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A common neurobiology for pain and pleasure

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Abstract | Pain and pleasure are powerful motivators of behaviour and have historically been considered opposites. Emerging evidence from the pain and reward research fields points to extensive similarities in the anatomical substrates of painful and pleasant sensations. Recent molecular-imaging and animal studies have demonstrated the important role of the opioid and dopamine systems in modulating both pain and pleasure. Understanding the mutually inhibitory effects that pain and reward processing have on each other, and the neural mechanisms that underpin such modulation, is important for alleviating unnecessary suffering and improving well-being.

"Nature has placed mankind under the governance of two sovereign masters, pain and pleasure." — Jeremy Bentham

Most of what is known about pain and pleasure derives from the study of each phenomenon in isolation. Recently, however, neuroscientists investigating opioid and placebo analgesia[1–3], drug addiction[4] and learning[5] have begun to bridge the gap between the pain and pleasure research fields. This development has been strengthened by the increasing focus on the subjective emotional feelings (hedonics) that are elicited by rewards and punishments (BOX 1).

Rewards and punishments are defined as something that an animal will work to achieve or avoid, respectively. Pleasure represents the subjective hedonic value of rewards. The term 'pain' encompasses both the hedonic (suffering) and motivational (avoidance) aspects of a painful experience. Clearly, seeking pleasure and avoiding pain is important for survival, and these two motivations probably compete for preference in the brain. Put simply, which of two coinciding pain and pleasure events should be processed and acted on first? Consistent with the idea that a common currency of emotion[6] enables the comparison of pain and pleasure in the brain, the evidence reviewed here points to there being extensive overlap in the neural circuitry and chemistry of pain and pleasure processing at the systems level. This article summarizes current research on pain–pleasure interactions and the consequences for human behaviour.

The utility of pain and pleasure

The large variability between the strength of a sensory stimulus and the resulting hedonic feeling is of great medical and neuroscientific interest. For instance, athletes can be oblivious to pain in the heat of competition, in which winning is the reward. A key factor for the interpretation of pain and pleasure is subjective utility[7]. For example, the reward value of a stimulus increases with the effectiveness of that stimulus in restoring bodily equilibrium (homeostasis)[6,8]. This effect, known as alliesthesia[6], is well-documented for food rewards, which are more pleasurable when they relieve a hunger state[9]. As the experience of pain represents a deviation from homeostatic balance[10], the same principle can be applied to pain and the pleasantness of its relief[11]. Similarly, when a perceived threat to an organism becomes greater, pain unpleasantness increases, enhancing defensive and avoidance mechanisms[12].

Pain and pleasure encourage the constant optimization of our internal homeostatic balance. Although pleasure-seeking and pain-avoidance generally increase our chances for survival, it is easy to envisage scenarios in which these two motivations are in competition. A simple case would involve a large reward that is only accessible at the 'price' of a small pain. Sometimes it seems that overcoming a small amount of pain might even enhance the pleasure, as reflected perhaps by the common expression 'no pain, no gain' or the pleasure of eating hot curries. Pain–pleasure dilemmas abound in social environments[13], and culture-specific moral systems, such as religions, are often used to guide the balance between seeking pleasure and avoiding pain (BOX 2). The subjective utility — or 'meaning' — of pain or pleasure for the individual is determined by sensory, homeostatic, cultural and other factors that, when combined, bias the hedonic experience of pain or pleasure.

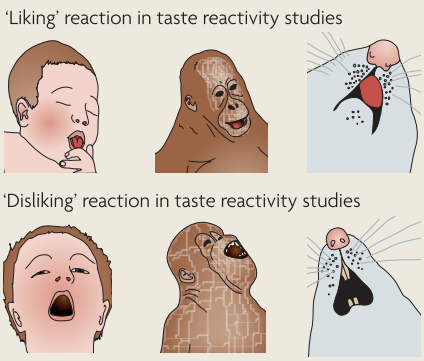
The Motivation-Decision Model

The processes that underlie the subjective interpretation of a sensory event can be understood as the manifestation of an unconscious decision process[4,14]. The decision process requires information about the homeostatic state of the individual (such as inflammation or hunger), sensory input and knowledge about impending threats and available rewards. According to the Motivation-Decision Model of pain, as put forward by Fields[4,14], the basic premise for the decision process is that anything that is potentially more important for survival than pain should exert antinociceptive effects. This allows the animal to ignore the pain and attend to the more important event. The Motivation-Decision Model predicts that pain–pleasure dilemmas in which a large reward is gained at the price of a small pain are resolved through the antinociceptive effects of the pleasurable reward (FIG. 1). In some instances, threatening and pleasure-related cues are more important for survival than pain, and it is assumed that any antinociceptive effects are mediated by the descending pain modulatory system, which is located in the brainstem. This circuit, which consists of excitatory and inhibitory cells, communicates with neurons in the prefrontal cortex, the hypothalamus and the amygdala to control the nociceptive afferent pathway in the spinal and trigeminal dorsal horn[4,14,15] (FIG. 2). Opiate drugs and endogenous opioids act on this descending system to produce pharmacological, placebo, stress-induced and pleasure-related analgesia[1,2,4,14–20].

Pain–pleasure interactions

Evidence of pleasure-related analgesia has been reported in various human and animal studies: pain is decreased by pleasant odours[21], images[22], pleasurable music[23], palatable food[16,17] and sexual behaviour[18,19]. In addition, considerable evidence suggests that expectation of treatment effect, which contributes to placebo analgesia, is a type of reward expectation[24,25]. Interestingly, when subjects who were not expecting an injection of pain-relieving morphine received

Box 1 | **The increasing focus on pain and reward hedonics**



Hedonic feelings — also known as qualia — drive motivation and behaviour. Qualia determine what it is like to be a human being[87]. No theory of the relationship between the brain and the mind is complete without accounting for hedonic feelings. In recent years, several exciting research directions have emerged in the pain and reward research fields that successfully combine the need for carefully controlled, 'objective' research methodologies with a focus on hedonics. One example is a body of work on 'liking' and 'wanting' — two subconscious reward processes that are thought to underpin conscious pleasure and motivation[31]. Using taste reactivity as a primary outcome measure (see figure), this research has used pharmacological stimulation and lesion techniques to determine causal relationships between neuronal signalling and hedonic feelings. In the pain field there is growing recognition that the 'subjective interpretation' or 'meaning' of pain determines the amount of pain-related suffering[15,88]. The definition of pain, according to the International Association for the Study of Pain, emphasizes the 'unpleasant' and 'emotional' aspects, and also includes subjective feelings of pain, which are not caused by tissue damage. Other research areas that are turning their attention to hedonic feelings include the fields of obesity research[89] and decision making: the shift in focus from 'cold' rational consideration to 'hot' emotion-based decision making has influenced cognitive neuroscience for more than a decade[90,91]. Even economists are now looking to hedonic feelings to explain human behaviour such as the 'warm glow' that accompanies donations to charity[92]. Figure modified, with permission, from REF. 31 © (2003) Academic Press.

a hidden injection, its analgesic effects were significantly reduced[26]. Although the placebo treatment might not be pleasurable in itself, reduced pain represents the better of two alternative outcomes (the other being unchanged pain levels), and therefore has a higher reward value.

A related phenomenon predicted by Fields' Motivation-Decision Model is the effect of pain on the ability to experience pleasure. By decreasing reward pleasantness, pain and other threatening events ensure that necessary action is taken to protect the individual, thus attenuating the normal reward-seeking behaviour. Correspondingly, decreased consumption of palatable foods is considered to be a measure of pain suffering and is reversible with morphine treatment[27] (FIG. 1). Similarly, sustained pain inhibits morphine reward in rodents; this is likely to be due to sustained activation of the κ-opioid system in the nucleus accumbens (NAc)[28]. In humans there is extensive co-morbidity between chronic pain and depression, which often involves a reduction in the ability of chronic pain sufferers to enjoy everyday pleasures (anhedonia)[29]. This reduction in pleasure might form part of a vicious cycle for the patients, in which both negative mood and lack of pleasure result in exacerbated pain, leading to more negative mood and anhedonia.

Opioids and hedonic feelings

Pain and reward are complex constructs that encompass motivational, hedonic and learning signals[30]. As the motivation to seek reward or avoid pain is generally correlated with the pleasantness or aversiveness of an event (respectively), it is difficult to disentangle the neuroanatomy of the hedonic and motivational components of pain and reward. In addition, we have only limited access to our own hedonic and motivational processes, which are thought to be primarily subconscious[31]. Importantly, however, the motivation and hedonic subsystems seem to be mediated by different neurotransmitters. Carefully controlled studies have found specific effects for two neurotransmitter systems: dopamine increases motivation for, but not the pleasure of, eating palatable foods[32,33], whereas the opioid system influences motivation indirectly by modulating subjective emotional feelings of pain and reward[34]. In summary, opioids are necessary for hedonic experience ('liking') but dopamine motivates you to get ready for it ('wanting')[31,35].

μ-opioids have been shown to cause a positive shift in affect across the hedonic spectrum: they enhance the pleasantness of sweet tastes and decrease the aversiveness of pain and bitter foods[31]. Both painful and pleasant events are associated with the release of endogenous μ-opioids in the brain and, importantly, in the NAc[19,36] (FIG. 1). Blocking of μ-opioid signalling with naloxone decreases the pleasantness of food rewards[34] and sexual behaviour[37] and reverses reward-related analgesia[16,18,26]. Interestingly, a recent conditional gene-knockout study showed a dissociation of μ-opioid-mediated reward and analgesia: only μ-opioid antinociception depends on an intact central serotonergic system[38]. The κ-opioid system presents another example of pleasure–analgesia dissociation: κ-opioids reduce pain but also induce feelings of aversion[39,40]. Furthermore, the κ-opioid activity caused by tonic (sustained) pain has

Box 2 | **The pain–pleasure dilemma**

"Pleasure is the greatest incentive to evil" — Plato

The increased neuroscientific interest in pleasure (BOX 1) perhaps reflects a greater general focus on pleasure and positive affect (happiness) in the Western world[85]. Historically, however, a strong belief in shame and stoicism (in the case of pleasure and pain, respectively) has prevailed. Learning to curb impulses for instant gratification and to tolerate some pain 'for the greater good' is an important part of child development. Considering the unnecessary pain of childbirth and the stress of child rearing, it is perhaps not surprising that patience, selflessness and stoicism are highly regarded traits in many cultures[13]. In neuroscience, prominent addiction researchers advocate a 'hedonic Calvinistic' approach to pleasure, in which the use of the reward system is restricted, as they believe that unregulated pleasure-seeking might lead to addiction[93]. The Calvinistic focus on moderation, or even abstinence, of pleasure has deep roots in Western culture and is powerfully connected with shame[94]. Whereas excessive reliance on shame and stoicism might cause unnecessary suffering[86], extreme pleasure-seeking and pain avoidance (hedonism) can have undesirable consequences such as drug addiction[93,95] and obesity[89]. However, the inability to take pleasure in everyday rewards is also a form of suffering[29]. In fact, paradoxical and risky human behaviours such as self-harm and skydiving have been related to a desire to alleviate emotional 'numbness', possibly owing to a dysfunction in the opioid and/or dopamine systems[78,96,97]. The strong historical association between shame, guilt and pleasure might help to explain a number of paradoxical human behaviours, as well as the historical preference for formulating scientific research questions in terms of behaviour rather than pleasure and other hedonic feelings.

been shown to disrupt the positive interaction between μ-opioids and mesolimbic dopamine[28].

Dopamine, motivation and analgesia

Considering the close association that exists between motivation, learning and hedonic feelings, it is not surprising that dopamine signalling has been consistently reported to correlate with stimulus reward value[41,42]. Striatal dopamine neurons also respond to aversive events[43,44] but, in contrast to the firing bursts that signal pleasant events or their cues, aversive stimulation causes a brief inhibition of baseline firing[45,46]. The many time-courses of the dopamine signal are often measured by different techniques, making the literature on the precise role of dopamine in pain and reward complicated and somewhat inconsistent[43,45] (BOX 3). For instance, on the one hand, positron emission tomography (PET) studies of baseline dopamine receptor availability provide a measure of tonic dopamine levels[43,47]. On the other hand, PET studies comparing receptor availability between two stimulus conditions measure dopamine signalling at the temporal mid-range between brief phasic activation and constant tonic firing[24,43,45,48]. Despite the complex effects and interactions of the various dopamine time-courses, it is clear that endogenous dopamine is involved in the processing of both pain and pleasure[3,30,41,43–46,48]. Pharmacological manipulation of dopamine levels has also been shown to modulate both pain and reward behaviours[20,30,45,49,50].

The precise role of dopamine in pain and reward processing is hotly debated. In the reward literature, one main question has been whether the dopamine signal is necessary for reward learning, salience, motivation or hedonics[30,35,45]. For pain, dopamine agonists, such as amphetamine, reduce tonic pain but do not change phasic pain behaviours[49]. Similarly, tonic but not phasic pain events are thought to induce endogenous analgesia through dopamine release in the NAc[43]. Dopamine receptor availability studies have shown that endogenous striatal dopamine release correlates positively with sensory and affective components of tonic pain in healthy subjects[43,48]. Although these studies in healthy volunteers provide clear demonstrations of dopamine's involvement in pain processing, they cannot unequivocally answer the question of directionality. The dopamine signal could reflect a sustained increase in dopamine that might exacerbate pain, but it could also reflect brief signals related to pain-avoidance motivation. Interestingly, in patients it seems that this normal interaction between the dopamine system and pain is disrupted. One study showed that, compared with controls, patients suffering from generalized pain (fibromyalgia) released less dopamine in the striatum yet found the stimulus (hypertonic-saline-induced deep muscle pain) more painful[48]. This result is consistent with a normal role for dopamine in endogenous antinociception[51]. Any analgesic effects of dopamine seem to rely on a reactive phasic dopamine system, and this might be disrupted in chronic pain conditions — perhaps through increased tonic dopamine levels that inhibit phasic release[48,51] (BOX 3).

In line with this evidence, and based on interactions between the descending pain system and the mesostriatal dopamine circuit for drug and food reward, the Motivation-Decision Model proposes that phasic dopamine has a key role in endogenous analgesia in situations in which reward is expected[4]. Evidence from human studies perhaps supports this concept, as low tonic dopamine levels, present in individuals with the catechol-*O*-methyltransferase (COMT) Val/Val polymorphism, produce high phasic dopamine[52] and concomitantly high endogenous-opioid release during tonic pain[53]. Val/Val subjects also reported significantly lower pain compared with Met/Met subjects with higher tonic dopamine levels. A recent molecular-imaging study investigated the link between reward expectancy, dopamine and analgesia more directly, and showed that inter-individual variation in NAc dopamine release during a placebo manipulation correlated with subsequent variability in placebo analgesia[3]. Furthermore, NAc activation during anticipation of a monetary reward accounted for 28% of the variance in the formation of placebo analgesia in the same individuals. This study therefore supports a direct link between dopamine and endogenous-opioid release with regards to reward and analgesia in humans.

Common regions for pain and pleasure

Although the opioid and dopamine systems are closely related neuroanatomically[54], they interact in complex ways. Phasic dopamine has been shown to increase opioid levels[55], whereas tonic dopamine decreases opioid levels[53,56]. Conversely, opioids upregulate phasic dopamine in the striatum (by inhibiting local GABAergic interneurons in the ventral tegmental area)[57,58] and downregulate slower striatal dopamine signalling, as measured by PET[59].

Just as the colocalization of opioid and dopamine pathways highlights the importance of interactions between these two systems, the striking overlap in regions that are involved in pain and pleasure processing (FIG. 2) might explain the modulatory effects

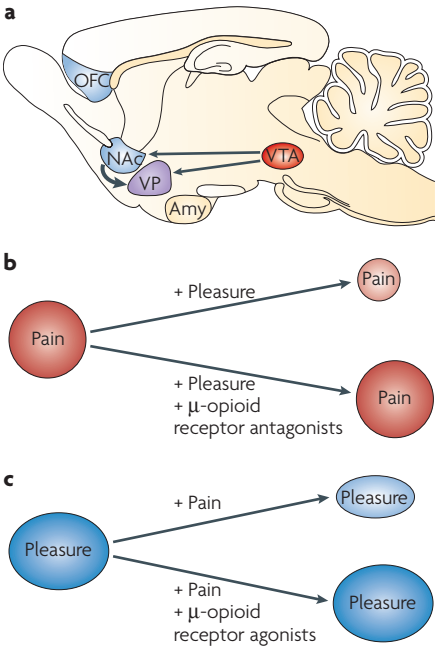
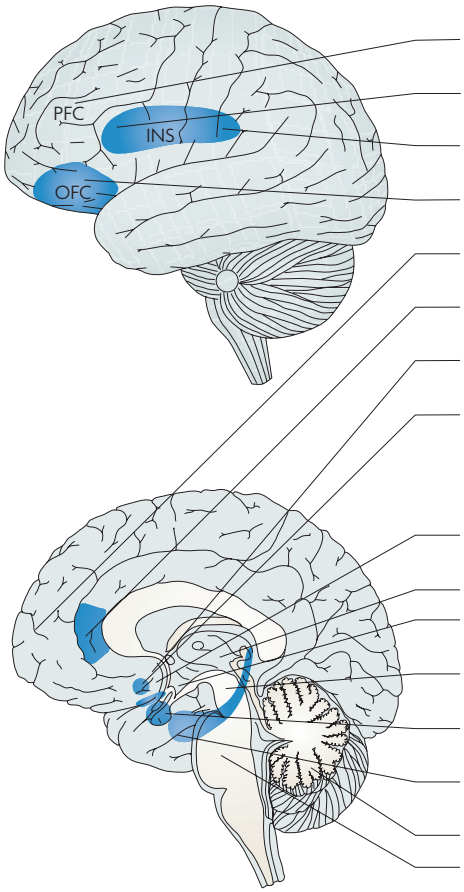


Figure 1 | **Schematic illustration of pain–pleasure inhibition.** The Motivation-Decision Model of pain[4,14] posits that anything of potentially greater importance than pain should have antinociceptive effects (be it a greater threat or the possibility of a reward). By the same evolutionary-psychology rationale, it is clear that anything that is potentially more important than a reward (such as an even greater reward or a threat for which action is needed) should similarly decrease its pleasantness, thus allowing for the appropriate avoidance or approach behaviours. The μ-opioid and mesolimbic dopamine systems are the prime candidates for systems that transmit signals relating to motivational and hedonic aspects of both pain and pleasure and, in particular, their interactions, as illustrated here. **a** | Both pain and pleasure have been shown to elicit opioid release in the orbitofrontal cortex (OFC), the amygdala (Amy), the nucleus accumbens (NAc) and the ventral pallidum (VP)[2,65,68]. Pleasure and reward expectation are also associated with increased phasic dopamine signalling from the ventral tegmental area (VTA) to the NAc and VP[42], which in turn causes increased μ-opioid release in the NAc[55]. Pain has been associated with both increases and decreases in mesolimbic dopamine signalling, depending on the type of measurement and pain model that have been used[42,43,46,48,49]. **b** | μ-opioid receptor antagonists, such as naloxone, reverse pleasure-related analgesia[16,18,19]. **c** | μ-opioid receptor agonists, such as morphine, have been shown to re-enable pleasure that has been previously reduced by concomitant pain[27].



Region	Pleasure/reward	Pain
Lateral prefrontal cortex	• Humans, fMRI, taste reward[101]	• Humans, H_2O PET, hyperalgesic pain [102] • Humans, fMRI, pain[103]
Anterior insula	• Humans, fMRI, food cravings[104] • Humans, H_2O PET, chocolate reward[75]	• Humans, fMRI, pain[105] • Humans, fMRI, placebo analgesia[106]
Posterior insula	• Humans, fMRI, hypothetical reward[107]	• Humans, direct brain stimulation[108] • Humans, fMRI, pain[105]
Orbitofrontal cortex	• Humans, fMRI, pleasant touch[74] • Humans, fMRI, chocolate reward[75]	• Humans, fMRI, pain[74] • Humans, fMRI, placebo analgesia[106]
Medial prefrontal cortex	• Humans, H_2O PET, pleasurable music[64] • Humans, fMRI, monetary reward[109]	• Humans, fMRI, pain[110,111]
Anterior cingulate gyrus	• Monkeys, electrophysiology[112] • Humans, H_2O PET, chocolate reward[75]	• Humans, fMRI, pain[113] • Humans, opioid PET[83]
Dorsal striatum	• Humans, fMRI, fruit juice[114] • Humans, fMRI, monetary reward[115]	• Humans, dopamine ligand PET, pain[43] • Humans, fMRI, pain[116]
Nucleus accumbens/ ventral striatum	• Humans, fMRI and dopamine ligand PET[3], monetary reward[65] • Rodents, hedonic hotspot, taste reactivity • Humans, dopamine ligand PET[41], drug reward	• Humans, dopamine ligand PET[43] • Humans, fMRI, expectation of pain[44] • Rodents, pain-induced analgesia[20]
Ventral pallidum	• Rodents, taste reactivity[62,65]	• Rodents, tracing, pain affect[72] • Humans, μ-opioid PET, sustained pain [2]
Thalamus	• Humans, H_2O PET, chocolate reward[75]	• Humans, fMRI, placebo analgesia[106]
Hypothalamus	• Humans, H_2O PET, pleasurable music[117]	• Rodents, tracing of nociceptive pathway[72] • Humans, direct brain stimulation[118]
Midbrain	• Humans, H_2O PET, chocolate reward[75] • Humans, H_2O PET, pleasurable music[64]	• Humans, fMRI, anticipation of pain[119] • Humans, fMRI, pain[120]
Amygdala	• Humans, H_2O PET, pleasurable music[64] • Primates, reward anticipation/learning[63]	• Humans, fMRI, pain[70,120]
Hippocampus	• Humans, fMRI, unexpected reward[121] • Humans, H_2O PET, pleasurable music[64]	• Humans, fMRI, pain[122] • Humans, fMRI, anticipation of pain[119]
Cerebellum	• Humans, fMRI, unexpected reward[121]	• Humans, fMRI, pain[123]
Brainstem	• Rodents, taste reactivity[124] • Rodents, conditioned place preference[40]	• Humans, fMRI, pain[123] • Rodents, pain[40]

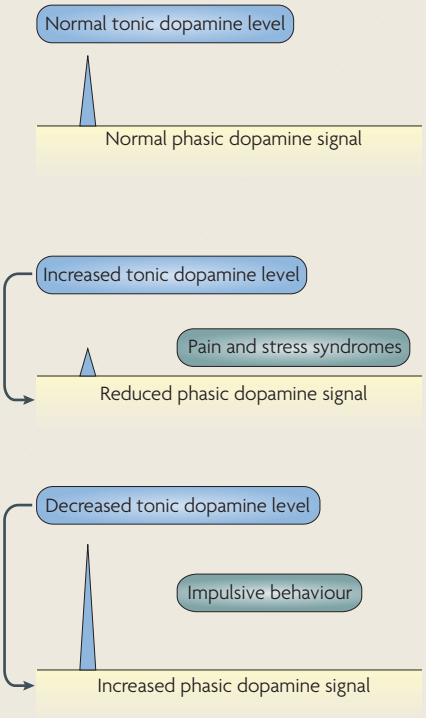
Figure 2 | **Brains regions implicated in pain and pleasure processing.** At the systems level, the major regions that have been implicated in pain and reward processing by functional imaging studies and direct brain stimulation in humans, as well as by electrophysiology and tracing studies in animals, show striking overlap. The studies included as examples in this figure unequivocally demonstrate the involvement of each region in both pain and pleasure processing. fMRI, functional MRI; PET, positron emission tomography.

of one over the other. Whether one or two neural systems (at any spatial scale) underpin aversive and appetitive processing in the brain[60] is still subject to debate[5]. Regions that are particularly well situated to mediate interactions between pain and pleasure include the NAc, the pallidum and the amygdala. These regions receive direct or indirect reward-related signals from dopamine neurons in the midbrain and are thought to signal either reward-prediction error (discrepancy between the expected and the received reward; NAc[42,61] and amygdala[61]) or hedonic reward value (pallidum[62] and amygdala[63,64]). The NAc and pallidum each contain a 'hedonic hotspot' in which μ-opioid stimulation increases the liking of rewards[65]. In fact, these two ~1mm^3 regions are necessary for the opioid-mediated enhancement of food palatability[65]. Different neuron populations in the amygdala have been found to encode the negative and positive hedonic value of reward and punishment cues[63]. Evidence from human patient studies also highlights the importance of the NAc and the pallidum for reward processing, as dysregulation or lesion of these regions is associated with anhedonia[66,67].

In addition to their participation in pleasure processing, the amygdala, the NAc and the pallidum have distinct but important roles for pain. All three regions have been shown to release endogenous μ-opioids during painful stimulation in humans[2,68]. The amygdala modulates pain perception through direct connections with the descending pain inhibitory system[69,70]. The amygdala and the NAc mediate both reward- and stress-induced analgesia[4,69], and these two regions show alterered endogenous-opioid analgesic activity in fibromyalgia patients[71]. Stress-induced analgesia can be blocked by intra-accumbens injection of dopamine and opioid antagonists[20]. The pallidum contains a population of encephalin-containing neurons that receive a large proportion of the signals that are generated by the unmyelinated primary afferent nociceptor pathway[72]. These pallidal 'pain affect' neurons seem to be located laterally to the pallidal pleasure hotspot[65,72]. Thus, it seems that two distinct subregions of the pallidum are involved in appetitive and aversive processing. A similar finding has been reported for the NAc. Whereas neurons located in the rostral part of the NAc shell mediate pleasure, stimulation of more caudal regions of the NAc causes a negative shift in affect[73]. A similar rostrocaudal 'hedonic gradient' in the ventral striatum was recently reported for economic gains and losses in humans[5]. In the amygdala, adjacent neuronal populations represent positive and negative hedonic value[63].

The close adjacency of such pain and pleasure hotspots suggests that functional interactions between them are involved in the mechanism by which pain decreases pleasure and rewards induce analgesia. Evidence

Box 3 | **Aristotle's 'Golden Mean' and phasic dopamine signalling**



To maintain homeostasis, animals must aim for the 'Golden Mean' — that is, the right balance between pleasure-seeking and pain-avoidance. The responsiveness of the phasic dopamine system (a system which is caused by brief bursts of neuronal firing and relates to reward motivation and prediction error) is important for the regulation of appetitive and aversive behaviours. Impulsive behaviour and schizophrenia have been linked to an excessively responsive phasic dopamine system[98], whereas depression, chronic pain and anhedonia have been associated with low responsiveness to reward cues[78,79].

Tonic dopamine activity refers to the level of extrasynaptic dopamine that is present at a steady-state concentration in the extracellular space[45,99]. The baseline dopamine concentration is thought to enable a number of behavioural processes, many of which are affected in Parkinson's disease[42]. Importantly, tonic dopamine levels regulate the responsiveness of the phasic dopamine system to salient environmental cues: high tonic dopamine attenuates phasic dopamine release[45,99] whereas low tonic dopamine facilitates phasic dopamine firing[98]. The level of tonic dopamine in the limbic striatum is in turn modulated by corticostriatal and hippocampal afferents and homeostasis[98,99].

Increased tonic dopamine is known to result from prolonged stress or pain[51] (see figure), a mechanism that might have evolved to ensure rest and low activity levels during injury. Unfortunately, the same mechanism is thought to cause increased pain sensitivity in certain pain syndromes through its inhibition of endogenous phasic dopamine antinociception[48,51]. Abstinence from addictive drugs has also been associated with hyperalgesia and increased tonic signalling. The resulting inhibition of phasic signalling is thought to underpin reduced responsiveness to pleasure (anhedonia) during abstinence, and can be reversed by re-administering the addictive drug[79]. At the other extreme, decreased tonic dopamine, causing hyper-responsiveness of phasic dopamine, has been related to positive symptoms in schizophrenia[98]. Impulsivity in schizophrenia is associated with excessive pleasure-seeking and substance abuse[100].

that separate neuronal populations encode aversive and appetitive processing in the amygdala, the NAc and the pallidum supports the existence of two neural systems for pain and pleasure at the within-region spatial scale. A similar finding has also been reported for higher cortical regions: different subregions in the orbitofrontal cortex represent the hedonic value of reward and punishment[74–77].

A common currency for hedonic experience

The robust evidence for opioid and dopamine involvement in the processing of pain and pleasure makes these two neurotransmitter systems the prime candidates for mediating the mutually inhibitory effects of pain and reward. Although both pleasurable and painful events are often accompanied by endogenous-opioid neurotransmission, the pleasure-enhancing and antinociceptive effects of μ-opioid agonist treatment suggest that endogenous μ-opioid signalling truly reflects pleasurable and analgesic effects in the brain. Similarly, although dopamine firing patterns differ in response to reward prediction, uncertainty and aversive events, the mutual reinforcement of phasic dopamine and opioid release is consistent with the idea that dopaminergic motivation signalling takes place during preparation for, or consummation of, a pleasurable reward. The finding that high tonic dopamine activity is associated with both increased pain and decreased pleasure, and that tonic over-activity of the dopamine system is known to reduce phasic dopamine and μ-opioid release, further corroborates the idea that interactions between μ-opioids and phasic dopamine signalling mediate pleasure and analgesic effects in the brain. These two neurotransmitter systems are thus likely to mediate the brain's common currency, allowing for action selection based on the comparison between competing pleasant and aversive events. As the Motivation-Decision Model suggests, being able to 'switch off' pain in order to gain a reward could increase survival, if the pain–pleasure (or cost–benefit) ratio is right. Similarly, aversive cues must be able to disrupt pleasure-seeking if the potential danger outweighs the potential gain.

An important and as yet unanswered question concerns the effects of chronic pain on the ability to enjoy rewards[29]. Anhedonia is a major symptom of depression, and several recent papers have suggested that it might be related to reductions in dopaminergic neurotransmission that are similar to those that are seen during abstinence of addictive drugs[78,79]. By contrast, positive mood and cognitive flexibility are thought to arise from a highly responsive phasic dopamine system[80]. The significant co-morbidity between chronic pain and depression suggests that these patients might also lose-out on the potential analgesic effects of the rewarding everyday events that they are no longer able to savour. A lack of reward-induced analgesia has been reported in 'anhedonic' stressed rats[81]. Indeed, endogenous-opioid activity is disrupted both during sad mood[82] and in chronic pain patients[83].

For Jeremy Bentham, a 'good life' consisted of the presence of pleasures combined with the absence of pains[7]. As we have seen, the inability to feel pleasure is associated with negative mood and depression. By contrast, positive affect is considered the hallmark of well-being[80] and might actually improve health[84]. Bentham's view might nevertheless be too simplistic. As stated in the beginning, closely related to the subjective interpretation of a sensory stimulus is the concept of meaning. Meaning allows for many alternative paths to well-being[85]. Consideration of this factor might help to explain the abundance of paradoxical aversive or life-threatening human behaviours found across society that are considered 'pleasurable'. Even suffering can be rewarding if it has meaning to the sufferer[86]. Continued study of the commonalities and differences between pain and pleasure is therefore necessary if we are to advance our understanding of human suffering and well-being.

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DATABASES

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