

REVIEW ARTICLE THEMED ISSUE

Opioid system and human emotions

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Emotions are states of vigilant readiness that guide human and animal behaviour during survival-salient situations. Categorical models of emotions posit neurally and physiologically distinct basic human emotions (anger, fear, disgust, happiness, sadness and surprise) that govern different survival functions. Opioid receptors are expressed abundantly in the mammalian emotion circuit, and the opioid system modulates a variety of functions related to arousal and motivation. Yet, its specific contribution to different basic emotions has remained poorly understood. Here, we review how the endogenous opioid system and particularly the μ receptor contribute to emotional processing in humans. Activation of the endogenous opioid system is consistently associated with both pleasant and unpleasant emotions. In general, exogenous opioid agonists facilitate approach-oriented emotions (anger, pleasure) and inhibit avoidance-oriented emotions (fear, sadness). Opioids also modulate social bonding and affiliative behaviour, and prolonged opioid abuse may render both social bonding and emotion recognition circuits dysfunctional. However, there is no clear evidence that the opioid system is able to affect the emotions associated with surprise and disgust. Taken together, the opioid systems contribute to a wide array of positive and negative emotions through their general ability to modulate the approach versus avoidance motivation associated with specific emotions. Because of the protective effects of opioid system-mediated prosociality and positive mood, the opioid system may constitute an important factor contributing to psychological and psychosomatic resilience.

Abbreviations

BOLD, blood oxygenation level dependent; fMRI, functional MRI; PAG, periaqueductal grey; PTSD, post-traumatic stress disorder

Introduction

Experiences of pleasure and distress colour our days vividly. It would be difficult to imagine how human life would be if we did not feel the dizzying excitement while going out with our new date, or the devastating grief upon hearing of a loss of a loved family member. A century of research has revealed that such feelings result from the activation of evolutionary old emotion systems that guide human and animal behaviour during survival-salient situations by adjusting the activation of the cardiovascular, skeletomuscular, neuroendocrine and autonomic nervous system (ANS) as well as higher-order cognitive functions (Levenson, 2003). Emotions are thus states of vigilant readiness that organize our lives by automatically orienting actions and governing approach versus avoidance motivation (Lang, 1995; Elliot *et al.*, 2013).

Both human and animal studies have confirmed that large-scale neural circuits spanning from the midbrain to the neocortex are intimately involved in triggering the emotion-specific survival responses. So-called categorical emotion models (Figure 1) specifically argue that evolution has shaped a limited set of basic emotions (typically anger, fear, disgust, happiness, sadness and surprise) with distinct neural and physiological substrates to support specialized

survival functions (Panksepp, 1982; Ekman, 1992). These basic emotions are also characterized by distinctive subjective feelings (such as 'I feel happy'), culturally universal expressions and have a discrete physiological and functional neural basis (Kreibig, 2010; Tracy and Randles, 2011; Nummenmaa *et al.*, 2014; Saarimäki *et al.*, 2016). However, it has also been proposed that behavioural, physiological and subjective activation patterns of emotions could be explained by lower-order systems, typically one governing pleasure versus displeasure ('valence') and another governing calmness versus arousal. The relative activity of these systems could then generate different patterns of emotional behaviour and experiences (Russell, 1980; Lang, 1995).

Among the three types of opioid receptors (μ receptor, δ receptor and κ receptor), the μ receptors mediate the effects of endogenous β -endorphins, endomorphins, enkephalins and various exogenous opioid agonists. The predominant action of μ receptor agonists in the nervous system is inhibitory, but they also have excitatory effects. Consequently, it is possible that the endogenous opioid system could contribute to emotional processing either by having a distinct influence on specific basic emotions, or by modulating the activity of the lower-order systems (valence and arousal), or the approach-avoidance motivation associated with each emotion. Here, we review recent human neuroimaging and pharmacological studies on the opioidergic basis of the basic emotion circuits. Our review will focus primarily on the μ receptor system, because it is currently the most well-studied system in humans.

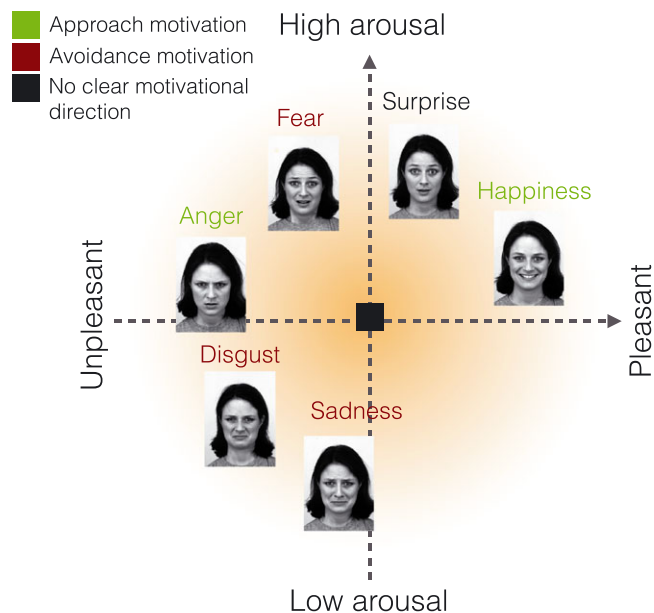


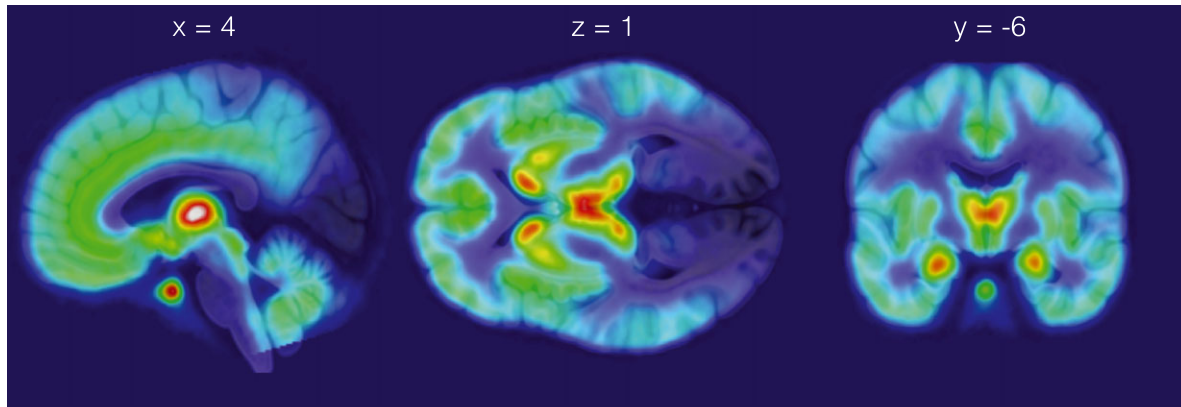
Figure 1

Theoretical models of emotions. The most widely accepted view considers emotions as discrete functional systems, so that each of them is specialized for a different survival function (Ekman, 1992; Panksepp, 1982). Dimensional models of emotion in turn explain behavioural, physiological and subjective similarity across emotions by lower-order dimensions or systems (typically one for pleasure-displeasure and another for calmness-arousal), whose relative activity may generate different patterns of emotionality (Russell, 1980). Both types of models assume, at least implicitly, that approach-avoidance motivation is an important property of all emotional states, partially independent of pleasure and arousal (Elliot *et al.*, 2013). Face stimuli are reprinted with permission from (Lundqvist *et al.*, 1988).

Opioid system and human emotion circuits

In humans, cerebral μ receptor availability and endogenous opioid release can be quantified *in vivo* by PET, using the μ receptor-selective radiotracer [^{11}C]-carfentanil (Figure 2A) and non-selective opioid receptor radioligands [^{18}F]-FDPN and [^{11}C]-DPN. Human PET studies suggest that the μ receptors are expressed abundantly in the brain circuits supporting emotional processing. To quantify the spatial overlap between the μ system and emotion circuits, we first computed the similarity of cerebral μ receptor distribution (average [^{11}C]-carfentanil BP_{ND} from 89 scans) with meta-analytic maps of emotion-specific activations in functional MRI (fMRI) studies in the Neurosynth database. This tool allows automated meta-analysis of brain activations observed in tens of thousands of fMRI studies (Yarkoni *et al.*, 2011; analysis date 15 November 2016). We searched the database separately for each basic emotion and related terms (Table 1) and retrieved the forward inference map of statistically significant (false discovery rate, <0.01) activations for each query. Subsequently, spatial correlations between the [^{11}C]-carfentanil BP_{ND} distribution and the emotion-wise activation maps derived from Neurosynth were computed. A separate map was also computed by combining all the emotions together. The results (Figure 2B) revealed consistent emotion-dependent activations in the μ receptor rich areas in the brain. A particularly reliable overlap was observed for happiness, pleasure and reward ($r = 0.44$) as well as for fear

A Distribution of μ receptors in the brain as measured with [^{11}C]carfentanil PET



B Overlap between human emotion circuit and the μ receptor system

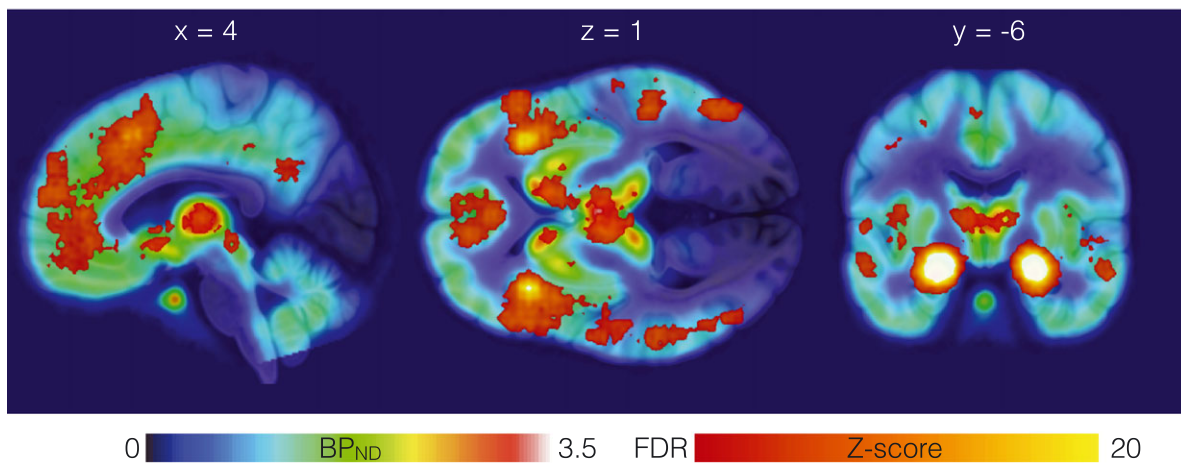


Figure 2

Overlap between the human emotion circuit and the μ receptor system. (A) Distribution of μ receptors in the human brain. Mean non-displaceable binding potential (BP_{ND}) image of 89 PET scans from healthy volunteers with the MOR-selective agonist radioligand [^{11}C]carfentanil. (B) Brain regions responding consistently (forward inference) during emotional experience and perception in fMRI studies in NeuroSynth meta-analysis ($n_{\text{studies}} = 1609$, $P < 0.05$ false discovery rate corrected) overlaid on the mean distribution of μ receptors as measured by [^{11}C]carfentanil PET.

Table 1

Search terms, number of studies included in the NeuroSynth meta-analyses and spatial correlation (r) with the emotion-specific meta-analytic activation patterns and μ receptor distribution in the brain

Target emotion	Search terms	Number of studies	Correlation (r) with μ receptor distribution
Anger	Anger, angry	175	0.18
Disgust	Disgust, disgusted, disgusting	78	0.20
Sadness and depression	Sad, sadness, depressive, depression	502	0.30
Fear and anxiety	Fear, fearful, anxiety, anxious	663	0.31
Happiness and reward	Happy, happiness, reward, rewarding	920	0.44
Surprise	Surprise, surprised	0	n/a
Emotion (unspecified)	Emotion, emotional	1609	0.38

All correlations shown are significant at $P < 0.001$

and anxiety ($r = 0.31$), whereas the least consistent effects were found for anger ($r = 0.18$), all P values < 0.001 .

The above results, however, only reveal overlap between μ receptor expression and emotion-driven blood oxygenation level dependent (BOLD) responses and do not provide causal evidence for μ receptor activation during emotion. To test this issue directly, we conducted a meta-analysis of opioidergic responses during emotions as quantified by PET in healthy volunteers. Altogether, 15 studies, 254 subjects and 149 foci were included in the analysis (Table 2). Summary maps were generated using the activation likelihood estimation-based meta-analysis of neuroimaging data as implemented in the GingerALE programme (Eickhoff *et al.*, 2005; 2009). Briefly, in this approach, activation coordinates reported in original studies are modelled as Gaussian kernels, and their net distribution is compared against a random distribution with permutation testing. To maximize statistical power in the small sample, we did not initially differentiate between positive and negative emotions in the analysis.

The analysis (Figure 3) revealed consistent emotion-dependent μ receptor activation in the key components of the emotion circuit, including regions involved in emotional saliency encoding and fear learning (amygdala and hippocampus), arousal and alertness modulation (thalamus) and appetitive motivation and reward (ventral and dorsal striatum). Despite significant cortical μ receptor expression (Figure 2A) and the contribution of the neocortex to emotional processing (Kober *et al.*, 2008), this analysis did

not reveal consistent emotion-driven cortical μ receptor responses. Essentially a similar pattern of results was observed when only negative emotions were included in the analysis. For positive emotions, activations were observed only in the left amygdala. However, it must be borne in mind that this analysis has significantly less statistical power, and more imaging work on endogenous opioid release during positive emotions in humans is required. Altogether these results suggest that the opioid system is in an excellent position for regulating the activity of specific emotions systems. We will next review its contribution to each of the six basic emotions.

Positive emotions: pleasure, happiness and euphoria

The mesolimbic reward system promotes motivated behaviour towards primary rewards that are essential for survival and homeostasis, such as eating and mating. The powerful pleasurable sensations upon receiving or consuming rewards promote subsequent repetition of the behaviour. Although **dopamine** is often considered as the principal neurotransmitter responsible for reward processing, opioids produce reward independently of dopamine (Hnasko *et al.*, 2005). In animals, μ receptor stimulation increases both the incentive motivation to seek food and the rewarding effects of food (Berridge *et al.*, 2010), and the injection of μ receptor agonists into the mesolimbic reward system is rewarding in its own

Table 2

Studies included in the ALE meta-analysis on μ receptor activation during emotions

Study	Experimental manipulation	Measured emotions	PET radioligand	Target molecule	Sample size
Bencherif <i>et al.</i> (2002)	Pain stressor	Pain	[¹¹ C]-carfentanil	μ receptor	8
Boecker <i>et al.</i> (2008)	Physical exercise	Euphoria, happiness	[¹⁸ F]-FDPN	$\mu/\delta/\kappa$ receptor	10
Burghardt <i>et al.</i> (2015)	Food consumption	Positive and negative affect	[¹¹ C]-carfentanil	μ receptor	7
Hsu <i>et al.</i> (2013)	Social acceptance versus rejection	Happiness, sadness	[¹¹ C]-carfentanil	μ receptor	18
Koepp <i>et al.</i> (2009)	Pleasant videos, music and mental imagery (pleasure)	Positive and negative affect	[¹¹ C]-DPN	$\mu/\delta/\kappa$ receptor	25
Prossin <i>et al.</i> (2016)	Mental imagery (sadness)	Negative affect	[¹¹ C]-carfentanil	μ receptor	28
Scott <i>et al.</i> (2007)	Pain stressor	Pain	[¹¹ C]-carfentanil	μ receptor	14
Scott <i>et al.</i> (2008)	Pain stressor	Pain	[¹¹ C]-carfentanil	μ receptor	20
Smith <i>et al.</i> (2006)	Pain stressor	Pain	[¹¹ C]-carfentanil	μ receptor	10
Wager <i>et al.</i> (2007)	Pain stressor	Pain	[¹¹ C]-carfentanil	μ receptor	15
Wey <i>et al.</i> (2014)	Pain stressor	Pain	[¹¹ C]-DPN	$\mu/\delta/\kappa$ receptor	8
Zubieta <i>et al.</i> (2001)	Pain stressor	Pain	[¹¹ C]-carfentanil	μ receptor	20
Zubieta <i>et al.</i> (2002)	Pain stressor	Pain, positive and negative affect	[¹¹ C]-carfentanil	μ receptor	28
Zubieta <i>et al.</i> (2003a)	Pain stressor	Pain, positive and negative affect	[¹¹ C]-carfentanil	μ receptor	29
Zubieta <i>et al.</i> (2003b)	Mental imagery (sadness)	Positive and negative affect	[¹¹ C]-carfentanil	μ receptor	14

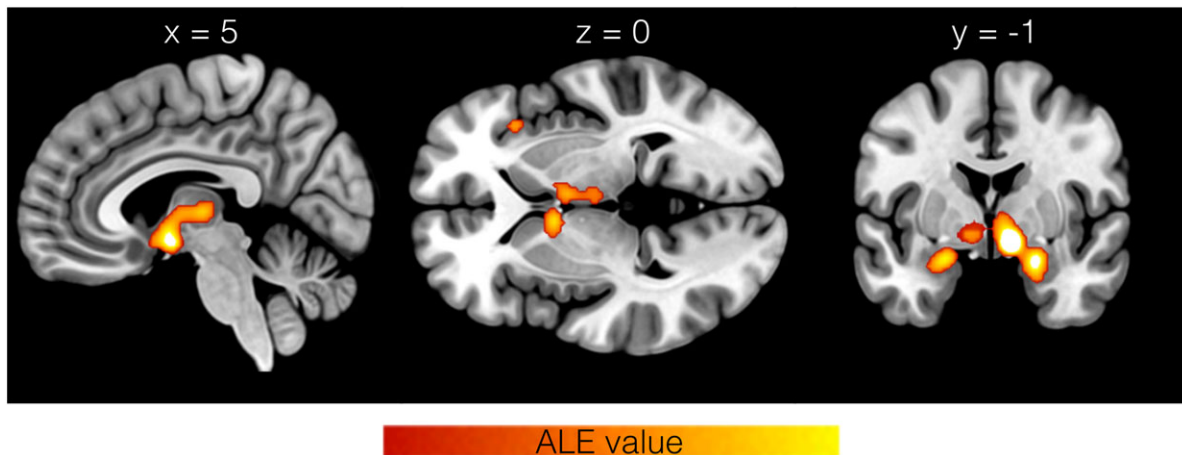


Figure 3

Opioidergic responses to emotions measured with PET. ALE meta-analysis map shows that limbic components of the emotion–motivation circuit show consistent opioidergic responses during emotional stimulation. The data are thresholded at $P < 0.05$, false discovery rate corrected.

right (Bozarth and Wise, 1981). Opiate addicts perceive sweetness as more pleasant than drug-naïve controls, and this effect is reversible by opioid antagonists (Langleben *et al.*, 2012; Green *et al.*, 2013). Similarly, in healthy volunteers, the opioid receptor blocker **naloxone** attenuates pleasure and concurrent BOLD responses to rewards in the anterior cingulate cortex (Petrovic *et al.*, 2008). Yet, in contrast to other rewards, μ receptor agonists decrease sexual desire and pleasure (Argiolas and Melis, 2013). Over 50% of patients on **methadone** maintenance treatment suffer from sexual dysfunction, most commonly due to decreased desire and libido (Yee *et al.*, 2014). This may be due to opioids' effects on **testosterone** and **oxytocin** levels, or more speculatively, saturation of the brain's reward centres (Argiolas and Melis, 2013).

Endogenous opioids may also be released during reward consumption and positive moods in humans. Food consumption and social acceptance trigger opioid release, as quantified by the μ receptor selective tracer [^{11}C]-carfentanil (Hsu *et al.*, 2013; Burghardt *et al.*, 2015). Similarly, euphoria triggered by strenuous physical exercise has been suggested to be linked to opioid release in the anterior cingulate, orbitofrontal and insular cortices, as quantified with the non-selective tracer [^{18}F]-**diprenorphine** (Boecker *et al.*, 2008). Finally, a self-induced positive mood was found to correlate with changes in [^{11}C]-diprenorphine binding in the amygdala (Koepp *et al.*, 2009). One early PET study also found that a high dose of oral **amphetamine** displaces the μ receptor selective tracer [^{11}C]-carfentanil and the resulting euphoric feelings correlate with this displacement in the ventral striatum. However, this finding has not been subsequently replicated (Guterstam *et al.*, 2013; Mick *et al.*, 2014).

Opioids are among the most commonly used illicit drugs in the USA, where 2.1% of the population have had an opioid use disorder during their lifetime (Grant *et al.*, 2016). The most important reason for their misuse is 'liking', the change in the subjective experience produced by the drugs (Comer *et al.*, 2012). Studies in opioid naïve subjects have found an increase in euphoria or pleasure upon administration of μ receptor agonists (Zacny and Gutierrez, 2003; Zacny and

Gutierrez, 2009; Riley *et al.*, 2010). However, numerous studies have failed to corroborate the finding (Lasagna *et al.*, 1955; Tedeschi *et al.*, 1984; Ipser *et al.*, 2013), for which there are a number of possible reasons. Firstly, the μ receptor agonists may have a biphasic effect on mood, where initial euphoric feelings are followed by dysphoria (Zacny *et al.*, 1992). Secondly, drug properties, such as its affinity for the μ receptor, administration route and dosage, genetic variations in the opioid system (Levrán *et al.*, 2012) and environmental factors, such as previous exposure to exogenous opioids (Comer *et al.*, 2010), may also play a role. Finally, the circumstances and baseline mood state in which the opioids are consumed interact with their effects. It is possible that opioid agonists' mood-altering potency is greatest when the individual is already in a dysphoric mood, and when the subject is in a neutral or slightly positive mood (as individuals tend to be, see Diener and Diener, 1996), the mood-altering potency of opioids would be more limited.

In summary, opioid agonists may produce euphoric effects and modulate the hedonic effect of other rewards such as food in humans. There is also evidence suggesting opioids are released during reward consumption and reception. However, more research is needed on the boundary conditions in which opioid agonists actually trigger subjective feelings of pleasure or euphoria, and what the temporal profile of opioid-induced rewarding sensations is.

Fear and anxiety

The mammalian fear circuit governs fight-or-flight responses when encountering physical or psychological threats. This circuit consists of a complex set of midbrain and medial temporal lobe structures [in particular, the amygdala, hippocampus and periaqueductal grey (PAG) matter] interacting with prefrontal systems accessing conscious feelings, thus allowing mammals to cope with acute and distal threats (Mobbs *et al.*, 2007). Although the serotonergic system plays a critical role in avoidance behaviour, fear, and anxiety (Deakin and Graeff, 1991), the majority of animal

data suggest that opioid agonists have an inhibitory effect on the mammalian fear circuit.

In rodents, μ receptor agonists administered either systemically or directly into the amygdala attenuate fear conditioning (Davis, 1979; Good and Westbrook, 1995). Accordingly, inhibiting the enzymatic degradation of opioids in the ventrolateral PAG accelerates fear extinction (McNally, 2005) whereas the opioid receptor antagonist naloxone injected into the same region inhibits fear extinction (McNally and Westbrook, 2003). Opioid agonists also reduce unconditioned fear when injected into the hippocampus and amygdala (Zarrindast *et al.*, 2008), whereas **naltrexone** injection into the amygdala blocks the anxiolytic effects of benzodiazepines (Burghardt and Wilson, 2006). Although the majority of evidence from pharmacological manipulation studies in animals suggests that μ receptor agonists are anxiolytic, contrary evidence also exists. For instance, Wilson and Junor (2008) showed that a μ receptor agonist injected into the central nucleus of the amygdala increased unconditioned fear in rats. Likewise, μ receptor knock-out mice are less anxious than wild-type mice (Filliol *et al.*, 2000). Interestingly, the effect of this genotype could be reversed by blocking δ receptors, which the authors suggested might be due to homeostatic interactions between the two receptor types. Accordingly, animal studies have shown that systemically administered δ receptor agonists decrease and antagonists increase anxiety (Chu Sin Chung and Kieffer, 2013).

The most compelling evidence showing that opioid agonists reduce clinical anxiety in humans comes from studies investigating the effects of opioids on the development of post-traumatic stress disorder (PTSD) (Saxe *et al.*, 2001; Bryant *et al.*, 2009; Holbrook *et al.*, 2010). Despite being uncontrolled cohort studies, these data suggest that **morphine** administration following an acute trauma could decrease the likelihood of subsequent PTSD. This effect is presumably mediated *via* inhibition of fear conditioning following the traumatic event and consequently protects against PTSD. However, in addition to *de facto* local attenuation of the fear circuit, the fear-reducing effect of opioid agonists could also equally well result from the down-regulation of the sensory processing of the fear-eliciting stimulus, increased (sensory or psychological) pain threshold or simply generalized sedation.

Liberzon *et al.* (2007) examined the μ receptor availability changes associated with PTSD and found that μ receptors were up-regulated in the orbitofrontal cortex and down-regulated in the amygdala and anterior cingulate cortex in PTSD patients exposed to combat, when compared to healthy controls. However, compared with the controls exposed to combat, the PTSD patients had decreased μ receptor availability in the orbitofrontal cortex and increased availability in the amygdala, rendering the results difficult to interpret. This is further complicated by a lack of data on the link between anxiety disorders and *in vivo* μ receptor levels, and conflicting results on the association between receptor availability and the personality traits associated with anxiety in healthy individuals (Tuominen *et al.*, 2012; Karjalainen *et al.*, 2016).

The findings from human experimental studies in healthy individuals are somewhat discordant. Firstly, the opioid

receptor agonist **oxycodone** had no effect on the subjective or neural responses to negative emotional images, suggesting that opioids do not significantly contribute to sensory emotional processing (Wardle *et al.*, 2014). Similarly, the partial opioid receptor agonist **buprenorphine** did not reduce anxiety during the Trier social stress test in drug-naïve volunteers, even though the cortisol responses were reduced (Bershad *et al.*, 2015). However, one fMRI study found that the opioid receptor antagonist naloxone enhanced Pavlovian fear conditioning and BOLD responses in the amygdala (Eippert *et al.*, 2008). Parallel inconsistencies also exist in human studies where naloxone has been used to either modulate the panicogenic effects of CO₂ inhalation or **lactate** infusion, or to treat anxiety disorders (Colasanti *et al.*, 2011).

In summary, animal studies in general show that μ receptor activation reduces fear learning and unconditioned fear responses, whereas their blockage facilitates these same processes. However, whether endogenous opioids are released in a fearful or anxiogenic situation has not been investigated in either animals or humans. Therefore, more research is needed to show the link between anxiety and the μ receptor system, as, in general, human studies have provided somewhat contradictory evidence. Most importantly, there is currently insufficient evidence that the pathophysiology of anxiety disorders is as a result of a dysfunctional opioid system.

Sadness and depression

Sadness is primarily triggered by social losses. Expressions of sadness recruit our social network to support us and unite during times of distress. Accordingly, neurobiological underpinnings of sadness in humans involve the PAG, dorsomedial thalamus and anterior cingulate cortices, regions that are implicated in separation distress in nonhuman mammals (Panksepp, 2003). Experimental studies in healthy volunteers have found that opioid antagonists trigger dysphoria (Grevert *et al.*, 1983; Delcampo *et al.*, 1992) and amplify negative feelings triggered by losses (Petrovic *et al.*, 2008). Transient sadness states also trigger deactivation of the μ receptor system in healthy subjects (Zubieta *et al.*, 2003b). Similar to sustained sadness, negative emotions triggered by social rejection (c.f. separation distress in animals) can also cause alterations in endogenous opioid release (Hsu *et al.*, 2013), and these effects are attenuated in depression (Hsu *et al.*, 2015).

Mounting evidence linking opioids and the sadness circuit comes from studies on depression, the psychiatric condition most clearly linked with sadness. Animal models of depression have demonstrated that buprenorphine has antidepressant-like effects that are mediated through both partial agonism of μ receptors and antagonism of κ receptors (Falcon *et al.*, 2016; Robinson *et al.*, 2016). A number of clinical studies have supported the notion that buprenorphine could be an effective treatment for refractory depression (Bodkin *et al.*, 1995; Nyhuis *et al.*, 2008), an effect that may be mediated through opioid receptors different from μ receptors in humans (Ehrich *et al.*, 2015).

Post-mortem measurements of μ receptor binding in suicide victims have yielded mixed results, with some studies finding higher binding (Gross-Isseroff *et al.*, 1990; Gabilondo *et al.*, 1995), some lower binding (Scarr *et al.*, 2012) and some no difference at all (Zalsman *et al.*, 2005). There are only two *in vivo* studies of μ receptor availability in depression. The first one found lower binding in the thalamus of depressed subjects (Kennedy *et al.*, 2006), but this study used a radiotracer displacement paradigm where interpretation of the baseline group differences is challenging. Additionally, a subsequent study failed to replicate this baseline difference (Hsu *et al.*, 2015). In conclusion, animal models and clinical studies on depression corroborate the idea that the opioid system underlies aspects of sadness and dysphoria. Nevertheless, the evidence regarding altered opioidergic neurotransmission in depression is still inconclusive.

Anger and aggression

The anger system mobilizes psychological and physiological resources for taking corrective actions against conspecifics that have threatened our mental or somatic well-being, thus leading to strong approach motivation. An acute injection of an opioid agonist temporarily reduces aggressive behaviour in mice (Espert *et al.*, 1993). However, in humans, the acute effects of opioid agonists seem to be the opposite of those in mice. Both **codeine** and morphine, administered acutely, increase laboratory-induced aggression in healthy volunteers (Spiga *et al.*, 1990; Berman *et al.*, 1993). These data parallel experimental work showing that acute anger episodes increase pain thresholds, interpreted as the result of endogenous opioid release (Janssen *et al.*, 2001). Opioid release during a fit of anger could function as a pre-emptive antinociceptive effect preceding a possible physical conflict. Conversely, the opioid antagonist naltrexone blocks anger-induced analgesia (Burns *et al.*, 2009). Further evidence comes from studies showing that an elevated propensity to experience anger is associated with a lowered pain threshold, possibly due to aberrant analgesic control *via* the endogenous opioid system (Bruehl *et al.*, 2002; 2003). Even though these studies are limited in number, they suggest that opioid agonists and antagonists may have opposing effects on anger and aggression in humans. However, to our knowledge, there are no human imaging studies on opioid release and anger. Moreover, the disparity between the human and mouse data makes their interpretation challenging. They may, however, reflect the different social functions of aggression and anger across species, or alternatively the general social-motivational state of the laboratory animals compared to the human subjects.

Disgust and surprise

Of the six basic emotions, only disgust and surprise have not been conclusively linked with the opioid system. The disgust system prevents intoxication and diseases by steering us clear from harmful substances, thus engaging the individual in avoidance behaviour. Nausea – the most common physiological symptom associated with the disgust emotion

– is a relatively common side-effect of exogenous opioid agonists (Furlan *et al.*, 2006), possibly mediated through the peripheral effects of the opioids. However, the nausea triggered by purely interoceptive changes is functionally distinct from the disgust triggered by an external stimulus (such as the smell of rotten meat), and the effects of the opioid system on disgust remain largely unresolved.

The emotion of surprise, in turn, acts as a ‘circuit breaker’ terminating our on-going actions when we encounter something not fitting with our expectations. Surprise can thus be both positive (e.g. winning in a lottery) and negative (e.g. being suddenly dismissed from our job), and it is not clearly associated with either approach or avoidance motivation. The opioid system may contribute to this type of novelty detection, as opioid receptors in the midbrain PAG regulate error prediction (McNally and Cole, 2006), and because large prediction errors could be considered as the most surprising events. But, as in the case of disgust, the exact contributions of the opioid system to surprise have not been clarified.

Opioids, affiliation and social emotions

Emotions are predominantly social functions. They manage our interpersonal behaviour in multiple ways, most saliently by promoting the establishment and maintenance of interpersonal bonds through strong pleasant sensations associated with social affiliation. The opioid system is intimately involved in social bonding and pleasure triggered by social contact, and it has been proposed that social and altruistic behaviours may have evolved from more elementary circuits that support nociception and analgesia (Panksepp *et al.*, 1978). Opioid antagonists promote social grooming and grooming solicitations in nonhuman primates, suggesting that endogenous opioid tone modulates attachment behaviour (Fabre-Nys *et al.*, 1982; Keverne *et al.*, 1989; Graves *et al.*, 2002). Exogenous opioid agonists similarly alleviate separation distress in puppies (Panksepp *et al.*, 1978), and bonding in monogamous adult voles is dependent on μ receptor activation (Burkett *et al.*, 2011; Resendez *et al.*, 2013).

Paralleling the animal data, genetic studies in human adults have found that the minor allele (G) of the OPRM1 A118G polymorphism is associated with avoidant social attachment (Troisi *et al.*, 2011). The OPRM1 A118G polymorphism is a single nucleotide polymorphism in the exon1 of the μ receptor gene distributed according to the Hardy–Weinberg equilibrium in the population (Bergen *et al.*, 1997). The G variant is a hypomorph decreasing the expression of μ receptors (Zhang *et al.*, 2005; Pecina *et al.*, 2015) but not their affinity (Mague *et al.*, 2009). Conversely, frontocortical μ receptor availability measured with PET is positively associated with the tendency to establish intimate social relationships in humans (Nummenmaa *et al.*, 2015), and social touching – the human equivalent of social grooming – also modulates opioidergic activity (Nummenmaa *et al.*, 2016). Finally, behavioural studies have found that pain threshold – a proxy of endogenous opioid release in the pain circuit or generally in the CNS – is increased by social behaviours promoting intragroup affiliation (Dunbar *et al.*, 2012; Tarr *et al.*, 2016), suggesting that endogenous opioid

release may have a causal role in the establishment of social structures in humans.

The opioid system is also involved in empathy, that is, the tendency to re-enact others' emotional states in the observer's own mind and body. Functional MRI studies have shown that the opioidergic link of the human affective pain system is engaged similarly during first-hand pain experience and when seeing others in distress (Singer *et al.*, 2004). Opioid-mediated placebo analgesia reduces empathetic concerns and activity in the brain's empathy circuit when seeing others suffering pain, and conversely, naltrexone increases unpleasant feelings and first-hand experience of pain even when seeing others being hurt (Rutgen *et al.*, 2015). In summary, the opioid system supports approach motivation towards social interaction, and actual engagement in social interaction has causal effects on opioidergic activity. Because the availability of social support is associated with beneficial effects on somatic health (Broadhead *et al.*, 1983; Holt-Lunstad *et al.*, 2015), endogenous opioidergic tone might constitute an important protective factor for somatic well-being *via* its links with prosocial behaviour and social attachment.

Opioids and emotion recognition

Recognizing the emotional expressions of others is crucial for social interaction, as it allows us to effortlessly 'read out' their goals, intentions and emotional-motivational states. Studies assessing the effects of acute opioid agonist/antagonist administration on emotion recognition in healthy volunteers are scarce. One study reported specific desensitization to recognizing facial expressions of fear following administration of the partial μ receptor agonist buprenorphine (Ipser *et al.*, 2013), whereas another found that naltrexone impaired recognition of sadness and fear (Wardle *et al.*, 2016). Additionally, one study found that morphine increases and naltrexone decreases attractiveness ratings for neutral facial expressions, suggesting general, transient opioidergic involvement in the encoding of social signals (Chelnokova *et al.*, 2014).

Substance abuse is in general associated with a reduction in emotion recognition accuracy (Fernandez-Serrano *et al.*, 2010). Opioid dependency impairs the recognition of facial expressions during maintenance treatment as well as complete detoxification (Kornreich *et al.*, 2003; Foisy *et al.*, 2005). Patients on opioid maintenance also show impairments in recognizing emotions from video clips depicting displays of basic emotions (McDonald *et al.*, 2013). One study has found a specific improvement in disgust expression recognition in methadone maintenance users compared to abstinent users (Martin *et al.*, 2006), yet it is also possible that opioid dependency-related impairments in expression recognition are mediated by emotion-recognition-impairing alexithymic traits in the substance abuse population (Craparo *et al.*, 2016). Taken together, definite conclusions regarding the role of the opioid system in emotion recognition cannot be reached at this stage because there are only a limited number of studies on the effects of opioid agonists/antagonists on emotion recognition in healthy volunteers. However, the preliminary findings suggest that opioid abuse impairs facial expression recognition.

Methodological considerations

In cross-sectional PET studies, binding potential (*BP*) can be used as an index of individual differences in receptor density (Hietala *et al.*, 1999). Thus, in activation PET studies using [^{11}C]-carfentanil, the observed decreases in *BP* probably reflect receptor internalization caused by the release of endogenous opioids (Quelch *et al.*, 2014). In these activation studies, altered receptor conformation and occupancy by endogenous neurotransmitter may also affect the *BP*, whereas it is unlikely that receptor synthesis would affect the *BP* given the time-scale of the experiments. In contrast to [^{11}C]-carfentanil, in a recent study the findings indicated that diprenorphine may not be sensitive to endogenous opioid release at all (Quelch *et al.*, 2014); thus, activation studies done with this tracer should be interpreted with caution.

The spatial accuracy of the human isotope imaging studies is typically relatively imprecise, and resolutions beyond $<2\text{mm}^3$ cannot be currently achieved. While this resolution allows imaging of even relatively small structures such as the amygdala, functionally dissociable circuits of opioid receptors expressed at smaller scales (Mansour *et al.*, 1987) cannot currently be investigated *in vivo* in humans. Also, because of the widespread distribution of μ receptors in the human brain (Figure 2A), the regions and mechanisms responsible for the effects of systemic pharmacological manipulations cannot be easily determined. However, pharmacological fMRI studies could be used to identify the specific mechanisms in question.

Most human studies reviewed here pertain to the μ system, although animal studies have established that different types of opioid receptors have distinct influences on mood-related processes (Lutz and Kieffer, 2013). Accordingly, future human studies should exploit advances in PET radiochemistry and address the contribution of δ (Madar *et al.*, 1996) and κ (Kim *et al.*, 2013; Vijay *et al.*, 2016) receptors to emotions. Finally, inducing emotions in human subjects in the laboratory is far from straightforward. Although a wide range of techniques have been proposed (Coan and Allen, 2007), it is still difficult to simulate the psychological, neural and visceral effects of some emotions, particularly in intensities comparable with those experienced in real life, in the constrained laboratory conditions (Adolphs *et al.*, 2016).

Conclusions

The endogenous opioid system is involved in a variety of affective processes. Our meta-analysis of fMRI and PET studies (Figure 2B) suggests that there is a significant overlap between the brain's opioidergic system and emotion circuits (as measured by fMRI) and that opioid release occurs in emotion-motivational circuits during different emotions (Figure 3). Although human studies on the opioidergic basis of emotions are still scarce, our review highlights three broad themes regarding opioidergic contribution to emotions. Firstly, the effects of opioids are not limited to any specific basic emotion system. Instead, opioids influence all basic emotions (yet no data exist for disgust

and surprise), suggesting that the opioid system has a general modulatory role in emotional processes. Secondly, despite the well-established calming as well as rewarding and antinociceptive effects of opioids, the observed pattern of opioid agonist/antagonist effects cannot be directly linked with the valence or arousal axis of the dimensional models of emotion. Thirdly, whether opioids increase or decrease subjective and behavioural components of an emotion is dependent on the main motivational stance associated with each emotion.

In general, opioid agonists strengthen approach-oriented emotions (anger, pleasure, prosociality and bonding) and weaken withdrawal-oriented emotions (fear, sadness). The role of the opioid system in motivational processing is further elucidated by work showing that baseline μ receptor density in the midbrain and frontal cortex is positively associated with personality traits associated with approach, activation, impulsiveness and prosociality (Love *et al.*, 2009; Nummenmaa *et al.*, 2015; Karjalainen *et al.*, 2016), whereas avoidance-related conditions such as major depression may be associated with a down-regulation of the μ receptor system (Kennedy *et al.*, 2006). However, these data are mostly based on self-reports and brain imaging, and currently, there are few human studies that have measured opioid-dependent changes during actual emotional behaviour.

Finally, our review highlights the importance of the endogenous opioid system in social functioning, both *via* its links to emotional and social-affiliative behaviour. Due to the well-established protective effects of opioid-system-mediated prosociality (Broadhead *et al.*, 1983; Holt-Lunstad *et al.*, 2015) and positive mood (Fredrickson, 2004), the opioidergic system may serve as a buffer against psychosomatic burden resulting from sustained avoidance-oriented emotions such as fear and sadness. Consequently, the endogenous opioid system may constitute an important factor contributing to psychological and psychosomatic resilience in humans.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander *et al.*, 2015).

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Conflict of interest

The authors declare no conflicts of interest.

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