): OFC, insula, hippocampal complex, L amygdala
Mei et al. [52]	12, 1F	—	H	DTX	BUP	Onset & peak	Early scan > late scan (heroin vs. neutral): left VTA, thalamus, paracentral lobule, middle temporal gyrus and calcarine sulcus, R amygdala, hippocampus, precentral gyrus and postcentral gyrus
Li et al. [49]	24, 0F	20, 0F	H	AB	—	Cross-sectional	OUD > HC (heroin vs. neutral): NAcc, caudate, putamen, dlPFC, OFC, MeFG, amygdala, hippocampus, MCC, midbrain, thalamus, ACC, PCC, subcallosal gyrus
Lou et al. [51]	17 SA, 0F 17 LA. 0F	—	H	DTX	—	Cross-sectional	STA > LTA (heroin vs. neutral): hippocampus, insula, thalamus, dorsal striatum, cerebellum, PCC, temporal, parietal, occipital
Li et al. [50]	19 SA,?F 18 LA,?F	—	H	AB	—	Cross-sectional	STA > LTA (heroin vs. neutral): ACC, mPFC, caudate, IPL, precuneus, middle occipital gyrus
Langleben et al. [47]	13, 2F	—	H	AB	XRNTX	Pre and post	Post > Pre (heroin vs. neutral): precuneus, MFG Post < Pre (heroin vs. neutral): amygdala, caudate, cuneus, precentral gyrus
Wang et al. [45]	30, 0F (15 SA, 15 LA)	17,?F	H	MMT	MMT	Post MMT	OUD > HC (heroin vs. neutral): PHG, dACC, thalamus, MiFG, precuneus, cerebellum, SFG; STA > LTA (heroin vs. neutral): caudate
Li et al. [48]	44, 0F (23 REL, 21 NR)	20, 0F	H	MMT	—	Cross-sectional	OUD > HC (heroin vs. neutral): NAcc, cerebellum, caudate, putamen, dlPFC, OFC, PHG, IPL, ITG, pons, ACC, precuneus, inferior occipital gyrus, mPFC, midbrain, SPL, STL, cingulate, fusiform NR < REL HC (heroin vs. neutral): NAcc, cerebellum
Walter et al. [43]	27, 8F	20, 6F	H	HMT	Heroin vs. saline	Random, DB, CO	OUD > HC (heroin vs. neutral - saline only): OFC (ROI analysis) Heroin > saline (OUD only): OFC (ROI analysis)
Wang et al. [44]	30,15F		H	XRNTX	—	Pre- & post ($n = 14$) 3-month tx	No change pre- to post- XRTNX (heroin vs. neutral) pre-tx activation in MFG and ACC (heroin vs. neutral) positively correlated with tx adherence (# of XRNTX injections)

N total sample size, F_n number of female participants, *Ref.* reference, *OUD* opioid-use disorder, *HC* healthy control, *F* female, *REL* relapse, *NR* no relapse, *SA* short-term abstinence, *LTA* long-term abstinence, *H* heroin, *AB* abstinent, *MMT* methadone maintenance treatment, *HMT* heroin maintenance treatment, *DTX* detoxed, *XRNTX* extended release naltrexone, *BUP* buprenorphine, *random, DB, CO* randomized, double-blind, cross-over, *NAcc* nucleus accumbens, *dlPFC* dorsolateral prefrontal cortex, *OFC* orbitofrontal cortex, *MeFG* medial frontal gyrus, *MCC* midcingulate cortex, *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex, *STN* subthalamic nucleus, *PHG* parahippocampal gyrus, *IPL* inferior parietal lobule, *ITG* inferior temporal gyrus, *mPFC* medial prefrontal cortex, *ROI* region of interest, *dACC* dorsal anterior cingulate, *MiFG* middle frontal gyrus, *MiTG* middle temporal gyrus, *MFG* middle frontal gyrus, *tx* treatment, *?* not reported

Table 2. Primary findings from fMRI studies of non-drug reward, affective and cognitive paradigms in individuals with OUD

Ref.	OUD (N, F_n)	HC (N, F_n)	Drug	Status	Acute drug?	Design	Task	Findings
Gradin et al. [57]	30, 0F	23, 0F	H	MMT	15 pre, 15 post MMT[#]	Cross-sectional	Monetary reward/loss	OUD < HC (win vs. no-win): caudate, IPL, precuneus, cuneus, cerebellum OUD < HC (loss avoidance vs. loss): insula, IFG, ventral striatum, caudate, PHG, SFG, MiFG, cerebellum
Yip et al. [58]	24, 16F	21, 12F	H	MMT	—	Cross-sectional	Monetary reward/loss	OUD < HC (reward vs. loss): PCC, precuneus, IFG, dlPFC, insula
Wang et al. [63]	16, 0F	16, 0F	H	AB	—	Cross-sectional	Affective images	OUD < HC (affective vs. neutral): amygdala
Schmidt et al. [64]	22, 8F	17, 4F	H	HMT	Heroin vs. saline	Random, DB, CO	Fearful faces	OUD > HC (fearful vs. neutral - saline only): L amygdala (ROI analysis) Heroin < saline (fearful vs. neutral - OUD only): L amygdala (ROI analysis)
Schmidt et al. [65][a]	22, 8F	17, 4F	H	HMT	Heroin vs. saline	Reanalysis of [64]	Fearful faces	OUD > HC (fearful vs. neutral – saline only): L fusiform-amygdala connectivity, R amygdala-R OFC connectivity Heroin < saline (fearful vs. neutral – OUD only): L fusiform – L amygdala connectivity, R amygdala-R OFC connectivity
Fu et al. [69]	20, 0F	18, 0F	H	AB	—	Cross-sectional	Go/NoGo	OUD < HC (Go/NoGo vs. Go): mPFC, ACC, IFG, MeTG. insula, uncus, PHG, precuneus, SPL, MITG
Schmidt et al. [70]	27, 7F	—	H	HMT	Heroin vs. saline	Random, DB, CO	Go/no-go	Heroin < saline (No-Go vs. Go; No-Go vs. Oddball, and Oddball vs. Go trials): IFG (ROI analysis)
Yucel et al. [71]	24, 11F	24, 11F	H	10 MMT 14 BMT	—	Cross-sectional	Multi-Source Interference	OUD < HC (con. vs. incon): lateral premotor, superior temporal, PMC OUD > HC (con. vs. incon): superior & inferior parietal, occipital, IPFC, cerebellum

N total sample size, F_n number of female participants, *Ref.* reference, *OUD* opioid-use disorder, *HC* healthy control, *F* female, *H* heroin, *MMT* methadone maintenance treatment, *BMT* buprenorphine maintenance treatment, *AB* abstinent, *HMT* heroin maintenance treatment, *random*, *DB*, *CO* randomized, double-blind, cross-over, *IPL* inferior parietal lobule, *IFG* inferior frontal gyrus, *PHG* parahippocampal gyrus, *SFG* superior frontal gyrus, *MiFG* middle frontal gyrus, *PCC* posterior cingulate cortex, *dlPFC* dorsolateral prefrontal cortex, *L* left, *ROI* region of interest, *R* right, *OFC* orbitofrontal cortex, *con.* congruent, *incon.* incongruent, *PMC* primary motor cortex, *lPFC* lateral prefrontal cortex, *ACC* anterior cingulate cortex, *MeTG* medial temporal gyrus, *SPL* superior parietal lobule, *MiTG* middle temporal gyrus, *?* not reported
[a]Re-analysis of [64]

Neural responses to drug cues have also been shown to change following prolonged abstinence. Findings from cross-sectional studies comparing abstinence subgroups (e.g., short- vs. long-term abstinent patients) indicate that longer abstinence durations are associated with decreased striatal and other corticolimbic activity to drug cues, although the precise anatomical loci of these findings varied across studies [45, 50, 51]. Similarly, prospective studies comparing baseline neural responses between individuals with and without a subsequent relapse indicate decreased striatal activity to heroin cues among non-relapsers [48]. Extant data therefore suggest that corticolimbic engagement to drug cues decreases with prolonged abstinence, and that individual differences in baseline reward responses to drug cues may contribute to variability in treatment response. However, longitudinal studies incorporating neuroimaging measures at multiple time points are needed to confirm these hypotheses.

Although somewhat varied across studies, findings from fMRI studies using drug cues to study OUD are generally consistent with current neurobiological theories of drug addictions: They indicate heightened engagement of corticolimbic neural circuitry to drug cues among current users relative to controls. In addition, existing data suggest that neural responses to drug cues are further increased following heroin administration, but are decreased following agonist (methadone), antagonist (naltrexone) or partial agonist (buprenorphine) medications [43, 46, 47, 52]. Thus, despite the differing pharmacological mechanisms of different forms of MATs (i.e., methadone vs. naltrexone vs. buprenorphine), these data raise the possibility of somewhat similar downstream effects of these medications on neural activity in response to drug cues. Finally, data from primarily cross-sectional studies indicates that corticolimbic responses to drug cues may decrease following prolonged abstinence [45, 50, 51]. Overall, these data support the hypothesis that brain regions involved in salience encoding and drug approach behaviors may be appropriate treatment targets for OUD interventions. However, further mechanistic work using longitudinal designs is needed to support this hypothesis.

Non-drug rewards

In contrast to typically heightened neural responses to drug cues, individuals with addictions typically exhibit blunted responses to non-drug rewards [54–56]. However, only two of the identified studies assessed reward processing in OUD using non-drug stimuli (Table 2). Using a reward/loss learning task Gradin and colleagues [57] observed decreased activity within regions including the dorsal caudate, insula, ventral striatum and inferior frontal gyrus among methadone-maintained individuals, relative to controls. Somewhat similar findings of decreased engagement within regions including the insula, inferior frontal gyrus, posterior cingulate and dorsolateral PFC have also been reported in a separate study of methadone-maintained individuals [58]. Thus, while somewhat limited, current data generally support the hypothesis that processing of non-drug rewards is diminished in methadone-maintained individuals. These data raise the possibility that adjunct treatments targeting reward mechanisms (e.g., contingency management, neurofeedback) might be beneficial in addressing residual reward processing deficits among methadone-treated individuals [35].

Both of the above-described studies reported interactions between methadone and reward responses, however anatomical loci and direction of associations differed across studies [57, 58]. Specifically, Gradin and colleagues reported positive associations between daily methadone dose and BOLD response within the midbrain and parahippocampal gyrus [57], whereas Yip and colleagues reported negative associations between daily methadone dose and BOLD response within the posterior cingulate and precuneus [58]. Furthermore, results from both studies diverge from a recent meta-analysis including individuals with alcohol, cocaine,

Table 3. Primary findings from resting state studies in individuals with OUD

Ref.	OUD (N, F_n)	HC (N, F_n)	Drug	Status	Design	Analysis	Findings
Wang et al. [74]	15, 2F	15, 2F	H	DTX	Cross-sectional	Seed-based (vACC)	OUD < HC: vACC to NAcc, PHG/amygdala, thalamus, PCC/precuneus
Jiang et al. [80]	24, 4F	24, 4F	H	MMT	Cross-sectional	ALFF	OUD > HC: bilateral angular gyrus, PCC/precuneus, supramarginal gyrus L MFG
							OUC < HC: bilateral dACC, OFC, PCC and L dlPFC, L MiTG, L ITG, L cuneus
							Association between methadone dose and ALFF in regions of increased ALFF
Liu et al. [83]	16, 0F	16, 0F	H	AB	Cross-sectional	Graph theory	OUD < HC: (global properties) small-worldness
							OUD > HC: (degree) IFG, MeFG, SFG, MCC, insula, L caudate, putamen, pallidus, R occipital lobe
							OUD < HC: (degree) ACC, PCC, parahippocampus, amygdala, hippocampus, thalamus, R caudate, fusiform, temporal lobe, cerebellum, L occipital lobe
							Association with duration of use: global efficiency
Xie et al. [76]	22, 0F	15, 0F	H	AB	Cross-sectional	Seed-based (amygdala)	OUD > HC: amygdala to bilateral precuneus, bilateral thalamus, and R insula
							OUD < HC: amygdala to the R IFG
							Association with impulsiveness score (OUD only): (positive correlation) R subcallosal gyrus, insula, PCC, thalamus; (negative correlation) L fusiform
Jiang et al. [79]	17, 2F	15, 3F	H	MMT	Cross-sectional	Graph theory	OUD < HC: (global properties) small-worldness; clustering coefficient
							OUD > HC: (degree and efficiency) L hippocampus, L inferior occipital gyrus, L lingual gyrus
							OUD < HC: (degree and efficiency) middle cingulate gyrus, L MiFG, L ITG, R precuneus, R thalamus
Wang et al. [75]	17, 0F	15, 0F	H	DTX	Cross-sectional	ALFF/seed-based	OUD < HC: right caudate, right dACC, right superior MPFC
							OUD > HC: bilateral cerebellum, left STG and left superior occipital gyrus
							OUD: inverse correlation between right caudate ALFF and heroin use
							OUD < HC: right caudate and dlPFC
							OUD > HC: right caudate and cerebellum
Xie et al. [77][a]	22, 0F	15, 0F	H	AB	Re-analysis of [76]	Seed-based (NAcc)	OUD > HC: NAcc to bilateral caudate, amygdala, thalamus and vmPFC
							OUD < HC: NAcc to bilateral dlPFC, insula, parietal lobe
Li et al. [82]	26, 3F (13 REL, 13 NR)	—	H	MMT	Cross-sectional	ICA (DMN)	NR < REL: posterior DMN
							NR > REL: anterior DMN
Schmidt et al. [85]	20, 8F	20, 6F	H	HMT	Random, DB, CO	ICA (BG/limbic network)	OUD < HC (placebo only): PCC-limbic conenctivity
							Heroin > saline (OUD only): striatal connectivity*
							*Correlated w/ reward response to heroin
Zhang et al. [82]	21, 0F	15, 0F	H	DTX	Cross-sectional	Seed-based (ACC)	OUD > HC: dACC to bilateral PCC, SFG, MPFC/rACC, insula, L caudate nucleus, OFC, R temporal area, postcentral gyrus, inferior parietal lobe, supramarginal gyrus, angular gyrus
							OUD < HC: dACC to L dlPFC
							OUD > HC: rACC to the cerebellum, postcentral gyrus, inferior parietal lobe, R precentral gyrus, superior parietal cortex, insula, putamen
							OUD < HC: rACC to bilateral STG, MTG, cuneus and retrosplenial cortex
							OUD > HC: sACC to bilateral precuneus, OFC, bilateral
							inferior parietal lobe, supramarginal gyrus, dACC/middle
							cingulate cortex, L middle occipital gyrus, fusiform
							OUD < HC: sACC to bilateral SFG, cerebellum, amygdala, parahippocampus, R STG
Chang et al. [72]	40, 0F (21 REL, 19 NR)	—	H	MMT	fMRI + 12 month FU	ReHo	NR < REL: mOFC, caudate, cerebellum
							NR > REL: PHG, MiTG, lingual gyrus, precuneus
							R caudate positively correlated with relapse[a]
Li et al. [81]	24, 0F	20, 0F	H	DTX	Cross-sectional	ICA (DMN)	OUD < HC: anterior DMN (MPFC)
							OUD: weaker MPFC connectivity was associated with baseline craving

Table 3 continued

Ref.	OUD (N, F_n)	HC (N, F_n)	Drug	Status	Design	Analysis	Findings
Qiu et al. [74]	14, 0F	—	CCS	NTX	Pre and post	ALFF	Post < pre: L postcentral gyrus, L middle occipital; L dlPFC; FC between R mOFC and R dlPFC; FC between L dlPFC and L IPL
Wang et al. [73]	30, 0F	30, 0F	H	MMT	Cross-sectional	Seed-based (R and L insula)	OUD < HC: R insula to L insula, OFC, putamen, caudate, amygdala OUD < HC: L insula to R putamen, insula, rolandic operculum, amygdala, caudate, inferior frontal lobe OUD > HC: L insula to L fusiform, middle temporal lobe OUD: stronger connectivity between R and L insula associated w/ lower risk of positive urine analysis

N total sample size, F_n number of female participants, *Ref.* reference, *OUD* opioid-use disorder, *HC* healthy control, *F* female, *REL* relapse, *NR* no relapse, *H* heroin, *MMT* methadone maintenance treatment, *HMT* heroin maintenance treatment, *AB* abstinent, *CCS* codeine-containing cough syrup, *DTX* detoxed, *fMRI* functional magnetic resonance imaging, *FU* follow-up, *NTX* naltrexone treatment, *Random*, *DB*, *CO* randomized, double-blind, cross-over, *ICA* independent component analysis, *DMN* default mode network, *ReHO* regional homogeneity, *ALFF* amplitude of low frequency fluctuations, *BG* basal ganglia, *vACC* ventral anterior cingulate cortex, *mOFC* middle orbitofrontal cortex, *PHG* parahippocampal gyrus, *MiTG* middle temporal gyrus, *R* right, *L* Left, *dlPFC* dorsolateral prefrontal cortex, *IPL* inferior parietal lobule, *PCC* posterior cingulate cortex, *IFG* inferior frontal gyrus, *NAcc* nucleus accumbens, *MeFG* medial frontal gyrus, *SFG* superior frontal gyrus, *MCC* middle cingulate cortex, *ACC* anterior cingulate cortex, *dACC* dorsal anterior cingulate cortex, *OFC* orbitofrontal cortex, *ITG* inferior temporal gyrus, *MiFG* middle frontal gyrus, *MPFC* medial prefrontal cortex, *STG* superior temporal gyrus, *vmPFC* ventromedial prefrontal cortex, *rACC* rostral anterior cingulate, *sACC* subcallosal anterior cingulate, *MCC* middle cingulate cortex

cannabis, nicotine, and gambling disorders, which reported increased activation of the ventral striatum, as well as frontal, cingulate, insular, parietal and occipital regions among addicted individuals relative to controls [59]. This discrepancy suggests that individuals with OUD may exhibit a distinct pattern of aberrant neural response to non-drug rewards compared to individuals with other substance-use disorders. Thus, while findings from both studies in OUD indicate residual alterations in reward processing of non-drug stimuli among methadone-treated individuals, further mechanistic work is needed to determine the specific effects of methadone on reward responses. Similarly, future studies are needed to determine the effects of naltrexone and buprenorphine on neural processing of non-drug rewards, particularly in light of existing data suggesting effects of these medications on processing of drug stimuli (reviewed above) [46, 47, 52].

Affect processing

Difficulties in emotion regulation, high rates of negative affect and alterations in processing of affective stimuli have been widely documented among individuals with addictions [60–62]. Overall, findings from studies of non-opioid addictions generally indicate reduced neural activation across a range of different regions in response to various emotional stimuli [37], and blunted amygdala responses to negative stimuli in particular [60, 61]. Consistent with this, a cross-sectional study of abstinent (inpatient) former heroin dependent individuals found decreased amygdala response in OUD individuals, relative to controls [63]. In contrast, using an ROI-based approach, Schmidt and colleagues [64] found an increased amygdala response to negative emotional faces among OUD patients receiving heroin maintenance therapy relative to controls, that was attenuated following acute heroin administration. Follow-up seed-based analyses in the same sample indicated increased connectivity between the fusiform (structure implicated in face processing) and amygdala that was also attenuated following heroin administration [65]. Thus, while extant data support the hypothesis of altered amygdala responses in OUD patients—and suggest sensitivity of these responses to opioid administration—the direction of findings overall remains equivocal (Table 2). Thus, further work across different patient groups (e.g., currently using, abstinent, medication-maintained individuals) is warranted. In addition, further work is needed to determine the extent to which alterations in amygdala reactivity may be specifically linked to emotion regulatory processes; e.g., as opposed to simply reflecting a more general blunting of neural responses to non-drug stimuli.

Inhibitory control

Response inhibition requires coordination of executive control processes and is central to models of addictive behavior [66, 67]. Go/no-go tasks are widely used to study neural mechanisms underlying response inhibition and error processing. Studies conducted in healthy controls consistently report engagement of the anterior cingulate during go/no-go task performance [68]. Relative to control participants, data indicate decreased anterior cingulate, lateral PFC and insular engagement among individuals with OUD during go/no-go task performance [69]. Decreases in lateral PFC engagement during Go/no-go performance following acute heroin (vs. placebo) have further been demonstrated [70]. In contrast, data from Yücel and colleagues [71] indicate increased lateral PFC engagement, but no evidence for alterations in cingulate engagement, among OUD individuals relative to controls during performance of a multi-source interference task involving inhibitory control. This stands in contrast to literature on individuals with other substance use disorders, which have more consistently reported decreased

Table 4. Primary findings from fMRI studies of acute opioid agonist and antagonist administration in healthy samples

Ref.	HC (N, F_n)	Acute drug	Design/task	Findings
Borras et al. [100]	10, 0F	NALX (4 mg), IV fixed-dose infusion	Noxious thermal stimuli, hand	NALX > Saline: insula, cingulate, lateral prefrontal, pallidum, lingual, fusiform, PHG, OFC, thalamus, caudate, hippocampus
Oertel et al. [98]	16, 8F	ALF (effect site: 25, 50, 75 ng/ml), TCI	Trigeminal pain stimulation, nasal	ALF < NoDrug: insula, amygdala/PHG, putamen
				ALF(neg. linear dose effect): insula, postcentral, ACC, amygdala/PHG, IFG
Upadhyay et al. [90]	24, 0F (12 BUP, 12 APREP)	BUP (0.2 mg/70 kg), IV fixed-dose infusion; APREP (96 mg/70 kg), IV fixed-dose infusion	phMRI; Noxious thermal stimuli, foot	BUP > NoDrug (phMRI): insula, thalamus, striatum, ACC, OFC, midbrain
				BUP > Saline (thermal): thalamus, striatum, ACC, PCC, MiFG
				APREP > NoDrug(phMRI): thalamus, striatum, amygdala, OFC, midbrain
				APREP > Sal (thermal): ACC, OFC, amygdala
Atlas et al. [93]	21, 11F	REM (indiv. calibrated; mean: 0.88 ng/ml), IV fixed-dose infusion	Noxious thermal stimuli, forearm	REM > NoDrug: fusiform, lingual, STG, MiTG, IPL, postcentral
				REM < NoDrug: striatum, insula, ACC, thalamus, amygdala, angular, supramarginal, MiFG
Upadhyay et al. [89]	36, 0F (12 low, 12 high, 12 SL)	BUP (low = 0.1 mg/70 kg; high = 0.2 mg/70 kg), IV fixed-dose infusion; BUP (SL = 2.0 mg), SL tablet	phMRI, resting-state	BUP-Low > saline (thermal): PCC, cingulate, putamen, thalamus
			Noxious thermal stimuli, foot	BUP-High > Saline (thermal): ACC, frontal, parietal, precuneus, PHG, temporal, putamen, thalamus
				BUP-SL > PBO (thermal): ACC, PCC, frontal, parietal, precuneus, temporal, putamen, thalamus
				Putamen connectivity (phMRI/rest):
				BUP-high/BUP-SL < Sal/PBO: insula, thalamus, cingulate, sensorimotor
Gear et al. [94]	13, 0F	NALX (0.4 mg), single IV injection; NALB (5 mg/70 kg), IV fixed-dose infusion	phMRI	NALB + saline > NoDrug: insula, thalamus, caudate, hippocampus, ITG, STG, fusiform
				NALB + saline < NoDrug: MiFG, OFC, postcentral, temporal pole
				NALX + NALB > NoDrug: insula, putamen, lingual
				NALX + NALB < NoDrug: SFG, OFC
Taylor et al. [88]	15,? F	NALX (0.1 mg/kg), single IV injection	Noxious thermal stimuli, forearm	NALX > NALX + TMS: MeFG, IPL, midbrain, medulla
			TMS of left dlPFC	NALX + TMS > Saline + TMS: midbrain, medulla
Gorka et al. [95]	14, 4F	OXY (low = 10 mg, high = 20 mg), oral tablet	Resting-state	dACC connectivity:
				High > PB/Low: OFC, MeFG, MiFG, SFG, IFG, MiTG
				High/low < PBO: insula, putamen
Wardle et al. [91]	14,? F	OXY (low = 10 mg, high = 20 mg) oral tablet	Emotional pictures task (EPT)	EPT: OXY effect: cuneus, postcentral, lingual, fusiform, thalamus
			Emotional face match task (EFMT)	EPT: OXY x Emo interaction: cuneus, STG
				EFMT: OXY effect: lingual;
				EFMT: OXY x Emo interaction: OFC, SFG
Murray et al. [97]	20, 10F	NTX (50 mg) or placebo	Random, BD CO	NTX < PLA (pleasant): dorsal ACC, MFG
			Pleasant and aversive food cues and tastes	NTX > PLA (aversive): amygdala, insula
Chu et al. [92]	10, 0F	Morphine (10 mg/70 kg), IV, followed by	Precipitated withdrawal model, resting state (ALFF)	Naloxone > morphine: gyrus rectus, IFG, MiFG, SFG, fusiform gyrus, temporal gyrus, caudate, putamen, pregenual cingulate, cerebellum
		Naloxone (10 mg/70 kg), IV		

Table 4 continued

Ref.	HC (N, F_n)	Acute drug	Design/task	Findings
				Naloxone < morphine: pre/post-central gyrus, precuneus, posterior insula, STG, cuneus, occipital lobe
Robinson et al. [99]	21, 11F	REM (indiv. calibrated; mean: 0.88 ng/ml), IV fixed-dose infusion	Noxious thermal stimuli, forearm	REM > NoDrug (pain network): lower ACC-insula coupling, lower within ACC and greater within insula connectivity
				ReEM > NoDrug (frontoparietal network): greater frontal-parietal coupling, lower within frontal and within parietal connectivity
Hayen et al. [96]	19, 10F	REM (effect site: 0.7 ng/ml), IV TCI	Resistive inspiratory breathlessness	REM < Sal: insula, ACC, SMA, sensorimotor, thalamus, supramarginal

N total sample size, F_n number of female participants, *Ref.* reference, *HC* healthy control, *F* female, *BUP* buprenorphine, *APREP* aprepitant, *SL* sublingual, *NTX* naltrexone, *Random, BD, CO* randomized, double-blind, cross-over, *NALX* naloxone, *IV* intravenous, *NALB* nalbuphine, *phMRI* pharmacological magnetic resonance imaging, *TMS* trans magnetic stimulation, *dlPFC* dorsolateral prefrontal cortex, *PHG* parahippocampal gyrus, *OFC* orbitofrontal cortex, *ITG* inferior temporal gyrus, *STG* superior temporal gyrus, *MiFG* middle frontal gyrus, *SFG* superior frontal gyrus, *MeFG* medial frontal gyrus, *IPL* inferior parietal lobule, *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex, *PBO* placebo, *?* not reported

activation of cingulate, insular, and frontal regions during inhibitory control [37]. As with findings from other task domains shown in Table 2 (non-drug reward processing, affective processing), findings from studies of inhibitory control in OUD individuals remain conflicting and the relationship between inhibitory control processes and clinical features of OUD remains unknown. Thus, further work across diverse OUD populations is urgently needed to identify targets for improved prevention and intervention efforts.

Resting state

In contrast to task-based fMRI studies, resting-state studies of OUD individuals aim to characterize differences in the "intrinsic" organization of the brain via analysis of spontaneous fluctuations in the fMRI signal while the brain is "at-rest"—i.e., in the absence of a task. Given the unconstrained nature of resting-state data, many different methods have been proposed for analysis. This methodological variability is reflected in the resting-state studies of OUD individuals identified here, with few manuscripts using comparable methods. Table 3 summarizes all identified resting state studies [72–85]. Given the large range of diverse analysis methods employed, we here focus on primary findings from studies using similar analysis approaches.

Independent component analysis (ICA) is a network-based analysis approach for identifying temporally coherent functional networks. Three studies have used ICA to probe connectivity within canonical (e.g., default mode, limbic) networks among individuals with OUD. Using this approach, Li and colleagues reported decreased anterior default mode network (DMN) connectivity among recently detoxed, medication-free, heroin dependent individuals, relative to controls [81]. Similarly, an ICA study focusing on limbic network connectivity found decreased connectivity between the posterior cingulate (part of posterior default mode) and a limbic network among heroin-maintained patients relative to controls, despite no between-group differences in within-network limbic connectivity [85]. A separate cross-sectional study comparing OUD individuals as a function of relapse status reported increased anterior DMN connectivity—in addition to decreased posterior DMN connectivity—among abstinent vs. relapsed patients [82].

Findings from two studies using seed-based approaches (functional connectivity between one or more a priori ROIs) using the anterior cingulate as a seed further indicate connectivity alterations between brain regions consistent with the posterior DMN (posterior cingulate, precuneus, retrosplenial cortex), however these studies were inconsistent in whether OUD exhibited greater connectivity compared to controls [74, 78]. Thus, ICA studies collectively report a pattern of altered DMN connectivity among OUD individuals that is characterized by decreased anterior (e.g., mPFC) and increased posterior (e.g., posterior cingulate) connectivity, whereas studies employing seed-based approaches have yielded less consistent findings.

Other approaches employed in resting state studies of OUD include graph theory and amplitude of low frequency fluctuation (ALFF) analyses. Graph theory is a method to characterize global and regional properties of whole brain functional networks. Two graph theory studies reported reduced small worldness (property where brain regions cluster into segregated networks, but communication between these networks is efficient due to highly connected hub regions [86]) and degree (the number of connections to a brain region) in the cingulate cortex for OUD individuals compared to healthy controls [79, 83]. ALFF is a method to quantify the amplitude of the power spectrum of the BOLD signal, and thus an indirect method for quantifying "spontaneous" neural activity. In two studies using this approach, consistent decreases in ALFF were observed in the dorsal ACC and in the DMN [75, 80] for OUD individuals compared to

Table 5. Clinical characteristics of studies reviewed

Ref	Recruitment route	MAT Status	Abstinence duration prior to study	Duration of heroin use/ dependence
Langleben et al. [46]	MMT clinic in USA	MMT	16 ± 13 months	n.r.
		54 ± 33 months		
Mei et al. [52]	Inpatient DTX clinic in China	DTX (scanned prior to TX or >8 h after first BUP dose)	50 ± 24 h	4.5 ± 4.4 years
Li et al. [49]	Residential treatment in China	AB, no MAT	21.7 ± 16 days	78.6 ± 50.1 months
Lou et al. [51]	Forced DTX center in China	DTX	STA: 1.2 ± 0.1 months	STA: 7.0 ± 1.0years
			LTA: 13.6 ± 0.4 months	LTA: 8.2 ± 1.1 years
Li et al. [50]	Drug rehab center in China	AB (post-methadone-assisted DTX)	STA: 23.6 ± 17.6 days	STA: 80.5 ± 54.4 months
			LTA:193.3 ± 42.7 days	LTA: 96.3 ± 69.5 months
Langleben et al. [47]	Court mandated OUD TX (selected XRNTX) in USA	AB	97 ± 123 days	12.5 ± 8 years
Wang et al. [45]	MMT in China	MMT Group A: <1 year; 7.92 ± 2.89 months	n.r	Group A: 48.6 ± 4 9.9 months
		Group B: >2 years; 29.62 ± 3.53 months		Group B: 49.64 ± 42.5 months
Li et al. [48]	MMT clinic in China	MMT	n.r.	Relapsers: 69.2 ± 68.5 months
		Relapsers: 18.3 ± 11.5 months		Non-relapsers: 92.3 ± 70.5 months
		Non-relapsers: 25.5 ± 17.3 months		
Walter et al. [43]	Centre of Substance Use Disorders in Switzerland	HMT	n/a	21.1 ± 5.7 years
		7.3 ± 4.4 years		
Wang et al. [44]	Local ads in China	Active users prior to enrollment, DTX as part of study	n/a	n.r.
Gradin et al. [57]	NHS addiction service in UK	MMT > 6 weeks at stable dose	n.r.	3 year minimum
Yip et al. [58]	RCT of cocaine use disorder treatment in USA MMT clinic	MMT > 2 months at stable dose	n.r.	n.r.
Wang et al. [63]	Forced DTX program in China (2–5 months post-DTX)	AB	3.4 ± 0.9 months	6.9 ± 2.9 years
Schmidt et al. [64, 65]	Centre of Substance Use Disorders in Switzerland	HMT > 6 months (>3 months at stable dose)	n/a	21 ± 6.4 years
Fu et al. [69]	Inpatient abstinence treatment in China	AB, no MAT	7.64 ± 2.16 weeks	6.25 ± 3.53 years
Schmidt et al. [70]	Centre of Substance Use Disorders in Switzerland	HMT > 6 months (>3 months at stable dose)	n/a	20.54 ± 6. 56 years
Yucel et al. [71]	Community treatment providers in Australia	MMT & BMT	24 h minimum	107.44 ± 60.87 months
		31.54 ± 32.55 months		
Wang et al. [74]	Individuals seeking DTX in China	Active users prior to enrollment	5.1 ± 0.29 h	19.9 ± 3.1 years
Jiang et al. [80]	Individuals seeking treatment in China	MMT	n.r.	10.83 ± 4.61 years
		6-7 days		
Liu et al. [83]	MMT clinic in China	MMT	4.76 ± 0.7 months	85.3 ± 46.2 months
		Duration n.r.		
Xie et al. [76]	Hospital in China	AB	8.05 ± 2.51 weeks	6.59 ± 3.72 years
Jiang et al. [79]	Hospital in China	MMT[a]	6–7 days	9.21 ± 5.28 years
		Duration n.r.		
		2 participants not on MMT[a]		
Wang et al. [75]	MMT clinic in China	AB	n.r.	81.5 ± 33.9 months
Xie et al. [77]	Hospital in China	AB	8.05 ± 2.51 weeks	6.59 ± 3.72 years
Li et al. [82]	MMT clinic in China	MMT > 3 months at stable dose	n.r.	n.r.
Schmidt et al. [85]	Centre of Substance Use Disorders in Switzerland	HMT > 6 months (>3 months at stable dose)	n/a	21.5 ± 6.10 years
Zhang et al. [78]	Forced DTX program in China	AB	8.05 ± 2.51 weeks	6.2 ± 3.53 years
Chang et al. [72]	MMT clinic in China	MMT > 3 months	n.r.	Non-relapsers: 275.7 ± 69.1 months
				Relapsers: 224 ± 64.5 months
Li et al. [81]	n.r.	AB	21.7 ± 16 days	78.6 ± 50.1 months
Qiu et al. [84]	Hospital in China	UROD + NMT	n.r.	4.96 ± 1.97 years
Wang et al. [73]	n.r.	MMT > 3 months	237 ± 424.35 days	7.66 ± 3.55 years

Ref. reference, *MMT* methadone maintenance treatment, *USA* United States of America, *n.r.* not reported, *DTX* detox, *TX* treatment, *BUP* buprenorphine, *AB* abstinent, *MAT* medication-assisted therapy, *STA* short-term heroin abstinence, *LTA* long-term heroin abstinence, *OUD* opioid use disorder, *XRNTX* extended release naltrexone, *HMT* heroin maintenance treatment, *n/a* not applicable, *NHS* National Health Service, *UK* United Kingdom, *RCT* randomized controlled trial, *BMT* buprenorphine maintenance treatment, *UROD* general anesthesia, *NMT* naltrexone maintenance treatment

healthy controls. However, the exact regions of the DMN and regions of increased ALFF were inconsistent across the two reports.

Preliminary data further indicate that resting state connectivity may be sensitive to manipulations of the opioid system: in a randomized, double-blind, cross-over study, Schmidt and colleagues [85] reported increases in striatal connectivity following acute heroin administration (vs. saline) that were positively related to subjective drug responses. In a separate within-subjects study, decreases in ALFF following naltrexone treatment (vs. baseline) were reported within primarily cortical regions including the medial OFC and DLPFC among codeine-dependent individuals [84]. Given the large number of methodological differences between these studies (e.g., drug, analysis approach, study population), further work directly comparing effects of opioid agonism vs. antagonism on resting state networks (in the same group of participants) is needed.

Across most studies, the DMN (including the PCC and mPFC) was consistently highlighted as exhibiting altered connectivity in OUD individuals relative to controls. However, the direction of these effects was varied. The discrepancy between the direction of DMN connectivity differences in OUD is likely influenced by the methodology used and the patient population being studied, making comparisons across studies difficult. Notable characteristics of study samples may also limit the generalizability of published results. For example, none of the identified studies were conducted in the United States, thus generalization of findings to the current demographically and clinically unique generation of opioid users in the United States may be limited [87]. Similarly, as with the majority of task-based studies, very few studies included female participants (see Fig. 1 for distribution of male and female participants across studies).

Manipulation of the opioid system in healthy controls

We identified 13 studies assessing the effects of opioidergic agents on brain activity in samples of healthy adults [88–100] (Table 4). A number of studies have examined the effects of opioid agonists and antagonists on brain responses to noxious stimuli in healthy individuals. Noxious or painful stimuli activate an established network of regions including the insula, anterior cingulate, thalamus, medial and lateral prefrontal areas, parietal cortex, striatal structures and somatosensory regions [101]. While specific patterns of brain activity may differ by modality (e.g., mechanical vs. thermal pain) [102], the effects of opioidergic agents on pain-related neural responses are largely consistent. Opioid agonists remifentanil and alfentanil reduced pain-related signaling in the thalamus, insula, cingulate, striatum, and sensorimotor regions [93, 96, 98]. By comparison, naloxone (antagonist) and buprenorphine (partial agonist) administration in healthy controls are associated with increased signaling across these regions in response to noxious stimuli [89, 90, 100]. In addition, naltrexone (antagonist) is associated with increased insula and amygdala activity to aversive food cues, but with decreased response within the dorsal anterior cingulate to appetitive food cues [97].

Several pharmacological fMRI (phfMRI) studies also characterized neural responses to opioidergic agents in the absence of stimuli. Compared to a no-drug condition, buprenorphine (partial agonist) and aprepitant (antiemetic) similarly increased neural signals in the striatum, midbrain, thalamus, and orbitofrontal cortex [90]. Both acute oxycodone and buprenorphine are further associated with reduced connectivity patterns between the insula and subcortical regions (e.g., thalamus, striatum) in healthy controls [89, 95]. Thus, phMRI findings suggest that, in the absence of stimuli, full (oxycodone) and partial (buprenorphine) opioid agonists appear to influence connectivity within a similar set of reward-related regions.

DISCUSSION

This systematic literature review identified 45 fMRI studies relevant to OUD, together comprising data from ~1400 individuals. Perhaps not surprisingly, neuroimaging methodologies (task type, analysis method) and clinical features (abstinence duration, medication status) varied widely across studies. However, cumulative evidence did converge for some domains—most notably drug cue reactivity and, to a lesser extent, drug challenge studies. Below we summarize findings from key domains and recommend directions for future clinically oriented neuroimaging work to help combat the current opioid epidemic.

Consistent with predominant theories of addictions, data indicate relatively widespread increases within parietal (precuneus, posterior cingulate), limbic (amygdala, striatum, hippocampus, thalamus), frontal cortical (anterior cingulate, dorsolateral prefrontal cortex, orbitofrontal cortex) and midbrain regions among OUD individuals in response to drug cues [45, 48, 49]. Emerging data further suggest that individual differences in baseline neural responses to drug cues may be linked to differences in treatment outcomes, such that reduced responses are associated with longer abstinence durations [45, 50, 51]. While replication of this latter finding in larger samples is required, these data raise the possibility that therapies specifically targeting neural responses to drug cues (e.g., cognitive bias modification; real time fMRI) might be effective adjuncts to existing therapies [31, 103, 104].

Findings from other domains (i.e., non-drug reward processing, affect processing, inhibitory control) have been far less consistent. This is likely due to the relative dearth of studies conducted in these domains (8 studies over three domains), as the overwhelming majority of identified OUD fMRI studies either utilized drug-cue paradigms or else assessed the brain "at rest". Furthermore, discrepancies in the specific tasks used and the analytic frameworks employed may also contribute to inconsistent patterns of results across studies. Thus, further work characterizing the functional neurobiology of OUD across other clinically relevant domains is urgently needed. In particular, task-based fMRI studies using standardized paradigms, which can be applied across species and analyzed using computational and cognitive modeling approaches, will help to elucidate the nature of cognitive and affective neural functioning in OUD.

Findings from resting-state studies generally support the hypothesis of altered DMN engagement among individuals with OUD, although the direction of these alterations has not been consistent across studies. As noted above, the identified resting state studies included a large number of methodological limitations, making interpretation of findings across studies problematic. In particular, given the variety of analysis methods employed (e.g., ALFF, ICA), the virtual absence of whole-brain analyses, and the relatively short durations of image acquisitions (e.g., ~5 min), collective findings from extant resting state analyses should be interpreted with caution. Thus, both acquisition of more data (i.e., longer durations) per subject (to improve within-subject reliability) and harmonization of analysis approaches and data pooling across studies are strongly recommended as important future directions for resting-state work in OUD populations [105–110]. As resting state analyses are particularly sensitive to motion effects, future studies should also incorporate more sophisticated motion correction techniques [111, 112] and test for possible effects of between-group (i.e., patients vs. controls) differences in motion on connectivity patterns.

Figure 2 summarizes primary findings from selected brain regions for studies involving manipulation of the opioid system (further details in Supplemental Table 1). Combined data generally indicate somewhat similar effects of opioid agonism in healthy controls and individuals with OUD (Fig. 2). For example, administration of both acute methadone (in patients) and oxycodone (in controls) is associated with decreases in neural

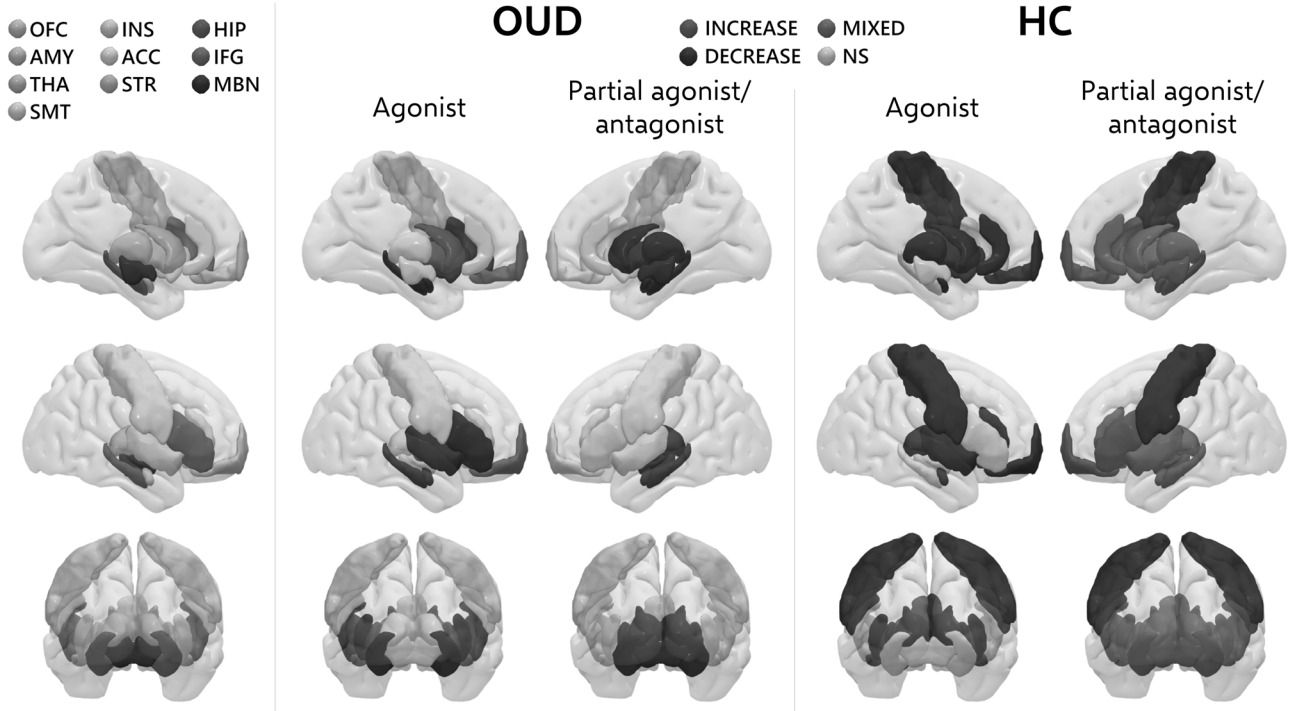

Fig. 2 Regional effects of opioidergic agents on neural function. Summarizes primary findings for selected brain regions from fMRI studies involving manipulation of the opioid system. OFC orbitofrontal cortex, INS insula, HIP hippocampus, AMY amygdala, ACC anterior cingulate, IFG inferior frontal gyrus, THA thalamus, STR striatum, MBN midbrain, SMT sensorimotor, OUD opioid use disorder, HC healthy control, NS no results. Based on data reported in refs [43, 46, 47, 52, 64, 70, 85, 89–91, 93–98, 100]. For studies including multiple conditions, e.g., ref. [89], results reported for neutral or resting state conditions were used for figure generation (see Supplemental Table 1 for details). Refer to Tables 1–4 of the primary manuscript for additional summaries of study findings

responses within the OFC and limbic regions [46, 95]. In contrast, acute heroin administration (in patients) is associated with increases in OFC and striatal regions. In addition, both antagonist (naltrexone) and partial agonist (buprenorphine) administration have been associated with relative decreases within limbic regions in studies of OUD individuals [47, 52], whereas findings on the effects of buprenorphine administration (during resting state) in controls have been mixed [89, 90]. Somewhat contrastingly, buprenorphine (partial agonist) and naloxone (antagonist) administration have also been associated with increased activity within the thalamus, insula, cingulate and striatum when paired with noxious stimuli in healthy controls [89, 90, 100]. Notably, none of the studies conducted in OUD individuals meeting our inclusionary criteria utilized noxious stimuli/assessed pain response. Given the very high prevalence rates of chronic pain among patients entering MAT [113], work in this area is urgently needed.

Despite the apparent relative concordance across some pharmaco-fMRI studies of OUD individuals and controls, numerous between-study methodological differences make direct comparison of findings problematic. For example, while several of the studies conducted in OUD employed randomized, double-blind, cross-over designs ("gold standard" for pharmacological challenge research), very few conducted in controls have done the same. Thus, further work to disentangle actual drug effects from those of expectation (placebo) effects, particularly among healthy individuals, is needed. In addition, no studies have controlled for possible medication-induced changes in metabolism, blood flow, and neurovascular coupling. Given that each of these factors can modulate the fMRI signal [114–116] and potentially lead to mischaracterization of neural activity, future studies also incorporating cerebral perfusion measures (e.g., pulsed arterial spin labeling) [117] are needed to better characterize the effects of opioidergic agents on neural activity across patients and controls.

Over the past two decades there has been a dramatic shift in opioid use initiation [87], with the overwhelming majority of heroin users also reporting prior misuse of prescription opioids [118]. Despite this, heroin was the primary opioid of abuse across all but one fMRI study, which studied codeine-dependent individuals [84]. As increases in prescription opioid abuse have occurred in tandem with changes in clinical and demographic features of individuals seeking treatment for OUD [87], future fMRI work specifically assessing the neural correlates of prescription opioid use and abuse (vs. heroin use) is urgently needed.

Need for consideration of sex as a biological variable in studies of OUD

The overall inclusion of women was very low across reviewed studies (<15% of all participants; Fig. 1) and no study included consideration of sex differences. This is part of a larger problem of underrepresentation of women and insufficient consideration of sex in clinical research more generally and addiction research specifically [119]. Sex differences have been demonstrated in the rates and clinical characteristics of individuals with OUD. While women have historically had lower rates of substance use and dependence, including heroin [120], this pattern is less clear in prescription opioids, with some studies reporting higher rates of recent [121] or regular use of prescription opioids [122] in women, but higher rates of abuse in men [123, 124]. These higher rates of prescription use in women are worrying since, among individuals seeking treatment for opioid use disorder, women are more likely to report first obtaining opioids from a legitimate prescription from their doctor [125, 126], while men are more likely to first obtain from an illicit source [127]. Furthermore, as with other drugs of abuse, there is evidence of "telescoping" (i.e., a faster transition in women relative to men from initial to problematic substance use) in OUD [128, 129]. Further, many large trials have

found sex differences in clinical correlates at treatment entry, for example with some samples showing more co-morbid psychiatric conditions and more psychological distress in women [125, 127, 130].

Several lines of evidence also indicate sex-specific effects of opioid administration and withdrawal. For example, differential sex effects of methadone and naltrexone on testosterone [126] and cortisol [131] levels, respectively, have been reported. Furthermore, endogenous gonadal hormones impact opioid effects. For example, estrogens can diminish opioids' antinociceptive effects [132], there is evidence of interactions and crosstalk between opioid and estrogen receptors [133], and estrogens may impact the antinociceptive and rewarding effects of methadone through effects on methadone metabolism [134]. In addition, recent preclinical work suggests sex-specific effects of acute opioid withdrawal and subsequent opioid replacement (with methadone or buprenorphine) on regional brain metabolism within regions including the anterior cingulate, amygdala and striatum [135, 136]. Thus, neuroimaging studies including equal numbers of male and female participants that are specifically powered to detect sex-specific effects are urgently needed in OUD.

Conclusions and recommendations for future work

fMRI has the potential to provide critical insights into the pathophysiology and treatment of psychiatric disorders. However, this potential has yet to be fully leveraged within the context of OUD. Extant data from other substance use disorders (e.g., cocaine-use disorder) generally support the hypothesis that individual differences in brain function are related to differences in treatment responses [24, 28, 32, 58, 137], yet only a small number of studies have used fMRI to study treatment mechanisms relevant to OUD. Of these, most studies have conducted cross-sectional comparisons of patients based on durations of abstinence or relapse status [45, 50, 51, 82]. Thus, little is known about how individual differences in baseline neural function might contribute to variability in treatment responses to behavioral and medication treatments for OUD. Further research in this area is not only critically important to aid in the refinement of existing treatments based on known brain mechanisms, and to advance pathophysiological understanding of OUD, but will also pave the way for individual assignment of patients to specific treatments based on clinically relevant neuromarkers [35, 138, 139]. Similarly, longitudinal research assessing neural responses over the course of treatment is needed to identify brain-based mechanisms of behavior change within the context of the opioid epidemic. Furthermore, neuroimaging research also has the potential to identify novel treatment targets that could facilitate the development of innovative prevention and intervention approaches.

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ADDITIONAL INFORMATION

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