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Pain and Pleasure: Masters of Mankind

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Nature has placed mankind under the governance of two sovereign masters, pain and pleasure. It is for them alone to point out what we ought to do, as well as to determine what we shall do.

Jeremy Bentham, 1789

For Bentham, the study of pleasures and pains was the study of hedonic feelings. All good feelings were pleasures, and "pain" could describe all that humankind sought to avoid (Bentham, 1789). Everyday expressions ("what a pain!", "my pleasure" etc.) indicate that this type of categorization of positive and negative hedonic feelings is still in use today. In modern-day science, however, the terms reward and punishment have largely replaced Bentham's pleasures and pains. For instance, a recent PubMed search of "reward and brain" yielded over 20 times more entries than "pleasure and brain." Reward and punishment are defined as something an animal will work to achieve or avoid, thus effectively circumventing the hedonic aspect inherent in pleasures and pains. This has allowed for a flourishing behavioral neuroscience literature on positive and negative reinforcement. The probability that a previously rewarded (or punished) response is emitted is considered an objective measure of the reinforcement value of that reward. In contrast, the hedonic value of a reward or punishment is by definition subjective.

The hedonic quality of pleasures and pains is the subject matter of this chapter. Exploring the relationship between the brain and subjective hedonic feelings (qualia) is necessary to understand "what it is like" to be a sentient being (Nagel, 1974). Here, we shall consider a simple continuum of hedonic feelings spanning from the extremely unpleasant through to the extremely pleasant (Figure 19.1). In general, it holds true that punishments feel unpleasant and generate negative affect (NA), whereas rewards cause pleasure and positive affect (PA). This relationship is not always straightforward, however. Importantly, even primary rewards or punishments are not always rewarding or aversive, although some affective responses to them may be hardwired. For instance, sweet tastes and tissue damage are associated with innate reflexive reactions such as smiling and withdrawal; this holds true across a range of species (Berridge, 2003). Nonetheless, having already devoured six big chocolate bars, the seventh would not feel like much of a reward; satiation has made its taste aversive (Small et al., 2001). Conversely, scratching an itchy bit of skin until it looks red and irritated can feel extremely pleasant despite causing tissue damage (Craig, 2003). This scenario can also illustrate the complex relationship between hedonic feelings and positive affect and negative affect. For eczema sufferers, scratching often exacerbates the skin condition (Carroll et al., 2005). Thus the pleasure of scratching may be diminished by fear and guilt, while resisting the "irresistible" itch can cause positive affect (Leknes et al., 2007). Here, we will consider reward, punishment, and positive affect/negative affect only in as much as these give rise to or affect hedonic feelings.

Pain and Hedonic Feelings

"Pleasure and pain were the earliest forms of emotion to evolve" (Jaak Panksepp, as cited in Phillips, 2003).

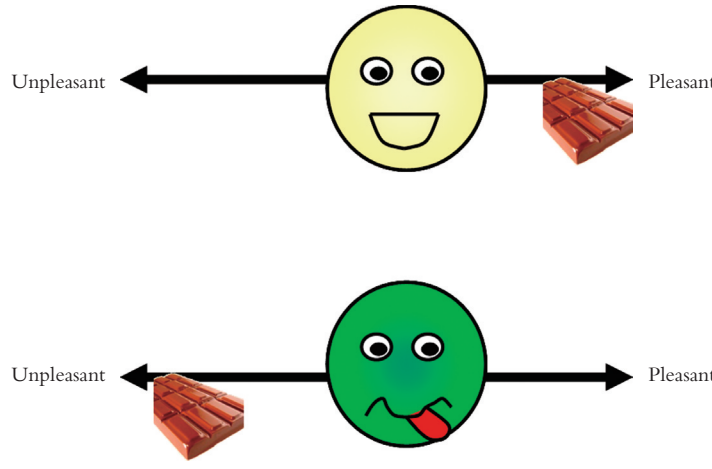

Figure 19.1 The inner state determines the pleasantness of a stimulus. While chocolate and other sweet foods are pleasurable under normal circumstances, the opposite may be true for someone with nausea.

Unlike pleasure (but like reward), pain is the subject of a vast field of neuroscientific and medical research. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Note that unlike for Bentham, pain no longer describes negative hedonic feelings such as unhappiness, irritation, and itch. Instead, pain research has mainly concerned itself with pain related to nociception. Pain is reliably induced by stimuli that activate nociceptive receptors in the skin, muscle, gut, and others. Although sensory pains vary qualitatively (consider a sharp pin-prick pain vs. a dull muscle ache), these feelings are similar enough to be classified as pain both in hedonic and physiological terms. Chronic pain syndromes such as poststroke and phantom pain are examples of painful conditions where the pain is not caused by stimulation of nociceptors in the periphery. Nevertheless, the subjective hedonic feeling of these pain syndromes mimics sensory pains, and central pain syndromes are thus encompassed by the IASP definition of pain. Most of the pain studies described in this chapter have used nociceptive stimulation to induce pain. Numerous attempts have been made to find objective measures for pain. Animal pain research largely relies on measures of avoidance behaviors such as tail flick latency, although some quantifications of suffering behavior have also been reported (Dickinson and Dearing, 1979; Szechtman et al., 1981). Although many human pain studies use subjective pain ratings to indicate the level of pain, others choose to assess nociceptive signalling, for example, by measuring electrical activity from peripheral neurons (Raja et al., 1999). Some still argue for objective measures of pain, such as quantification of reflexes (Gerdelat-Mas et al., 2007). With the advent of functional brain imaging, many hope that a technique that will provide the elusive objective measurement of pain has been found. A number of brain regions light up in neuroimaging studies of pain. Some, notably the insula, thalamus, and dorsal anterior cingulate cortex (ACC), are reported with great consistency (Tracey, 2005). Rainville and colleagues (1997) used hypnotic suggestion to show that activity in the ACC varies with the affective component of pain processing, leaving the thalamus and the insula as the main candidate regions for an objective marker of nociceptive input. Direct electrical stimulation of insular cortex in epilepsy patients causes intense feelings of pain (Ostrowsky et al., 2002). Interestingly, however, both the insula and the thalamus have recently been shown to activate during hypnotic suggestion of pain in the absence of nociceptive stimulation (Raij et al., 2005).

The role of subjective interpretation of pain as the determinant of the hedonic pain experience is becoming increasingly recognized within the pain field, especially in the study of the factors that increase pain unpleasantness (Fairhurst et al., 2007; Gracely et al., 2004; Wiech et al., 2006). However, little research focuses on the role of pleasure or positive emotion for pain (but see Strand et al., 2006, 2007). Medical treatment for pain is concerned with reducing negative emotion (analgesia) more than increasing positive emotion. Although opiate and other analgesics are frequently abused and are known to induce euphoria (Franklin,

1998), few studies have systematically assessed positive affect related to pain or pain relief. We believe that the field of pain research may benefit from looking to Bentham's wider definition of pain as well as his focus on subjective hedonic feelings. For instance, comparing pain with unpleasant sensations such as itch and nausea, and also with pleasant sensations and emotions, could elucidate common emotional components of sensory hedonic feelings. Similarly, studying the interactions between pain and other hedonic emotions may further our understanding of both pains and pleasures. To our knowledge, neuroimaging studies of pain have not identified a single brain region that has not also been implicated in aspects of reward processing. The insula encodes taste and food cravings (Pelchat et al., 2004; Small and Apkarian, 2006); the ACC represents reward size (Koyama et al., 2001; Rogers et al., 2004); and the amygdala is involved in anticipation of pleasant taste (O'Doherty et al., 2002) and in the experience of intense pleasure when listening to music (Blood and Zatorre, 2001). The thalamus is involved in drug cravings and dysregulation of reward motivation (Volkow and Fowler, 2000). In addition, opioids and dopamine, which are perhaps the two most well-defined neurotransmitter systems involved in modulation of pain (Fields, 2004; Scott et al., 2006; Wood, 2006; Zubieta et al., 2005), are also crucial for positive hedonic processing (Robinson and Berridge, 2001; Schultz, 2004). Much remains to be learned about the function of these neurotransmitter systems in mediating pleasure–pain interactions.

In terms of evolutionary psychology, both seeking pleasures and avoiding pains are important for survival and may compete for preference within the brain (Fields, 2006). In the face of a large food reward, which can only be obtained at the cost of a small amount of pain, for instance, it would be beneficial if the pleasurable food reduced pain unpleasantness. Cabanac (2002) argues that the brain must contain a common currency that allows motivations for pleasures and pains to be weighed against each other. This chapter will summarize the research on interactions between pleasure and pain and other factors influencing the hedonic quality of pains and pleasures. The most important of these is homeostasis.

Homeostasis and Opponent Process Theory

The state of the body and the mind determines the pleasantness or unpleasantness we experience when we perceive a stimulus. The seventh chocolate bar eaten in a row is aversive because the body is already more than sated on cocoa, sugar, and fat. For Bentham (1789), the key to pleasures and pains is subjective utility. If overeating and skin damage are not useful to you, they should not be pleasant. These ideas are conceptualized in homeostatic theory.

All organisms strive to maintain optimal internal equilibrium. The notion of homeostasis was first introduced in relation to automatic regulatory processes such as thermoregulation (Cannon, 1929). Later findings have highlighted the relationship between homeostasis and emotion. Michel Cabanac showed that the pleasantness of a stimulus increases the more effective that stimulus is in restoring bodily homeostasis (Cabanac, 1979). When someone's core temperature is too low, stimuli that would normally feel too hot become pleasant (Cabanac, 1971). In other words, homeostatic utility determines the hedonic value of a stimulus. This effect is well-documented for primary rewards such as food and drink, which taste better when relieving a hunger or thirst state (de Araujo et al., 2003; Kringelbach et al., 2003; Small et al., 2001). Similarly, pain unpleasantness increases with greater perceived threat (Price et al., 1987).

In a certain sense, hedonic feelings exist to encourage the constant optimization of our internal homeostatic balance. Unpleasant sensations such as pain and itch have probably evolved as homeostatic alarm signals, notifying us of imbalances in the mechanical, thermal, or chemical status of the tissues of the body (Stante et al., 2005). Unfortunately, when itch and pain become chronic, these sensations retain the interruptive quality of alarm signals, constantly pulling attention toward the unpleasantness of the condition and disrupting other thoughts and activities (Eccleston and Crombez, 1999). In contrast, positive hedonic feelings more often signal that a goal has been reached, and pleasure does not seem to have the same interruptive effect on attention.

According to the opponent process theory, the homeostatic system strives to neutralize any deviation from the optimal balance of the organism, whether pleasurable or aversive, both externally or internally generated: "There are certain systems in the brain, the business of which is to suppress or reduce all excursions from hedonic neutrality" (Solomon and Corbit, 1974, p. 143).

In this model, an unpleasant stimulus or emotion would trigger not only a negative affective reaction, but also a process of opposite valence, which has a slower onset and offset (Figure 19.2A,B). If the

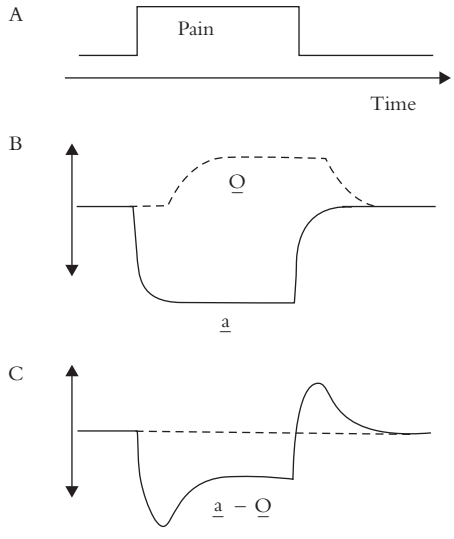

Figure 19.2 The opponent process theory. A outlines the event. The arrows in B and C signal hedonic valence. a is the primary process, reflecting negative valence. o is the opponent process. Panel C shows the net result of the two opposing processes. The late peak reflects pleasant relief. (Adapted from Solomon and Corbit, 1974.)

unpleasant sensation is suddenly terminated, the activity of the positive affective process causes us to perceive positive emotion (Figure 19.2C). The opposite pattern is proposed for positive hedonic experiences, which, according to Solomon and Corbit, are followed by a dysphoric "low" when abruptly terminated. Although the opponent process model is almost certainly too simplistic, it provides a putative mechanism for explaining such phenomena as anticlimaxes and the euphoria of risk-taking. Similarly, it accounts for the pleasure of relieving an itch (for most people) as well as the pleasure of not doing so (for someone anxious about the consequences of scratching). The idea that pleasure can be caused by relief from something unpleasant is not a new one: in his *Discourse on the Nature of Pleasures and Pain,* Verri holds that all pleasures are the results of relief from pain, and that pleasure is limited by the quantity of the pain it removes (Guidi, 1994 cites Verri, P., 1781). The neuroscience of pleasurable relief is discussed further in the next section.

Solomon and Corbit (1974) made no distinction between homeostatic control of externally and internally generated feelings. Inspired perhaps by the popularity of classic and operant conditioning research in the 1960s and 1970s, the authors emphasized the role of homeostatic mechanisms in learning and expectation. In brief, learning that A precedes B ultimately leads to the affective reaction to B shifting forward in time and becoming associated with A. The opponent process initially associated with B also shifts forward in time. For instance, an eczema sufferer may learn that scratching during the day increases itchiness in the evening, and so feels guilt and fear when he scratches. This shift of affect toward the "cue" (A) means that if B fails to occur after A, B's opponent process will take place instead. For our eczema sufferer, this effect is apparent as the pleasant relief he feels when for once the itch *has not* increased after a day of scratching. Within neuroscience, the reward learning literature has provided evidence for opponent hedonic reactions to counterfactual outcomes. When an expected monetary or food reward is omitted, the resulting negative affective reaction has been called "frustrative non-reward" (Siegrist et al., 2005; Tucker et al., 2005).

Anticipated Emotions, Frustration, and Relief

In fact, since animals will work to avoid it, frustrative nonreward matches the definition of a punishment. Similarly, the effort we are willing to exert to relieve something unpleasant tells us that relief is a type of reward. As to the hedonic aspect of relief and frustration/disappointment, it is clear that these belong to opposite ends of the hedonic continuum. In our laboratory, we have found evidence for a positive hedonic reaction associated with relief from pain (Leknes et al., 2008). In brief, the results from our laboratory confirm the predictions stipulated in the opponent process theory as follows: (1) The sudden termination of a painful sensation elicits positive affect, as measured by subjective ratings of relief pleasantness. (2) The relief associated with the offset of pain increases with the intensity of the pain sensation. (3) The pleasantness of relief from pain increases with the efficacy and speed of return to homeostatic balance, as evidenced by the higher positive hedonic ratings when the skin is gently cooled after burning heat pain. In addition, findings from a study by Donald Price and colleagues (1980) are consistent with the notion that when pain is signaled by a cue, both the negative pain-related affective reaction and its opponent process are shifted forward in time to be elicited by the cue. In fact, this effect is so strong that subjects even reported positive affect when their skin was heated to a painful

level—mild pain had become a relief relative to the expected severe pain stimulus (Price et al., 1980).

A recent study has investigated the hedonic value of waiting for pain, which they call dread (although despite the obvious hedonic connotations of this term, the authors present their findings largely in terms of neuroeconomical utility rather than hedonic displeasure). Berns and colleagues (2006) report compelling evidence for unpleasantness conferred onto the pain cue: several subjects found waiting for the painful electric shocks so aversive that they opted for increasing pain intensity just to shorten the wait. Little research has focused on the pleasure of waiting for something good, despite theoretical suggestions that the anticipation may even be the best part. In a comment to Berns et al., Loewenstein (2006, p. 305) enthuses over the idea that we "derive pleasure and pain directly from information, rather than from any material benefits that the information procures." Similarly, Rozin emphasizes the role of anticipatory pleasure: "In terms of real life, most pleasure may come from memory or anticipation, as opposed to online experience" (Rozin, 1999, p. 113). A recent suggestion that the ability to enjoy anticipatory pleasure depends on personality traits may spur more research in this area (Gard et al., 2006).

The above findings on anticipated emotions and counterfactual outcomes may also inform the interpretation of data from extinction learning paradigms. The process of "unlearning" or extinguishing the association between a cue and an outcome is generally more time-consuming and less successful when the cue is only partially predictive of the outcome. During partially reinforced reward learning, frustration from reward omission can become "counterconditioned" by the occasional reward (Tucker et al., 2005). Because of this, the animal trained on a variable reward schedule more easily tolerates later frustrations: it does not give up, "hoping" for a pleasant food reward despite repeated disappointment. An intriguing thought is that extinction learning in general, far from being "unlearning" or associating a conditioned stimulus with no outcome, instead involves the forming of new associations with the opposite valence. Extinction of fear conditioning would thus entail appetitive learning, in which the cue previously associated with fear becomes predictive of pleasant relief. Presumably then, as cue-related fear dissolved, relief would decrease until eventually the cue would elicit little hedonic affect. In support of this prediction, an important region associated with extinction of fear associations in human subjects is the ventromedial prefrontal cortex (Phelps et al., 2004), a region consistently implicated in the encoding of positive hedonic feelings (Knutson et al., 2003; O'Doherty et al., 2003). The ventromedial prefrontal cortex has a very high opiate receptor density (Baumgartner et al., 2006), and activation in this region has been shown to decrease in response to unexpected reward failure (Knutson et al., 2001a,b; Ramnani et al., 2004).

Another prediction of the opponent process theory supported by neuroscience research is based on what Solomon and Corbit call Pavlovian "backward conditioning." Here, the conditioned stimulus follows the termination of the unconditioned stimulus closely in time and becomes associated with the relief or dysphoria following a pain or a pleasure. An elegant study of fruit flies illustrates this concept. Tanimoto and colleagues (2004) varied the interval between a neutral odor and an electric shock, and showed that if the odor precedes the shock, the fruit flies will avoid this odor. When the odor was presented immediately after the shock, however, it became a signal of safety from pain. The flies would later approach this odor as they would approach the smell of food. Although we may never know what pleasure feels like for a fruit fly, the results from this study nevertheless illustrate the similarity between primary rewards and obtaining relief from primary punishers.

Dopamine and Opioid Involvement in Pleasure and Pain

The title of a recent paper sums up current thinking on the role of these two neurotransmitters: "Opioids for Hedonic Experience and Dopamine To Get Ready for It" (Barbano and Cador, 2007). The role of dopamine in reward processing is well established, and for a long time, dopamine was dubbed "the pleasure molecule." This hypothesis is no longer supported, however (Salamone et al., 1997). Instead, it appears that opioids underpin hedonic 'liking', whereas dopamine's role is primarily in motivation or 'wanting' (Berridge, 2007). The opioid-driven pleasure circuit overlaps considerably with the dopamine system, to the point where some cells take part in both circuits. But its role and chemistry are quite different (Berridge, 2003). While dopamine neurons signal salient events even when these are unrelated to primary rewards (Blatter and Schultz, 2006), endogenous opioids have been shown to encode relative taste preference (Taha et al., 2006), and microinjection of opioids into the nucleus accumbens (NAc), the ventral pallidum, the ventral tegmental area (VTA),

and the periacqueductal gray (PAG) increase pleasure-related facial expressions in rodents (Pecina and Berridge, 2000; Smith and Berridge, 2007). Perhaps reflecting the fact that things pleasurable often induce 'wanting', opioids may increase dopamine release in the NAc through the inhibition of GABAergic neurons at the VTA (GABA disinhibition).

Not all opioids are involved in positive hedonic processing, however. While opiate agonists that bind preferentially to μ-opiate receptors cause a feeling of elation, kappa selective opiates generate negative affect in humans (Burgdorf and Panksepp, 2006). Of the endogenous μ-specific opiates, endomorphin-2 appears to have stronger rewarding effects than endomorphin-1 (Huang et al., 2004; Wilson et al., 2000; Zangen et al., 2002). All known μ-opioid subtypes have potent analgesic effects, however. Microinjection of μ-opioids directly into the NAc has been shown to induce antinociception, and microinjection of naloxone into the NAc attenuates the antinociceptive effect of systemically administered morphine (Dill and Costa, 1977). Dopamine activity can also cause pain suppression (Shimizu et al., 2004; Wood, 2006).

The close overlap between the rewarding and analgesic effect of opioids forms the basis of the affective analgesia hypothesis, which in its weakest form holds that pleasure ("reinforcement") can drive the neural substrate of analgesia (Franklin, 1998). A stronger form of the hypothesis—that pleasure and analgesia are identical—has been rejected. For one thing, there are multiple mechanisms of analgesia, including the classic descending inhibitory control system driven by aversive events (Fields, 2004). In fact, the biological significance of endogenous pain control is generally seen in the context of behavioral conflicts where the injured individual must disengage from pain in order to fight or escape (Melzack and Casey, 1968). Both pain- and pleasure-induced analgesia appear to be mediated via the mesolimbic reward system as well as brainstem modulatory nuclei and can be blocked by opioid and/or dopamine antagonists (Forsberg et al., 1987; Gear et al., 1999; Reboucas et al., 2005). According to the motivation-decision model of pain, both types of analgesia act via an all-or-none decision circuit, exerting bidirectional control over pain (Fields, 2006). The circuit consists of ON- and OFF-cell populations in midbrain and medullary pain-modulatory nuclei (the PAG and the rostroventral medulla [RVM]). The cells have a reciprocal activity pattern where OFF-cell silence *permits* a pain response and ON-cell activity facilitates it. Conversely, OFF-cell activity blocks responses to noxious stimuli (Fields, 2006). Taken together, the opioid and dopaminergic mechanisms underlying pleasure- and pain-related analgesia lend support to the idea of a "common currency," which helps the brain make decisions to optimize survival.

Self-Harming, Chilli Peppers, and Masochism

Often, however, the decisions we make seem paradoxical. If it is really better to avoid pain, why do so many people engage in painful and/or potentially harmful activities? Boxers, marathon runners, and soldiers are obvious examples, but even the pleasure of scratching a mosquito bite and eating a spicy meal may be a direct consequence of the tissue damage these activities bring about. The desire for relief from an unpleasant homeostatic state may be key to understanding at least some of these activities, as has been suggested in the case of skydiving (Seymour et al., 2005) and self-cutting (Korner et al., 2007). Subjective reports from borderline personality patients who self-harm imply that the physical pain provides relief from the mental pain they are experiencing (Korner et al., 2007). As is described in more detail below, skydivers experience more anhedonia and derive less pleasure from everyday rewards than individuals who do not take part in extreme sports (Franken et al., 2006). It is certainly possible that thrilling activities like skydiving provide "relief" from an otherwise flat affective state. Interestingly, both the above paradoxical behaviors have been related to changes in dopamine and opioid neurotransmitter systems. Treatment with the predominantly μ-opioid antagonist naltrexone reduces self-harming (Symons et al., 2004), suggesting that opioid release caused by the physical pain is key to maintaining this behavior. Evidence from positron emission tomography (PET) studies of the role of the μ-opioid in emotion regulation suggests a possible mechanism by which self-cutting may relieve mental pain. When people are feeling sad, μ-opioid neurotransmission is reduced in several brain regions, including the rostral ACC (Zubieta et al., 2003). Physical pain, on the other hand, increases μ-opioid activation in this and other regions, especially when subjects believe their pain is being reduced (Zubieta et al., 2005). Both sadness and anhedonia are also associated with disruptions of dopaminergic signaling in the brain (Tremblay et al., 2005).

Another interesting case of paradoxical and potentially self-injurious behavior is the frequent human consumption of chilli peppers. Chillies "burn" in the mouth and on the skin because they contain the

irritant capsaicin, and preparations containing this substance are used in pain research to cause burning pain and hyperalgesia (Dirks et al., 2003; Zambreanu et al., 2005). Some capsaicin creams are also used in the treatment of persistent pain, as the initial burning sensation is followed by a period of antinociception (Dray, 1992). Since capsaicin is neurotoxic to certain sensory neurons in the skin (Chard et al., 1995; Hail, 2003), it makes sense from a homeostatic point of view that applying it to the skin or eating it in a hot curry should feel unpleasant. In fact, plants such as chilli peppers and garlic appear to use thermoTRP-activating capsaicin and allicin to deter mammalian predators from consuming the plant (Dhaka et al., 2006). So why do so many people enjoy foods containing these irritants? One interesting explanation is suggested in Harold McGee's book on *the Science and Lore of the Kitchen* (McGee, 2004). Since many "spicy" compounds induce a temporary inflammation in the mouth, they may enhance pleasure by making eating more *sensual* and intense; the mouth and tongue are tender and more sensitive to touch and temperature.

"I have just run the hot water tap and put my hands underneath it, with the water as hot as I could bear for as long as I could bear. The water was probably hotter than most people could stand, certainly beyond the temperature to cause pain. That was why I did it" (Launer, 2004, p. 383). Dermatologist and eczema sufferer John Launer explains that when the itch becomes intolerable, most people with eczema know that the only thing that will "crack" the itch is to subject themselves to pain. While applying cool water to the skin will relieve the itch only briefly, pain—even when applied to an unaffected body part—will provide longer-lasting itch relief (Mochizuki et al., 2003; Ward et al., 1996). This is probably the reason that scratching a mosquito bite until the skin looks red and flared can often feel pleasurable; the tissue damage caused by nails biting into the skin "cracks" the attention-grabbing and unpleasant itch sensation. The unpleasant homeostatic imbalance caused by itch is thus an example of a state for which pain becomes beneficial (Craig, 2003).

For many athletes, whether ballet dancers, boxers, or football players, entry into the athletic community is marked by willingness to endure pain (Downey, 2007). The role of pain in athletic activities is not well understood and is unlikely to be explained by a single factor. It is possible that the pain endured during physical activity, like the painful burn of capsaicin cream or the exquisite hurt of self-cutting, produces relief from another, ongoing pain. It may also be that this type of pain enhances other, pleasurable sensory experiences, like a hot curry increasing sensitivity in the mouth. What is known is that during training, many athletes learn to distinguish between "normal" and other pain signals—some should be endured and others paid attention to (Downey, 2007). Janal and colleagues (1994) investigated the pain sensitivity of runners and nonrunners in their paper "Are Runners Stoical?" A significant difference between the two groups was found only for cold pain, a sensation the athletes were accustomed to from running in cold weather. Changes in athletes' pain sensitivity during competitions has been attributed to stress-induced endogenous opioid analgesia (Sternberg et al., 1998). It is likely that the endogenous opioid system is involved in antinociception during all kinds of athletic pain, and endorphins are generally thought to be responsible for the feeling of well-being, which often follows vigorous exercise (Morgan, 1985).

As a positive hedonic feeling, post-training well-being may in turn make athletes remember their pain as less unpleasant. Daniel Kahneman and colleagues (1993) have found that adding a better end to a painful procedure changes subjects' memories of the pain they experienced. A few minutes of less intense pain added to the end of a medical procedure led subjects to remember less overall pain, and although this procedure involved experiencing pain for a longer time, it was the subjects' preferred option. Finally, while on the topic of paradoxical behaviors, let us not forget that enduring some discomfort is an efficient way of increasing the pleasure of returning to homeostasis. Who has not tried fasting for a few extra hours before a feast, or stayed in the sun until almost unbearably hot before jumping into a refreshing pool?

Whether similar homeostatic mechanisms are involved in sexual masochism—perhaps the most paradoxical of all human behaviours—is not known. For all the activities outlined above, although there is evidence that the hedonic feelings associated with the pain become less intense, there is little proof that the pain is experienced as pleasurable *in itself*. While the overall experience adds up to be pleasurable, the painful sensation itself is seldom seen as the direct cause of pleasure. This appears to hold true even in extreme pain-seeking subcultures of a nonsexual nature. Such pain-seeking behavior appears to be similar to the type of thrill-seeking seen in extreme sports, and stress- and fear-induced analgesia undoubtedly diminishes the pain intensity of these activities. In contrast, although little study has been done in this field, we know of at least one subculture where even extremely intense pains may cause

pleasure, and where the main mechanism for analgesia may be pleasant sexual arousal. Contrary to popular belief, however, pain may not be the main goal for sexual masochists. Instead, it has been argued that the main purpose of pain in sadomasochistic (SM) interactions is to denote power (Cross and Matheson, 2006). In support of this notion, many important symbols and activities in SM relations are more to do with handing over personal autonomy (i.e., bondage) than with pain per se (Moser and Kleinplatz, 2006). The peculiar mixture of pain, power games, and sex central to the SM subculture is distasteful to many, and this dichotomy was exploited in an elegant neuroimaging study on disgust and sexual arousal (Stark et al., 2005). Two groups of subjects viewed disgust-inducing, erotic, neutral, and SM-related images. The researchers report a striking resemblance between brain activation patterns in healthy subjects viewing erotic images compared with SM subjects looking at images of SM interactions (see Figure 19.3). When the non-SM group viewed the SM-related images, however, their brain activation was more similar to that of either group feeling disgust.

Pain, Reward, Mood, and Placebo

Many theories have been put forth to explain why sadomasochists associate pain with sexual arousal and pleasure, but little empirical evidence exists to support these (Cross and Matheson, 2006). What is clear is that for most sexual masochists, pain is only pleasurable within an SM context. The context in which pain is experienced has been shown to strongly influence pain perception both in studies of pain in both experimental and clinical populations (Benedetti et al., 2005; Moseley and Arntz, 2007; Price et al., 1987). As has been suggested above, when pain occurs within a context of available rewards, the pain modulatory system may induce antinociception (Fields, 2006). In this section, we present evidence for the analgesic effects of both primary and secondary rewards, and discuss a possible interaction with positive mood.

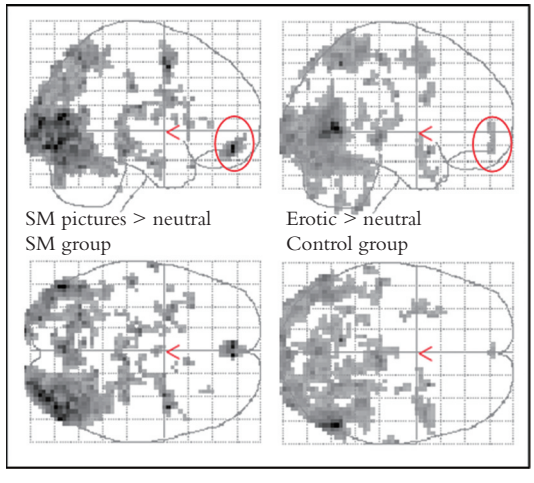

Figure 19.3 "Glass brains" from SPM analysis of the SM and control groups viewing SM-related and erotic images, respectively. The circles indicate the ventromedial prefrontal cortex. Other common regions were identified using region of interest analysis, notably the amygdala. (Image adapted from Stark et al, 2005.)

Although it cannot fully explain pain-seeking in sexual masochists, endogenous opioid release appears to play a role in sexual behavior in humans and in animals (Coolen et al., 2004), and may be the main mechanism of antinociception in sexual contexts. Endogenous opioids underpin positive hedonic feelings in sexual contexts. Treatment with the μ-opioid antagonist naloxone reduced subjective arousal and reported pleasure in human male orgasms (Murphy et al., 1990). Naloxone blocks mating-induced conditioned place preference in both female and male rats (Paredes and Martinez, 2001) and may even bring about conditioned place aversion (Agmo and Berenfeld, 1990). The link between sexual behavior and endogenous opioids may be phylogenetically ancient; as naloxone was also found to reduce appetitive sexual responses in quails (Holloway et al., 2004). Furthermore, in the somewhat provocatively titled article "Vaginal Stimulation-Produced Analgesia in Rats and Women," Komisaruk and Whipple (1986) review evidence for the antinociceptive effects of sexual behavior in females. Szechtman and colleagues (1981) gave copulating male rats electric shocks and reported a pattern of antinociception consistent with increasing levels of pleasure and endogenous opioid release before and during mating. For a brief period immediately after ejaculation, the rats were more sensitive to pain, consistent with the notion a opioid-opponent "dysphoric" low following the positive hedonic feelings of mating (Solomon and Corbit, 1974). In addition, sexual behavior–induced antinociception in male rats is naloxone-reversible (Forsberg et al., 1987). A final point of interest from the literature on pain in sexual contexts relates to the roughly 20% of laboratory rats, which fail to initiate mating within a certain time window when placed next to female rat. Painful procedures such as the tail pinch have proven efficient for speeding up mating in these

"noncopulators" (King and Alexander, 2000). Since endogenous opioids are released during pain (Zubieta et al., 2001), this arousing effect of pain may also be mediated by opioids.

Endogenous opioids are also involved in both the hedonic 'liking' and analgesic effect of eating. As mentioned, microinjection of opioids into the brain's reward network increases 'liking' behavior in rodents (Berridge and Robinson, 2003). In humans, naloxone reduces the hedonic value of sweet high-fat snacks (Drewnowski et al., 1992; Fantino et al., 1986) and decreases consumption of palatable foods in binge-eaters (Drewnowski et al., 1995). Sweet foods and drinks increase pain tolerance, especially in neonates (Blass and Hoffmeyer, 1991), women (Mercer and Holder, 1997), and people with low blood pressure (Lewkowski et al., 2003). In rats, sweet substance–induced analgesia is naltrexone-reversible (Reboucas et al., 2005). Furthermore, Pearce and Dickinson (1975) showed that when hungry rats learn that a painful electric shock predicts a food reward, this Pavlovian pairing will attenuate the defensive reactions elicited by the shock. The authors contend that this *counterconditioning* reduced shock aversiveness, "because after such conditioning the shock activates both the positive and negative systems, thus allowing the positive system to attenuate the activity in the negative one" (Pearce and Dickinson, 1975, p. 177). They also showed that the antinociceptive effect of the counterconditioning is dependent on the balance between the hedonic value of the food reward and the shock, and is ineffective if the shock is too severe. Note that these rats were kept at 80% of their normal bodyweight, such that the subjective utility and pleasantness of the food reward was likely to "outweigh" a substantial level of pain.

Several studies of pain and emotion in humans have used positive and negative affective pictures to compare pain sensitivity in pleasant and unpleasant contexts. The findings point to a linear pain modulation effect where subjective pain ratings are reduced in the positive image context and enhanced in the negative context compared to when they view neutral images. This pain modulatory effect is echoed in the amplitude of brain event-related potentials (Kenntner-Mabiala and Pauli, 2005) and appears to extend into clinical populations (Rhudy et al., 2006). Villemure and colleagues (2003) found a similar effect using pleasant and unpleasant odors to modulate pain perception. This study went one step further and also showed that the odors modulated pain through their effects on mood. It is not unlikely that the pain-modulatory effects of viewing pleasant images, partaking in sexual behaviors, or eating tasty foods also rely on the influence of mood. In addition, pleasant music was recently shown to decrease experimental thermal pain ratings (Roy et al., in press). The hedonic value of the music had no effect on perception of innocuous warm stimulation, however.

Perhaps the best-studied effect of context on pain perception is the placebo analgesic effect. Typically, subjects in placebo studies are led to believe that an inactive substance (the placebo treatment) has potent analgesic effects. This *meaning response* (Moerman and Jonas, 2002) has been remarkably effective across a range of studies using different methodologies in various clinical and nonclinical populations (Benedetti et al., 2005; Bingel et al., 2006; de la Fuente-Fernandez and Stoessl, 2002; Levine et al., 1978; Mayberg et al., 2002; Petrovic et al., 2002, 2005; Wager et al., 2004; Zubieta et al., 2005). Placebo treatment rarely causes complete pain relief, but even a weak effect makes it the better of two hedonic outcomes. According to psychologist Barbara Mellers, such comparison effects are very powerful-enough to make a loss that is the better of two losses more pleasurable than a gain that is the worse of two gains (Mellers, 2001). Neuroimaging data supports the notion that expectation of placebo is equivalent to expectation of a positive hedonic outcome. In 2001, de la Fuente-Fernandez and colleagues reported dopamine release in the nigrostriatal system during placebo treatment of patients with Parkinson's disease. The authors argued that the dopamine release underpinned expectation of reward—in this case, the anticipation of therapeutic benefit. Similarly, placebo treatment of anxiety is thought to rely on reward expectation (Petrovic et al., 2005). In support of this idea, a neuroimaging study of pain and cooling relief reported that anticipation of pain relief was processed in the same way as reward expectation in the brain (Seymour et al., 2005).

Pleasure-Seeking, Evolution, and Morality

The close relationship between homeostatic processes and hedonic feelings point to an evolutionary benefit for pleasure-seeking, pain-avoiding individuals. This contrasts sharply with the pleasure-conservative views expressed in many scientific papers, religious scriptures, etc. In an influential paper in *Science*, Koob and Le Moal (1997) describe pleasure as a "limited resource" (p. 56) and argue for the benefits of a "hedonic Calvinistic" approach where the use of the

reward system is restricted. These researchers are experts on drug addiction, and their view of pleasure is likely influenced by the detrimental consequences of "pleasure-seeking" for drug addicts. It is important to keep in mind, however, that the pleasures sought by nonaddicts are significantly more diverse than those of a dedicated drug fiend (Kelley and Berridge, 2002). One important difference between drugs of abuse and natural rewards relates to satiety. Although it is well established that addictive drugs exert their positive hedonic effects via the brain's naturally evolved "reward system" (Volkow and Fowler, 2000), the sensory-specific satiety effects triggered by natural rewards such as food appear to be missing. Sensory-specific satiety is the reason the pleasure of eating chocolate will diminish as we work our way through bar after bar, while at the same time increasing the tastiness of other foods (Kringelbach et al., 2003). This mechanism prevents one-tracked pleasure-seeking and ensures consumption of diverse rewards, edible and otherwise. Through this diversifying effect, sensory-specific satiety appears to foster important health benefits: for instance, a varied diet enhances the cancer-fighting ability of antioxidant metabolites (Halvorsen et al., 2006).

In contrast, addictive drugs such as cocaine fail to trigger a decrease in positive affect with repeated exposure. Instead, frequent drug use appears to modify the brain's reward system, increasing affinity for the addictive drug and decreasing the pleasure associated with food, social rewards, and other normally enjoyable activities (Volkow et al., 2002). Research on the increasing obesity epidemic in the Western world points to startling similarities with drug addiction, suggesting that high-energy foods such as sugar and fat may sometimes override the brain's natural satiety system in the same way as a recreational drug (Volkow and Wise, 2005). Another class of nonpharmacological rewards, which may exert drug-like effects on the brain's reward system, is extreme sports activity. Here, the main link is anhedonia: "the inability to find enjoyment in food, sex, physical recreational pastimes, as well as socializing, humor and achievement" (Marbach and Lund, 1981, p 75). The idea is simple: because of the similarity between drug-induced euphoria and the intense hedonic feelings experienced by skydivers, their enjoyment of everyday pleasures is lower than that of, for example, rowers, who do not experience such "natural high" on a regular basis (Franken et al., 2006). However, in terms of their adverse effects, "addiction" to extreme sport thrills and drug addiction are not comparable.

It appears, then, that so long as we avoid addictive drugs and seek a variety of rewards, we are not at risk of exhausting our "limited resources" of pleasure. The "Calvinistic" focus on moderation or even abstinence of pleasures has deep roots within Western culture, however. A prevailing belief is that a dichotomy exists between virtue and morality on the one hand, and self-interest or pleasure on the other (Wringe, 1999). In the pertinently named essay "Shame, Pleasure and the Divided Soul," Moss (2005) explains that for Plato, feelings of shame can separate a person's judgments about what is pleasant from his judgments about what is good: "appeals to a person's feelings of shame and admiration may be able to succeed, when rational arguments have failed, in bringing him to see that a harmful pleasure is to be avoided, or that a beneficial pain is to be pursued" (Moss, 2005, p 3).

Unlike some religious fanatics, however, Plato was not opposed to pleasures in general. His "harmful pleasures" and "beneficial pains" highlight the potential conflict between immediate and delayed gratification. Many believe that what sets us apart from animals is our ability to override our instinct for immediate rewards in favor of some greater good. Neuroimaging data supports the idea that the human capacity for appreciating delayed or abstract rewards is processed separately from the phylogenetically older immediate gratification system (McClure et al., 2004). In animals, both delays and effort discount the hedonic value of a reward, possibly due to increased uncertainty of reward receipt (Rudebeck et al., 2006). For humans, an important part of childhood development is learning to resist the lure of immediate pleasures in order to obtain greater and often more abstract rewards. The ability to delay or restrict pleasures is often considered a virtue. In the words of writer Paul Bischke (2003), "the motive of virtue is to enact and embody what is good, right, and fitting." The use of the term "fitting" is important: the definition of a virtue changes between cultures and within cultures over time. For instance, "temperance" to all pleasures is advocated in the Bible, but whether this refers to complete abstinence from pleasures or merely refraining from overindulgence is still subject to debate. Interestingly, even the reputedly frugal Calvin did not advocate absolute abstinence: "it is permissible to use wine not only for necessity, but also to make us merry" (as cited in Bischke, 2003). All in all, the strong historical association between virtue on the one hand, and shame, guilt, and pleasure on the other, may help explain the apparent preference for formulating scientific research questions in terms of reward rather than pleasure.

Meaningful Suffering?

While temperance is considered a virtue with respect to pleasures, stoicism in the face of pains is also highly regarded in many cultures (Downey, 2007; Janal et al., 1994; Tudor, 2001). For instance, Harper (2006) reports that within the British Armed Forces, a prevalent view is that physical activity will only be beneficial if it is painful. The everyday expression "no pain, no gain" implies that this type of belief is not restricted to a military context. Self-flagellation is another example of paradoxical pain-seeking human behaviors, motivated perhaps by the abstract pleasure of feeling closer to God. According to Parker (1997), God may bring new self-awareness, love for the divine, or the reconciliation of enemies through suffering: "these gifts are immeasurably wonderful and more than compensate for any suffering that one might endure" (Parker, 1997, p. 207). The belief that suffering has real, though perhaps incomprehensible, meaning is comforting and is generally preferred over the belief that suffering is meaningless. In a paper published in the journal *Pastoral Psychology*, the therapists Driscoll and Edwards (1983) discuss various Christian takes on meaningful suffering. They claim that a popular misconception among Christians is that there is automatic merit to suffering, and that by suffering one shows oneself to be a better Christian. Suffering is part of life, to be endured to enter heaven (Davidhizar and Giger, 2004). In contrast, one of the earliest concepts portrayed in the Old Testament is that of a God who blesses the righteous and afflicts the wicked, so that suffering was the consequence of a violation of God's will (Driscoll and Edwards, 1983). Tudor, writing in the context of prisoners' accepting their punishment as meaningful suffering, divides suffering into different categories, including the following: (1) the cost to achieve a goal; (2) a necessary condition for virtue, such as courage, fortitude, stoicism; and (3) a necessary condition for understanding other people and the world through empathy. Interestingly, a study of congenital insensitivity to pain showed that a normal personal experience of pain is not required for perceiving and feeling empathy for others' pain (Danziger et al., 2006). C.S. Lewis formulated a moderate Christian interpretation of suffering, which was also based on empathy: through our actions, we cause both suffering and joy for ourselves and for others, and our actions therefore have personal and ethical importance, which otherwise they would not have. It is easy to understand that God would allow our actions to matter, and there is no need in this view to suggest that God in any way wants us to suffer (C.S. Lewis, as cited in Driscoll and Edwards, 1983).

As discussed above in relation to positive hedonic feelings, the context in which we experience pain determines what meaning we assign to it (Moseley and Arntz, 2007). As we have seen, the diminished suffering experienced during placebo analgesia directly relates to the more positive context of the treatment, perhaps via the same antinociceptive mechanism, which mediates pain relief from viewing pleasant images, smelling delicious scents, or listening to lovely music. The meaning of suffering is especially important in the case of persistent, chronic pain, which often constitutes a threat to the patients' identity and sense of self (McCracken et al., 2004). Like excessive pleasure, persistent suffering is associated with shame: "I am not the kind of woman who complains of everything" (Werner et al., 2004). Research from Rita Charon's laboratory has shown the importance of narrative and sense of self in the treatment of chronic pain. Patients in their clinic who were allowed time to relate a coherent story of their pain and suffering to their doctor showed more improvement from treatment than did the patients who were allocated a regular appointment with the pain clinician (Charon, 2006).

Concluding Remarks

In this chapter, we have used theories of homeostasis as a framework for understanding the *how* and *why* of hedonic feelings. This framework allows us to explain a range of paradoxical human behaviors, notably the many situations in which people willingly subject themselves to pain. It is important to remember that purely "mental" (emotional) changes are considered deviations from homeostasis in the same way as changes in physiological body state. Another important consideration is that homeostatic processing is often subconscious: we are not aware of most homeostatic imbalances, since they are easily remedied through subconscious processes. A pertinent example is posture changes, which most people make frequently with little awareness (Gallagher and Cole, 1995). Thus the pleasures we experience and can introspect on may in fact inform us of underlying needs that we would otherwise not be aware of.

Much is known about the physiology of nociceptive signalling from the periphery, but it is clear that to understand how the subjective, hedonic feeling of pain arises in the brain, how nociception-related signalling is *interpreted* into pain, we must extend our focus to

include a number of other factors. Both negative and positive hedonic feelings influence the interpretation of nociceptive signals in the brain. More research is warranted on how expectation, learning, and memory for pain influence the hedonic pain experience. For instance, expectation has a value in itself (Berns et al., 2006; Gard et al., 2006; Mellers, 2001), *and* changes interpretation of nociceptive signals (Fairhurst et al., 2007; Koyama et al., 2005). Expectation and context interact in a powerful way: the negative hedonic feelings are higher when the pain is worse than expected, or even if it is simply the worse of two or more alternative outcomes. Conversely, placebo analgesia treatment represents the best of two outcomes and is characterized by decreased unpleasantness. The same mechanisms are at work for positive hedonic feelings: people are frustrated when they get less than they expect (Abler et al., 2005), less than other people, or simply less than they could have received (e.g., Prisoner's Dilemma; Singer et al., 2004), and this diminishes their pleasure (Mellers, 2001; Ursu and Carter, 2005). The context can also be defined by motivation for abstract goals, such as reducing another's (or others') suffering, which can also decrease the hedonic component of pain by changing its meaning—it hurts but "no pain, no gain," remember?

Much work remains before we will fully understand the interactions between negative and positive hedonic feelings. As reviewed here, however, the indications that pleasures can reduce pain-related suffering are already numerous. As we have seen, the opioid and dopamine systems play an important role for both pleasures and pains. These neurotransmitters are likely to underpin pain and pleasure interactions, such as decreases in pain in the context of pleasures (food, music, sex, etc). More research on these effects could lead to novel treatments of pain and suffering. In the chronic pain field, it is becoming increasingly clear that the effect of persistent pain on patients' sense of self is key to their suffering (Jensen, 2007). To understand the human self, we must know *what it is like* to be a sentient being: we must study hedonic feelings, pleasures as well as pains. Taken together, the available evidence suggests that seeking a variety of pleasures is beneficial not only in itself, but also because pleasures may reduce pain and suffering.

Acknowledgments

The authors would like to thank Lorimer Moseley, John Keltner, and the editors of this book for their insights and helpful comments on earlier versions of this manuscript.

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