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EMOTION & ADDICTION (K MORIE, SECTION EDITOR)

Effects of Acute Drug Administration on Emotion: a Review of Pharmacological MRI Studies

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Abstract

Purpose of Review Many drug users claim to use drugs to cope with negative emotions, which may, in turn, result in persistent emotional blunting or anhedonia even when they are not using drugs. The purpose of this review is to describe the ways acute administration of psychoactive drugs impacts brain regions during emotion-related tasks, as a first step in understanding how drugs influence emotion processing in the brain.

Recent Findings Drugs have varying effects on neural responses to emotional stimuli. In general, alcohol, analgesics, and psychedelics reduce neural reactivity to negative emotional stimuli in the amygdala and other brain regions. Other drugs produce mixed effects: Stimulants such as caffeine and modafinil increase brain activation while viewing emotional stimuli, whereas MDMA decreases activation during presentation of negative images. The effects of cannabinoids (cannabidiol and THC) are mixed. There are also inconsistent findings on the associations between neural responses to emotional stimuli and subjective drug effects.

Summary Consistent with the notion that individuals might use drugs non-medically to diminish the experience of negative emotions, several drugs of abuse decrease neural responses to negative stimuli in limbic brain regions. These neural actions may underlie the reported "emotional blunting" of drugs, which may contribute to drug-seeking behavior. Future work is needed to examine these limbic responses in relation to self-reports of changes in affect, both during acute administration and after extended drug use.

Keywords phMRI · Emotion · Alcohol · Cannabinoids · Analgesics · Stimulants

Introduction

Emotional blunting is a common symptom in many psychiatric disorders, including substance use disorders [1, 2]. Blunted emotional responses may pre-date and facilitate drug use, may be a consequence of long-term drug use, or may result directly from the effects of the drugs on emotional state and brain function. A growing number of controlled studies have examined the effects of acute drug administration on responses to emotional stimuli, and on the corresponding neural changes using functional magnetic resonance imaging (fMRI). These studies address two main ideas: (i) that drugs dampen responses to negative emotional stimuli, adding to their attractiveness to users, and (ii) that drugs either dampen or enhance responses to other, non-drug rewards, affecting the relative salience of the drug itself and perhaps the motivation to continue to take the drug (e.g., [3]). In this review, we examine the findings from recent studies that used fMRI in combination with drug administration, a technique often referred to as pharmacological MRI (phMRI) to study how drugs alter neural responses to negative and positive emotional stimuli.

phMRI is a powerful translational tool used to address both basic science and clinical questions. phMRI studies typically utilize a within-subjects design, where the same participants receive both the drug and a placebo across multiple study

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sessions. In many cases, participants will ingest a drug (or placebo) before undergoing fMRI scanning during the time of expected peak drug effects, and participants are often monitored for subjective and physiological drug effects throughout each study session. In the case of phMRI with alcohol or ketamine, some researchers have administered intravenous infusions before and/or during fMRI scanning. Using phMRI researchers can examine the effects of drugs on the brain in regions that are critically involved in cognitive and affective functions in healthy humans. These functions include emotion processing, which involves the amygdala [4•], reward anticipation, which typically recruits the striatum [5], and self-regulation and decision-making, which often involve the anterior cingulate cortex and prefrontal regions [6, 7]. Importantly, phMRI provides an opportunity to simultaneously study drug effects on neural circuits and on emotional and cognitive experiences. The studies reviewed here describe the influence of drugs on the neural correlates of emotion, and ultimately, they may shed light on how the brain changes with chronic drug use.

For this review, we sought to examine the neural responses to emotional stimuli under the influence of commonly used recreational drugs in healthy human participants. Articles published within the past 15 years were identified through online search engines (e.g., PubMed, Google Scholar) and were only included if they (a) reported data from healthy human participants, (b) involved acute drug administration in combination with fMRI (i.e., phMRI), and (c) required participants to complete a task involving emotion or mood while undergoing phMRI. Tables 1, 2, 3, 4, and 5 include 21 papers that fit these criteria.

Overview of Acute Drug Effects

Alcohol

Several phMRI studies have assessed the effects of alcohol on neural activation during processing of negative emotional stimuli (Table 1). In general, these studies have found that alcohol decreases neural responses to negative stimuli. Gilman et al. [33] reported that alcohol attenuated activation in the amygdala, insula, parahippocampal gyrus, and visual processing areas when viewing fearful faces in healthy adults. Similarly, Sripada and colleagues [34] found that alcohol attenuated amygdala activation to fearful and angry faces (contrasted with happy faces) in heavy social drinkers (defined as ≥ 10 drinks per week with 1–5 binge episodes). To examine the role of habitual drinking in these effects, Gilman et al. [35] compared activation in the amygdala to fearful and neutral faces in heavy drinkers (20–40 drinks per week) and social drinkers (1–14 drinks per week). The social drinkers exhibited the expected attenuation of amygdala response to fearful faces after intravenous alcohol, but the heavy drinkers did not show the expected increase in amygdala response during emotional faces even during the placebo session. This dampened response among heavy drinkers may indicate long-term blunted emotional responses in these individuals.

Other studies have examined the effects of alcohol on neural responses in brain areas typically involved in reward processing. Gilman et al. [33, 35] reported that alcohol increased activity in the nucleus accumbens in healthy social drinkers while viewing neutral faces. Moreover, in both studies, alcohol-related activation in the nucleus accumbens was positively correlated with subjective ratings of intoxication. These findings are consistent with the idea that alcohol increases the rewarding effects of social stimuli [36]. In heavy drinkers, a similar dose of alcohol failed to activate these brain regions and also failed to produce subjective reports of intoxication [35]. This may indicate tolerance to the effects of alcohol or a long-term change in reactivity to emotional stimuli. Many questions remain about how alcohol affects reward function, and whether it facilitates or dampens responses to different types of reward (e.g., social reward, monetary reward).

Some other studies suggest that alcohol may affect responses to emotional stimuli regardless of valence. Padula et al. [37] found that compared to placebo, alcohol diminished insula activation to emotional faces (contrasted with shape stimuli), regardless of whether the emotion displayed was happy, angry, or fearful. These researchers speculated that alcohol might decrease interoceptive awareness (i.e., attention to and evaluation of internal sensory signals) and reduce anticipatory processing of emotional faces, both of which would be consistent with emotional blunting. Diminished interoceptive awareness as a result of alcohol use could have short-term and long-term consequences on emotion processing, as perceptions of bodily states play an integral role in emotional experiences. In contrast to the other studies reviewed here, Padula and colleagues [37] failed to detect effects of alcohol on amygdala activation during presentation of negative emotional faces, despite using similar procedures.

In summary, alcohol-based phMRI studies suggest that alcohol affects emotional functioning in several ways. It can blunt responses to negative stimuli, perhaps providing relief of negative affective states. It can also enhance responses to neutral stimuli in reward-associated brain regions, further augmenting direct rewarding effects of alcohol; however, these effects are susceptible to change depending on the frequency of alcohol use. Finally, alcohol may alter interoceptive processing by dampening awareness to internal sensations, which may also contribute to emotional blunting.

Cannabinoids

Most studies of cannabinoids in healthy human participants focus on actions of the primary active constituent of cannabis,

Table 1 Studies examining phMRI of acute alcohol using emotion-related tasks in healthy human participants

Drug, dose, and reference	Sample	Emotion-related task used	Subjective effect measures	fMRI results	Subjective effects
Alcohol (0.08 g%, i.v.) Gilman et al., 2008	5 men, 7 women	Neutral and fearful face stimuli [8]	PANAS, BAES, DEQ	↓ Alcohol attenuated increased activation to fearful faces (vs. neutral faces) in amygdala, insula, parahippocampal gyrus, and visual processing areas compared to placebo. ↑ Alcohol increased striatal activation to neutral faces compared to placebo.	Feelings of intoxication were positively correlated with alcohol-induced increased activation in L-nucleus accumbens and L-caudate to neutral faces.
Alcohol (0.8 g/kg, oral) Sripada et al., 2011	10 men, 2 women	Emotional face assessment task [9•]	BAES	↓ Alcohol attenuated R-amygdala reactivity to fearful and angry faces (vs. happy faces) compared to placebo. ↓ Compared to placebo, alcohol decreased activation in regions of visual cortex and increased activation in superior frontal gyrus and superior, middle, and inferior temporal regions when viewing faces (vs. shape stimuli).	Subjective effects were not significantly correlated with alcohol-related changes in amygdala activation.
Alcohol (0.68 ml/kg for females or 0.75 ml/kg for males, oral) Padula et al., 2011	7 men, 5 women	Emotional face assessment task [10]	SHAS	↔ Amygdala activation did not differ between alcohol and placebo. ↓ Alcohol attenuated bilateral insula activation to faces (vs. shape stimuli) compared to placebo, regardless of whether the faces were happy, angry, or fearful.	Subjective responses were not directly compared to fMRI results.
Alcohol (0.08 g%, i.v.) Gilman et al., 2012	14 men (social drinkers), 14 men (heavy drinkers)	Neutral and fearful face stimuli [8]	BAES, DEQ	↓ Alcohol attenuated amygdala activation to fearful faces (vs. neutral faces) compared to placebo among social drinkers. Heavy drinkers showed no difference in amygdala responses to fearful faces (vs. neutral faces) at either session. ↑ Social drinkers had alcohol-related increases in activation in L-nucleus accumbens, R-cingulate gyrus, and temporal regions when viewing neutral faces.	Increased alcohol-related nucleus accumbens activation was positively related to subjective ratings of intoxication for social drinkers. Subjective ratings of intoxication were attenuated for heavy drinkers.

L left, *R* right, *PANAS* Positive and Negative Affect Scale [11], *BAES* Biphasic Alcohol Effects Scale [12], *DEQ* Drug Effects Questionnaire [13], *SHAS* Subjective High Assessment Scale [14]

Table 2 Studies examining phMRI of acute cannabinoids using emotion-related tasks in healthy human participants

Drug, dose, and reference	Sample	Emotion-related task used	Subjective effect measures	fMRI results	Subjective effects
THC (7.5 mg, oral) Phan et al., 2008	8 men, 8 women	Emotional face processing task [15•]	DEQ, VAS (stimulated, high anxious, sedated, hungry)	↓ THC attenuated R-amygdala reactivity to both fearful and angry faces (vs. happy faces) compared to placebo. ↑ THC increased amygdala responses to happy faces (vs. shape stimuli) compared to placebo.	THC attenuation of amygdala activation to fearful and angry faces was not significantly correlated with subjective effects of THC.
THC & CBD (10 mg THC, oral; 600 mg CBD, oral) Fusar-Poli et al., 2009	15 men	Facial expression of emotion: stimuli and tests [16•] Neutral faces, mildly fearful (50% fear), and intensely fearful (100% fear)	VAMS, STAI, AIS, PANSS	↓ THC decreased activation to fearful faces (vs. fixation) in R-inferior frontal gyrus, R-superior temporal gyrus, and L-medial frontal gyrus; ↑ increased activation in L-precuneus compared to placebo. ↓ CBD attenuated activation to fearful faces (vs. neutral faces) in L-anterior cingulate cortex, R-posterior cingulate, L-amygdala, and R-cerebellum compared to placebo.	THC significantly increased subjective ratings of anxiety, intoxication, and psychotic symptoms compared to placebo. CBD did not produce subjective effects that differed from placebo. Subjective drug responses were not related to neural responses to neutral or fearful faces.
THC & CBD (10 mg THC, oral; 600 mg CBD, oral) Fusar-Poli et al., 2010	15 men	Facial expression of emotion: stimuli and tests [16•] Neutral faces, mildly fearful (50% fear), and intensely fearful (100% fear)	VAMS, STAI, AIS, PANSS	↔ THC did not alter connectivity between anterior cingulate cortex and amygdala while viewing intensely fearful faces (vs. fixation) compared to placebo. ↓ CBD attenuated connectivity between anterior cingulate cortex and amygdala while viewing intensely fearful faces (vs. fixation) compared to placebo.	Connectivity was not assessed in relation to subjective drug responses.
THC (7.5 mg, oral) Rabinak et al., 2012	8 men, 8 women	Emotional pictures task (IAPS, [17])	DEQ, ARCI	↔ THC did not alter amygdala response, regardless of picture valence, compared to placebo. ↓ THC attenuated activity in subgenual anterior cingulate cortex while viewing negative (vs. neutral) pictures compared to placebo.	Changes in subgenual anterior cingulate cortex following THC were not correlated with subjective drug effects.
THC (6 mg + 3 × 1 mg, inhaled vapor) Bossong et al., 2013	11 men	Emotional face processing task ([15•]; fearful and happy faces only)	VAS (feeling high, internal perception, external perception, alertness, contentedness, calmness, anxiety)	↓ THC decreased activation to fearful faces (vs. shape stimuli) in bilateral occipital cortex and R-superior parietal gyrus compared to placebo. ↑ THC increased activation to happy faces (vs. shape stimuli) in R-supplementary motor area, compared to placebo.	Changes in brain activity as a result of THC were not significantly correlated with subjective drug response.
THC (7.5 mg, oral) Gorka et al., 2015	8 men, 8 women	Emotional face processing task [9•]	DEQ, VAS (stimulated, high anxious, sedated, hungry)	↑ THC increased functional connectivity between L-basolateral amygdala and R-rostral anterior cingulate cortex/medial prefrontal cortex when viewing angry and fearful faces (vs. happy faces), compared to placebo. ↔ THC did not alter functional connectivity between these regions when viewing happy faces (vs. shape stimuli).	THC-induced alterations in functional connectivity between amygdala and prefrontal cortex were not related to self-reported changes in affect or subjective drug effects.
THC (10 mg, oral) Bhattacharyya et al., 2017	14 men	Facial expression of emotion: stimuli and tests [16•]	STAI, AIS, PANSS	↑ THC increased R-amygdala activation while viewing fearful faces (vs. neutral faces) compared	CB1 receptor density in R-amygdala was also positively correlated with subjective reports of THC-induced anxiety.

Table 2 (continued)

Drug, dose, and reference	Sample	Emotion-related task used	Subjective effect measures	fMRI results	Subjective effects
		Neutral faces, mildly fearful (50% fear), and intensely fearful (100% fear)		to placebo. However, during the placebo session fearful faces *decreased* R-amygdala activation. ↑ PET imaging indicated that increased density of CB1 receptors in R-amygdala was associated with THC-related increases in R-amygdala activation when viewing fearful faces.	
THC (10 mg, oral) Colizzi et al., 2018	12 men (cannabis non-users), 12 men (modest cannabis users)	Facial expression of emotion: stimuli and tests [16•] Neutral faces, mildly fearful (50% fear), and intensely fearful (100% fear)	VAMS, STAI, AIS, PANSS	↑ THC increased activation of L-precuneus, cuneus, and L - posterior cingulate and decreased activation of left fusiform gyrus while viewing fearful faces (vs. neutral faces) compared to placebo among cannabis non-users.	Larger decreases in L-fusiform gyrus following THC were associated with increased severity of reported psychotic negative symptoms on the PANSS in cannabis non-users.

L left, *R* right, *IAPS* International Affective Picture System, *DEQ* Drug Effects Questionnaire [13], *VAS* Visual Analog Scale, *VAMS* Visual Analog Mood Scale [18], *STAI* State Trait Anxiety Inventory [19], *AIS* Analogue Intoxication Scale [20], *PANSS* Positive and Negative Syndrome Scale [21], *ARCI* Addiction Research Center Inventory [22]

Δ9-tetrahydrocannabinol (THC). Synthetic THC (e.g., dronabinol), like whole-plant cannabis, has inconsistent effects on mood and anxiety, sometimes enhancing mood and decreasing anxiety, and in other cases increasing anxiety (for a recent review on this topic, see [38]). Based on the phMRI studies reviewed here (Table 2), THC has inconsistent effects on neural responses to emotional stimuli. THC attenuated amygdala reactivity to fearful and angry faces [9•], and attenuated subgenual anterior cingulate cortex activation while viewing negative pictures [39]. Bossong et al. [40] found that THC decreased activation to fearful faces in bilateral occipital cortex and superior parietal gyrus. However, Fusar-Poli et al. [41] found mixed actions: THC decreased activation in frontal regions like inferior frontal gyrus, superior temporal gyrus, and medial frontal gyrus while subjects viewed fearful faces, but increased activation in precuneus. One study indicated that the effect of THC on response to emotional stimuli was related to individual differences in CB1 receptor density [42]. In this case, however, THC *increased* amygdala response to fearful faces compared to placebo. The increase in amygdala response was positively correlated with both amygdala CB1 receptor density and with subjective reports of THC-induced anxiety. Amygdala response during phMRI was largely unrelated to subjective drug effects. Additionally, only two studies reported effects of THC on neural responses to positive emotional stimuli. Phan and colleagues [9•] found that THC increased amygdala response to happy faces compared to shape stimuli, and Bossong et al. [40] found that THC increased activation to happy faces in supplementary motor area. Neither of these results was related to subjective effects of THC.

Several studies also assessed effects of THC on functional connectivity between amygdala and frontal brain regions while subjects viewed emotional stimuli. Gorka et al. [43] found that, as compared to placebo, THC increased functional connectivity between basolateral amygdala and prefrontal regions (rostral anterior cingulate cortex/medial prefrontal cortex) while viewing angry and fearful faces, which were combined to index social threat. THC did not alter functional connectivity between these regions when viewing happy faces. In contrast, Fusar-Poli et al. [44] also examined connectivity between anterior cingulate cortex and amygdala but did not find any differences between THC and placebo sessions. These findings on functional connectivity are somewhat unexpected and seem to indicate that acute THC might enhance emotion regulation under conditions of social threat.

In addition to THC, Fusar-Poli and colleagues [41, 44] also examined effects of cannabidiol (CBD) using phMRI while participants viewed fearful faces. Although CBD does not reliably produce detectable subjective effects, there is some evidence that it reduces anxiety [45]. Compared to placebo, CBD decreased activity in both the anterior and posterior cingulate, as well as the amygdala, while subjects viewed fearful

Table 3 Studies examining phMRI of acute analgesics using emotion-related tasks in healthy human participants

Drug, dose, and reference	Sample	Emotion-related task used	Subjective effect measures	fMRI results	Subjective effects
Oxycodone (10 mg, 20mg, oral) Wardle et al., 2014	10 men, 7 women	Emotional pictures task (IAPS, [23]) Emotional faces matching task [15•, 24]	DEQ, VAS (dreamy, nauseated), STAI, ARCI, POMS	↔ No differences were observed in amygdala or nucleus accumbens activity to emotional face stimuli or emotional pictures when comparing placebo with both doses of oxycodone. ↓ Oxycodone (20 mg) decreased activation in medial orbitofrontal cortex to happy faces (vs. neutral faces) compared to placebo. Oxycodone did not alter neural responses to angry or fearful faces.	Subjective effects of oxycodone were not directly compared with neural responses during emotional tasks.
Ketamine (0.12 mg/kg i.v. bolus + 0.25 mg/kg/hour i.v. infusion) Scheidegger et al., 2016a	12 men, 11 women	Emotional pictures task (IAPS, [23])	STAI, 5D-ASC	↓ Ketamine reduced activation in bilateral amygdala and bilateral hippocampus when viewing negative and neutral pictures compared to placebo. ↓ Ketamine reduced activation in bilateral amygdala and L-hippocampus when viewing positive pictures compared to placebo. Ketamine-induced reductions in amygdala and hippocampus were more pronounced for negative and neutral pictures, than for positive pictures.	Increased ketamine-induced alterations in consciousness were associated with reduced activation in bilateral amygdala and L-hippocampus while viewing negative stimuli.
Ketamine (0.12 mg/kg i.v. bolus + 0.25 mg/kg/hour i.v. infusion) Scheidegger et al., 2016b	12 men, 11 women	Berlin affective word list [25]	STAI, 5D-ASC	↓ Ketamine decreased activation while viewing negative stimuli in L-Insula and R-dorsolateral prefrontal cortex compared to placebo. ↓ Ketamine decreased activation in R-insula regardless of stimuli valence, compared to placebo.	Changes in brain activity as a result of ketamine were not significantly correlated with subjective drug response.
Ketamine (0.5 mg/kg i.v. infusion) Reed et al., 2019	6 men, 9 women	Emotional processing task [26, 27] Included sad, angry, happy, and neutral faces.	MADRS	↓ Ketamine attenuated activation in L-temporal gyrus and increased activation in a cluster including R-frontal gyrus, anterior cingulate and insula while viewing emotional faces, compared to placebo. Analyses of neural responses to emotional faces were not separated by emotion valence.	Neuroimaging results were not compared with subjective reports of depressive symptoms.

L left, *R* right, *IAPS* International Affective Picture System, *DEQ* Drug Effects Questionnaire [13], *VAS* Visual Analog Scale, *STAI* State Trait Anxiety Inventory [19], *ARCI* Addiction Research Center Inventory [22], *POMS* Profile of Mood States [28], *5D-ASC* Five Dimensional Altered States of Consciousness Scale [29], *MADRS* Montgomery-Åsberg Depression Rating Scale [30]

Table 4 Studies examining phMRI of acute stimulants using emotion-related tasks in healthy human participants

Drug, dose, and reference	Sample	Emotion-related task used	Subjective effect measures	fMRI results	Subjective effects
MDMA (0.75 mg/kg, 1.5 mg/kg, oral) Bedi et al., 2009	7 men, 2 women	Facial emotion recognition task Stimuli derived from Ekman & Friesen series of Pictures of Facial Affect	DEQ, VAS (stimulated, anxious, sedated, down, elated, sociable, nauseated), POMS	↓ High dose MDMA reduced L-amygdala reactivity to angry faces (vs. neutral faces) compared to placebo and low dose MDMA. ↑ Low dose MDMA enhanced ventral striatum activity to happy faces (vs. neutral faces) compared to placebo.	Neuroimaging results were not directly compared with subjective reports of drug effects.
Caffeine (250 mg, oral) Smith et al., 2012	14 men	Emotional face processing task [15•]	STAI, MAPSS	↑ Caffeine increased periaqueductal gray activation and decreased medial prefrontal cortex activation to angry and fearful faces (vs. happy faces) compared to placebo. ↔ Caffeine did not influence amygdala activation in response to angry and fearful faces (vs. happy faces) compared to placebo.	Participants with lower dietary intake of caffeine had higher caffeine-induced activation of basolateral amygdala for angry and fearful faces (vs. happy faces).
Modafinil (600 mg, oral) MDMA (125 mg, oral) Methylphenidate (60 mg, oral) Schmidt et al., 2018	12 men, 12 women	Facial expression of emotion: stimuli and tests [16•] Neutral faces, mildly fearful (50% fear), and intensely fearful (100% fear)	STAI, AMRS	↑ Modafinil increased brain activity during fearful face processing (vs. neutral face processing) compared to placebo in clusters containing (a) bilateral amygdala and anterior cingulate cortex, (b) R- putamen, pallidum, and supplementary motor area, and (c) L-pallidum, caudate nucleus, and thalamus. ↑ Modafinil also increased brain activity during fearful face processing (vs. neutral face processing) compared to MDMA in R-amygdala.	Increased modafinil-induced subjective feelings of fearfulness and depressiveness were positively correlated with brain activation in R-middle and inferior frontal gyrus while viewing fearful faces.

L left, *R* right, *DEQ* Drug Effects Questionnaire [13], *VAS* Visual Analog Scale, *POMS* Profile of Mood States [28], *STAI* State Trait Anxiety Inventory [19], *MAPSS* Mood, Alertness, and Physical Sensations Scale [31], *AMRS* Adjective Mood Rating Scale [32]

faces. CBD also attenuated connectivity between the anterior cingulate and amygdala, relative to placebo [44]. In contrast, THC decreased activation in frontal regions (IFG, superior temporal gyrus, and medial frontal gyrus) and increased activation in precuneus when viewing fearful faces compared to placebo [41]. Unlike CBD, THC did not appear to alter connectivity between anterior cingulate and amygdala [44].

Overall, cannabinoids appear to have some efficacy in attenuating amygdala reactivity to negative emotional faces (e.g., [9•, 41]), and some studies show evidence of attenuated responses in frontal regions (e.g., [39, 40]) and differential response to THC depending on stimuli valence (e.g., [9•, 40]). However, more recent work has also shown that THC can increase activation in posterior brains regions like the precuneus, cuneus, and posterior cingulate [46] as well as increase functional connectivity between basolateral amygdala and frontal regions [43] while processing negative emotional stimuli. Preliminary insight into the mechanism underlying THC effects on amygdala reactivity comes from ambitious studies assessing both phMRI and PET imaging. Specifically, data suggests that increases in amygdala reactivity to fearful faces following THC administration may be related to increased amygdala CB1 receptor density [42]. However, further combined phMRI and PET imaging work is needed to explore whether this finding applies more broadly to emotions other than fear and to different doses of THC.

There is little information linking the subjective effects of cannabinoid drugs with their neural effects. Although the effects of THC are known to vary across individuals, few studies have examined subjective responses to THC and CBD in relation to brain activity. The one exception is Colizzi et al. [46], who reported that decreased left fusiform activity while viewing fearful faces after THC administration was associated with increased severity of negative psychotic symptoms in cannabis non-users. More work is needed to understand the acute and chronic effects of cannabinoids on emotion processing, particularly as they relate to the subjective effects experienced. This is especially relevant considering the ever-increasing availability of cannabis as a result of continually evolving legal and recreational regulations.

Analgesics

Analgesic medications, or medications used to alleviate the experience of physical pain, have been shown to exert effects on "emotional pain" as well in recent years. Acute doses of pain-relieving medications, usually opioids, can blunt emotional reactivity to stimuli [47], and the long-term use of these medications can alter emotional responses as well. Ipser et al. [48] found that a small dose (0.2 mg) of the μ-opioid agonist buprenorphine acutely reduced sensitivity to fearful faces among healthy young adults, despite having no noticeable effects on mood. Similarly, Bershad et al. [49] found that buprenorphine reduced orienting attention to fearful faces, but not angry, sad, or happy faces. To our knowledge, no studies have yet examined these effects in relation to neural circuitry during emotion processing tasks. Few recent studies have used phMRI to examine the acute effects of opioids and other analgesics (e.g., ketamine) during emotion processing in healthy participants.

Only one study examining an opioid drug (oxycodone) with phMRI is included in Table 3. Wardle et al. [50•] did not find any differences in amygdala or nucleus accumbens activity between oxycodone and placebo while viewing emotional stimuli. However, they did find that a higher dose of oxycodone reduced activity in medial orbitofrontal cortex, a brain region often involved in reward processing and decision-making, while viewing happy faces compared to placebo. Importantly, this study was conducted with healthy volunteers who were deemed to be at low risk for developing opioid use disorder and the authors cite other work suggesting that the influence of oxycodone on emotional processing might be more pronounced in individuals at greater risk for developing opioid addiction (e.g., [51]). The ongoing opioid epidemic likely makes it difficult to continue pursuing phMRI research with opioid drugs considering their high abuse potential.

Beyond opioid medications, there has been some interest in the potential emotion-modulating effects of the analgesic acetaminophen, which have yielded mixed results. No study to our knowledge has investigated the effects of acetaminophen on responses to emotional facial expressions, but it has been shown to reduce neural responses to social rejection [52], and another study reported that acetaminophen blunted emotional ratings of both negative and positive images [47]. There have been few fMRI studies of the effects of acetaminophen on emotion processing, and this is an important area for future research.

Ketamine, a dissociative anesthetic drug that has recently garnered significant attention as a novel treatment for depression [53], has also been used to study emotion processing with phMRI. Sheidegger and colleagues [54] found that ketamine reduced brain activity to negative and neutral stimuli in amygdala and hippocampus, and reductions in activation while viewing negative stimuli were associated with greater subjective reports of altered consciousness as a result of ketamine. In a separate working memory task with the same participants, ketamine decreased activation in left insula and right dorsolateral prefrontal cortex to negative affective words, and decreased activation in right insula to positive, negative, and neutral words [55]. These findings are consistent with prior work that examined neural responses to emotional pictures 24 h after a single intravenous dose of ketamine and found decreased activation in pregenual anterior cingulate cortex while viewing negative emotional pictures, compared to a pre-ketamine baseline scan [56].

Ketamine also influences processing of emotional faces. Fearful faces elicited attenuated activity in the amygdala and

Table 5 Studies examining phMRI of acute psychedelics using emotion-related tasks in healthy human participants

Drug, dose, and reference	Sample	Emotion-related task used	Subjective effect measures	fMRI results	Subjective effects
Psilocybin (0.16 mg/kg, oral) Kraehenmann et al., 2015	16 men, 9 women	Amygdala reactivity task [15•] Negative and neutral stimuli only	PANAS, STAI	↓ Psilocybin attenuated R-amygdala reactivity to both negative and neutral face stimuli (vs. shape stimuli) compared to placebo.	Psilocybin-induced positive mood was correlated with attenuation of amygdala reactivity as a result of psilocybin.
LSD (100 μg, oral) Mueller et al., 2017	9 men, 11 women	Neutral faces, mildly fearful (50% fear), and intensely fearful (100% fear) Stimuli derived from Ekman & Friesen series of Pictures of Facial Affect	Single item VAS assessing subjective drug effects	↓ LSD attenuated activation in L-amygdala and R-medial frontal gyrus to fearful faces (vs. neutral faces) compared to placebo.	Attenuated amygdala reactivity to fearful faces as a result of LSD was correlated with subjective ratings of LSD-induced drug effects.

L left, *R* right, *PANAS* Positive and Negative Affect Scale [11], *STAI* State Trait Anxiety Inventory [19], *VAS* Visual Analog Scale

superior temporal gyrus following ketamine administration, and it also increased activation in visual processing regions and areas of the striatum when viewing neutral faces compared to fearful faces [57]. In contrast, Reed et al. [58] found that ketamine increased activation in frontal gyrus, anterior cingulate, and insula and decreased activation in left temporal gyrus while viewing emotional faces. While this study used both positive and negative emotional faces, the analyses considered all faces grouped together, not separated by stimulus valence, which might account for these discrepant results. Taken together, these studies suggest that ketamine acutely reduces brain activation to negative emotional stimuli, which could contribute to its efficacy as a treatment for patients with major depressive disorder.

Stimulants

Stimulant drugs produce inconsistent effects on emotional reactivity and its neural correlates (Table 4). Several studies have found that chronic use of stimulants affects neural responses to emotional stimuli: Bottelier et al. [59] found that amphetamine users had greater amygdala reactivity to fearful faces compared to controls, while Kim et al. [60] reported that abstinent methamphetamine users showed lower insula activity during negative emotional stimuli. In terms of acute administration, Bottelier and colleagues [59] found that methylphenidate did not alter amygdala activation in response to fearful faces for either amphetamine users or healthy controls. Schmidt et al. [61•] studied the acute effects of modafinil and methylphenidate on neural activity while healthy volunteers viewed fearful faces. Modafinil, but not methylphenidate, increased activation in the bilateral amygdala and anterior cingulate cortex, as well as parts of the striatum and thalamus. However, the dose of modafinil used in this study was three times the dose used to enhance cognitive performance in healthy participants. Smith et al. [62] examined the effects of caffeine on emotional stimuli using phMRI and found that it increased activation in periaqueductal gray, a part of the midbrain that is heavily involved in motivated and defensive behaviors, while participants viewed threat-related stimuli compared to placebo. In the same study, caffeine decreased medial prefrontal cortex activity to threat-related stimuli but did not affect threat-related amygdala activation. In addition to prototypical stimulants, researchers have also examined the acute effects of 3,4 methylenedioxymethamphetamine (MDMA) using phMRI. MDMA not only resembles other stimulant drugs in some ways (e.g., increasing cardiovascular reactivity and feelings of alertness) but also produces feelings of empathy and social connection (for review, see [63]). Bedi et al. [64] reported that MDMA reduced amygdala activity to angry faces, but not fearful faces, and increased activation in ventral striatum while viewing happy faces. Schmidt et al. [61•] also examined MDMA but did not find differences in neural responses to fearful faces compared to placebo, despite some behavioral evidence of MDMA-related impairment in fearful face recognition. Taken together, these findings suggest that some stimulant drugs (e.g., modafinil, caffeine) can increase neural reactivity to negative emotional stimuli in limbic and midbrain regions, while others (e.g., MDMA) can enhance reactivity to positive emotional stimuli. There are many remaining unknowns about the effects of stimulants on neural responses to emotional stimuli, and further work is needed to clarify differences across drugs, across drug doses, and across samples with varying histories of drug use.

Psychedelics

Several studies have examined the effects of psychedelic drugs on neural responses to emotional stimuli (Table 5). Kraehenmann and colleagues [65•] explored the effects of psilocybin on amygdala reactivity to negative and neutral pictures and found that psilocybin reduced amygdala reactivity compared to placebo. Moreover, these authors found that the extent of the decrease in amygdala reactivity was related to increases in subjective reports of positive mood. These findings are interesting in view of recent studies suggesting that psychedelics may have potential for treating depression (for review, see [66]).

In a recent behavioral study, Dolder et al. [67] found that both 100-μg and 200-μg doses of LSD impaired participants' abilities to identify fear on the facial emotion recognition task. Unfortunately, fMRI data were not collected in this study. However, Mueller and colleagues [68] did collect fMRI after a 100-μg dose of LSD and found decreased amygdala reactivity to fearful faces compared to placebo. This effect was correlated with subjective ratings of LSD-induced drug effects such that higher subjective responses were associated with greater attenuation of amygdala activity while viewing fearful faces. Other studies have investigated the potential emotion-modulation effects of very low "micro-doses" of LSD that are below the threshold necessary to produce subjective effects. For example, Bershad et al. [69] showed that even 13ug of LSD affects amygdala seed–based functional connectivity during resting state. The clinical implications of these effects of LSD are currently being evaluated by multiple research groups worldwide, and these studies have certainly helped shape the course of renewed interest in the therapeutic potential of psychedelic compounds, particularly for treating psychiatric disorders like depression and PTSD.

Conclusions

Overall, this review of the current literature finds that many psychoactive drugs do reduce neural responses to emotional stimuli in limbic brain areas like the amygdala. Alcohol consistently reduces amygdala reactivity to negative emotional stimuli like fearful faces. Results for cannabinoids are equivocal, particularly for THC, with studies finding both increased and decreased amygdala activity to emotional stimuli, as well as increased and decreased functional connectivity between amygdala and anterior cingulate cortex. CBD appears to attenuate amygdala reactivity and connectivity between the amygdala and anterior cingulate cortex, but fewer studies have examined CBD. Ketamine consistently reduces neural responses to emotional pictures regardless of valence, and effects are seen in areas beyond amygdala (e.g., hippocampus, insula, frontal regions). Some stimulants appear to increase reactivity to negative emotional stimuli, with the exception of MDMA, which was shown to attenuate amygdala reactivity to negative stimuli and enhance ventral striatum activity to positive stimuli. Finally, psychedelics appear to reduce amygdala activation to negative emotional stimuli, but these compounds have not yet been explored with positive emotional stimuli.

Further insights in this area will likely be driven by modifications to phMRI methodologies. For several of the presently reviewed studies (e.g., [41, 42, 44, 46]), data were collected with a 1.5T MRI scanner. It is likely that further advances in available technology, including more sensitive instruments (e.g., 7T MRI scanners) and declining costs will pave the way for more complete data. One further concern with phMRI studies is that because the primary metric of brain activity used by fMRI is BOLD response, drugs that promote or deter vasoconstriction or vasodilation could influence BOLD response independent of task-based effects. Additional scanning procedures (e.g., arterial spin labeling) may help disentangle the physiological effects of some drugs on BOLD response from the combined effects of drug and task.

Several limitations of the studies reviewed here are important to consider. First, reduced neural response is not necessarily indicative of diminished subjective experiences of emotion. Some studies attempt to address this issue by reporting correlations between drug-induced changes in brain activation and subjective reports of drug effects or emotional response, but this information is not widely available across studies. Second, the tasks reviewed here focused on emotional stimuli, but did not include emotion-related experiences like receiving a monetary reward. Other phMRI studies are available on this topic, particularly those investigating the effects of stimulant drugs. Third, the present review focused on acute drug effects; however, another important area of investigation is the influence of repeated drug use on emotion processing. Prolonged substance use is likely to alter neural responses, particularly in emotional contexts, as tolerance for substances increases, and some studies have shown that both neural responses and subjective drug effects are blunted in heavy users (e.g., [35, 46]).

Future Directions

The studies reviewed here reflect the current, incomplete picture of how drugs affect neural responses to emotional stimuli. Future work is needed to understand the relationships between effects of drugs on neural activity, especially in limbic regions and behavioral and self-report measures of affect. Understanding the circuits through which drugs produce cognitive and emotional effects will help to minimize risks, and optimize benefits, from drug administration.

This review identified several gaps and inconsistencies in the current literature. Importantly, we found a dearth of

phMRI studies with drugs that are at the center of significant current public health crises, notably opioids and methamphetamine. Individuals with opioid use disorder [70] or methamphetamine use disorder [71] exhibit deficits in emotion recognition and social cognition, suggesting that these deficits may either predate and predispose certain people to use these drugs, or reflect the consequences of prolonged use. Our review also revealed inconsistencies in the effects of certain drugs, in particular cannabinoids such as THC and CBD. Not only are the effects of these drugs on neural function inconsistent but also the drug-induced changes in neural responses were largely unrelated to subjective effects (if any) experienced by participants. phMRI studies with cannabinoids are urgently needed to understand the sources of variability in response to this category of drugs.

Future phMRI studies will likely be able to capture a more nuanced understanding of emotion processing by using more immersive and ecologically valid tasks. For example, most of the studies reviewed here used stimuli that consist of static pictures of faces posed in emotional expressions, while dynamic emotional stimuli, such as faces that morph into an emotion, provide a more sensitive measure [72]. Other types of emotional stimuli such as movie clips (e.g., [73]), can elicit a wider range of emotional experiences, allowing for comparisons regarding tonic and dynamic aspects of emotion processing (e.g., [74]). In summary, the results of this review raise questions that can be addressed empirically, in innovative ways, to improve our understanding of the motivations for and emotional implications of use of these drugs for non-medical purposes.

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