by rTMS of primary motor cortex. *Curr. Biol.* **14**, 252–256 (2004).

44. Tong, C., Wolpert, D. M. & Flanagan, J. R. Kinematics and dynamics are not represented independently in motor working memory: evidence from an interference study. *J. Neurosci.* **22**, 1108–1113 (2002).

45. Tong, C. & Flanagan, J. R. Task-specific internal models for kinematic transformations. *J. Neurophysiol.* **90**, 578–585 (2003).

46. Cunningham, H. & Welch, R. Multiple concurrent visual-motor mappings: implications for models of adaptation. *J. Exp. Psychol. Hum. Percep. Perform.* **20**, 987–999 (1994).

47. Seidler, R. Multiple motor learning experiences enhance motor adaptability. *J. Cogn. Neurosci.* **16**, 65–73 (2004).

48. Willingham, D. B., Salidis, J. & Gabrieli, J. D. Direct comparison of neural systems mediating conscious and unconscious skill learning. *J. Neurophysiol.* **88**, 1451–1460 (2002).

49. Mayr, U. Spatial attention and implicit sequence learning: evidence from independent learning of spatial and nonspatial sequences. *J. Exp. Psychol. Learn. Mem. Cogn.* **22**, 350–364 (1996).

50. Schmidtke, V. & Heuer, H. Task integration as a factor in secondary-task effects on sequence learning. *Psychol. Res.* **60**, 53–71 (1997).

51. Shin, J. & Ivry, R. Concurrent learning of temporal and spatial sequences. *J. Exp. Psychol. Learn. Mem. Cogn.* **28**, 445–457 (2002).

52. Aizenstein, H. J. *et al.* Regional brain activation during concurrent implicit and explicit sequence learning. *Cereb. Cortex* **14**, 199–208 (2004).

53. Sakai, K., Kitaguchi, K. & Hikosaka, O. Chunking during visuomotor sequence learning. *Exp. Brain Res.* **152**, 229–242 (2003).

54. Wright, D. L., Black, C. B., Immink, M. A., Brueckner, S. & Magnuson, C. Long-term motor programming improvements occur via concatenation of movement sequences during random but not during blocked practice. *J. Mot. Behav.* **36**, 39–50 (2004).

55. Shea, J. & Morgan, R. Contextual interference effects on the acquisition, retention, and transfer of a motor skill. *J. Exp. Psychol. Hum. Learn. Mem.* **5**, 179–187 (1978).

56. Simon, D. & Bjork, R. Metacognition in motor learning. *J. Exp. Psychol. Learn. Mem. Cogn.* **27**, 907–912 (2001).

57. Osu, R., Hirai, S., Yoshioka, T. & Kawato, M. Random presentation enables subjects to adapt to two opposing forces on the hand. *Nature Neurosci.* **7**, 111–112 (2004).

58. Misanin, J. R., Miller, R. R. & Lewis, D. J. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science* **160**, 554–555 (1968).

59. Nader, K., Schafe, G. & LeDoux, J. The labile nature of consolidation theory. *Nature Rev. Neurosci.* **1**, 216–219 (2000).

60. Sara, S. Strengthening the shaky trace through retrieval. *Nature Rev. Neurosci.* **1**, 212–213 (2000).

61. Karni, A. The acquisition of perceptual and motor skills: a memory system in the adult human cortex. *Brain Res. Cogn. Brain Res.* **5**, 39–48 (1996).

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TIMELINE

The emotional brain

Tim Dalgleish

The discipline of affective neuroscience is concerned with the neural bases of emotion and mood. The past 30 years have witnessed an explosion of research in affective neuroscience that has addressed questions such as: which brain systems underlie emotions? How do differences in these systems relate to differences in the emotional experience of individuals? Do different regions underlie different emotions, or are all emotions a function of the same basic brain circuitry? How does emotion processing in the brain relate to bodily changes associated with emotion? And, how does emotion processing in the brain interact with cognition, motor behaviour, language and motivation?

How are emotions and moods embodied in the brain? This is the central question that is posed by affective neuroscience — an endeavour that integrates the efforts of psychologists, psychiatrists, neurologists, philosophers and biologists. Affective neuroscience uses functional neuroimaging, behavioural experiments, electrophysiological recordings, animal and human lesion studies, and animal and human behavioural experiments to seek a better understanding of emotion and mood at the neurobiological and psychological levels and their interface.

In this article, I outline the historical development of affective neuroscience (see TIMELINE). I begin by reviewing the pioneering work of William James[1] and Charles Darwin[2]. This is followed by discussion of the early functional neuroanatomical models of emotion of Walter Cannon and Philip Bard[3–6], James Papez[7] and Paul MacLean[8]. I then briefly outline our current knowledge of the contributions of key brain regions, including the prefrontal cortex (PFC), amygdala, hypothalamus and anterior cingulate cortex (ACC), to the processing of emotions, before considering contemporary theoretical accounts of how these regions might interact. Finally, some thought is given to the future directions of affective neuroscience.

Two fathers of affective neuroscience
In 1872, Charles Darwin published a groundbreaking book — *The Expression of the Emotions in Man and Animals*[2]. It was the culmination of 34 years of work on emotion and made two important contributions to the field. The first was the notion that animal emotions are homologues for human emotions — a logical extension of Darwin's early work on evolution[9]. Darwin sought to show this by comparing and analysing countless sketches and photographs of animals and people in different emotional states to reveal cross-species similarities (FIG. 1). He also proposed that many emotional expressions in humans, such as tears when upset or baring the teeth when angry, are vestigial patterns of action. The second contribution was the proposal that a limited set of fundamental or 'basic' emotions are present across species and across cultures (including anger, fear, surprise and sadness).

These two ideas had a profound influence on affective neuroscience by promoting the use of research in animals to understand emotions in humans and by giving impetus to a group of scientists who espoused the view that different basic emotions had separable neural substrates[10].

Around 10 years later, James, in his seminal paper entitled 'What is an Emotion?'[1], controversially proposed that emotions are no more than the experience of sets of bodily changes that occur in response to emotive stimuli. So, if we meet a bear in the woods, it is not the case that we feel frightened and run; rather, running away follows directly from our perception of the bear, and our experience of the bodily changes involved in running is the emotion of fear. Different patterns of bodily changes thereby code different emotions. Similar ideas were developed in parallel by Carl Lange in 1885 (REF. 11), providing us with the James–Lange theory of emotions.

The James–Lange theory was challenged in the 1920s by Cannon[3,4] on several grounds: total surgical separation of the viscera from the brain in animals did not impair emotional behaviour; bodily or autonomic activity cannot differentiate different emotional states; bodily changes are typically too slow to generate emotions; and artificial hormonal activation of bodily activity is insufficient to generate emotion. Recent research has cast doubt on Cannon's claims. Emotional responses can be distinguished (at least partly) on the basis of autonomic activity[12]; emotions were less intense when the brain was disconnected from the viscera in Cannon's studies; and some artificial manipulations of organ activity can induce

emotions — for instance, intravenous administration of cholecystokinin (a gastric peptide) can provoke panic attacks[13].

The James–Lange theory has remained influential. Its main contribution is the emphasis it places on the embodiment of emotions, especially the argument that changes in the bodily concomitants of emotions can alter their experienced intensity. Most contemporary affective neuroscientists would endorse a modified James–Lange view in which bodily feedback modulates the experience of emotion (see below).

Early neuroanatomical theories

The Cannon–Bard theory. Cannon's criticism of the James–Lange theory arose from his investigations with Bard of the effects of brain lesions on the emotional behaviour of cats. Decorticated cats were liable to make sudden, inappropriate and ill-directed anger attacks — a phenomenon that Cannon and Bard labelled 'sham rage'. Cannon and Bard argued that if emotions were the perception of bodily change, then they should be entirely dependent on having intact sensory and motor cortices. They proposed that the fact that removal of the cortex did not eliminate emotions must mean that James and Lange were wrong.

On the basis of data such as these, Cannon and Bard proposed the first substantive theory of the brain mechanisms of emotion[5,6]. They argued that the hypothalamus is the brain region that is involved in the emotional response to stimuli and that such responses are inhibited by evolutionarily more recent neocortical regions. Removal of the cortex frees the hypothalamic circuit from top–down control, allowing uncontrolled emotion displays such as sham rage.

Cannon and Bard's work illustrates the benefits of two important methodologies in affective neuroscience. First, the use of animal emotions as human homologues, as proposed by Darwin[2]. And second, the use of surgical brain lesions to understand emotions, based on the logic that any changes after surgery must reflect processes that involved the lesioned part of the brain.

The Papez circuit. In 1937, James Papez pro-posed a scheme for the central neural circuitry of emotion — now known as the 'Papez circuit'[7] (FIG. 2). Papez proposed that sensory input into the thalamus diverged into upstream and downstream — the separate streams of 'thought' and 'feeling'. The thought stream was transmitted from the thalamus to the sensory cortices, especially the cingulate region. Through this route, sensations were turned into perceptions, thoughts and memories. Papez proposed that this stream continued beyond the cingulate cortex through the cingulum pathway to the hippocampus and, through the fornix, to the mammillary bodies of the hypothalamus and back to the anterior thalamus via the mammillothalamic tract. The feeling stream, on the other hand, was transmitted from the thalamus directly to the mammillary bodies, allowing the generation of emotions (with downward projections to the bodily systems), and so via the anterior thalamus, upwards to the cingulate cortex. According to Papez, emotional experiences were a function of activity in the cingulate cortex and could be generated through either stream. Downward projections from the cingulate cortex to the hypothalamus also allowed top–down cortical regulation of emotional responses. Papez's paper was a remarkable achievement, especially given that it was allegedly written in just a few days. Many of the pathways that Papez proposed exist, although there is less evidence that all the regions he specified are central to emotion.

MacLean's limbic system. A more broadly supported anatomical model (in terms of current data) of the brain regions that are involved in emotion was proposed by Paul MacLean in 1949 (REF. 8) (FIG. 3). MacLean's model elaborated on Papez's and Cannon and Bard's original ideas and integrated them with the knowledge provided by the seminal work of Kluver and Bucy. In 1939, Kluver and Bucy[14] had shown that bilateral removal of the temporal lobes in monkeys led to a characteristic set of behaviours (the 'Kluver–Bucy syndrome') that included a loss of emotional reactivity, increased exploratory behaviour, a tendency to examine objects with the mouth, hypersexuality and abnormal dietary changes, including copraphagia (eating of faeces). These studies indicated a key role for temporal lobe structures in emotion — a centrepiece in MacLean's theory.

MacLean viewed the brain as a triune architecture[15]. The first part is the evolutionarily ancient reptilian brain (the striatal complex and basal ganglia), which he saw as the seat of primitive emotions such as fear and aggression. The second part is the 'old' mammalian brain (which he originally called the 'visceral brain'), which augments primitive reptilian emotional responses such as fear and also elaborates the social emotions. This brain system includes many of the components of the Papez circuit — the thalamus, hypothalamus, hippocampus and cingulate cortex — along with important additional structures, in particular the amygdala and the PFC. Finally, the 'new' mammalian brain consists mostly of the neocortex, which interfaces emotion with cognition and exerts top–down control over the emotional responses that are driven by other systems.

MacLean's essential idea was that emotional experiences involve the integration of sensations from the world with information from the body. In a neo-Jamesian view, he proposed that events in the world lead to bodily changes. Messages about these changes return to the brain where they are integrated with ongoing perception of the outside world. It is this integration that generates emotional experience. MacLean proposed that such integration was the function of the visceral brain, in particular the hippocampus, and three years later he introduced the term 'limbic system' for the visceral brain[16].

MacLean's limbic system concept survives to the current day as the dominant conceptualization of the 'emotional brain', and the structures that he identified as important have been the focus of much of the research in affective neuroscience since his original publication. However, the notion of the limbic system has more recently been criticized on both empirical[17] and theoretical grounds[18]. A number of the limbic system structures — the hippocampus, the mammiliary bodies and the anterior thalamus — seem to have a much smaller role than MacLean imagined. Some of
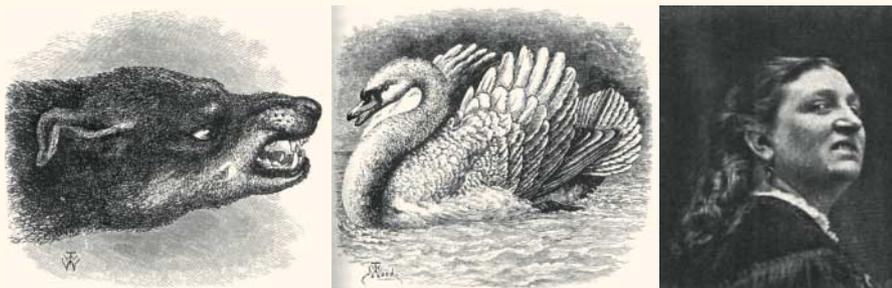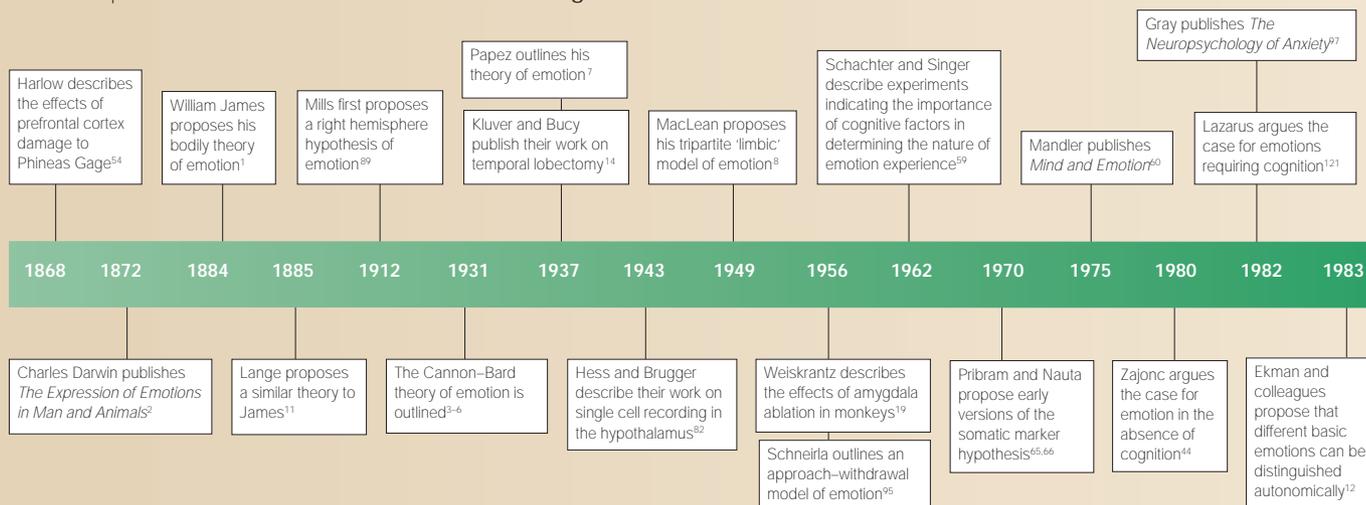

Figure 1 | **Darwin's drawings.** Drawings and photographs used by Darwin[2] to illustrate cross-species similarities in emotion expression — in this case, anger/aggression.

Timeline | **Historical milestones in understanding the emotional brain**

1868	1872	1884	1885	1912	1931	1937	1943	1949	1956	1962	1970	1975	1980	1982	1983

Above timeline:

Harlow describes the effects of prefrontal cortex damage to Phineas Gage[54]

William James proposes his bodily theory of emotion[1]

Mills first proposes a right hemisphere hypothesis of emotion[89]

Papez outlines his theory of emotion[7]

Kluver and Bucy publish their work on temporal lobectomy[14]

MacLean proposes his tripartite 'limbic' model of emotion[8]

Schachter and Singer describe experiments indicating the importance of cognitive factors in determining the nature of emotion experience[59]

Gray publishes *The Neuropsychology of Anxiety*[97]

Mandler publishes *Mind and Emotion*[60]

Lazarus argues the case for emotions requiring cognition[121]

Below timeline:

Charles Darwin publishes *The Expression of Emotions in Man and Animals*[2]

Lange proposes a similar theory to James[11]

The Cannon–Bard theory of emotion is outlined[3–6]

Hess and Brugger describe their work on single cell recording in the hypothalamus[82]

Weiskrantz describes the effects of amygdala ablation in monkeys[19]

Schneirla outlines an approach–withdrawal model of emotion[95]

Pribram and Nauta propose early versions of the somatic marker hypothesis[65,66]

Zajonc argues the case for emotion in the absence of cognition[44]

Ekman and colleagues propose that different basic emotions can be distinguished autonomically[12]

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them seem to be more involved in higher cognitive processes such as declarative memory. Nevertheless, other brain regions identified by Cannon and Bard, Papez and MacLean seem to be integral to emotional life — notably, the 'reptilian brain' (the ventral striatum and the basal ganglia) and the limbic structures of the amygdala, hypothalamus, cingulate cortex and PFC. In the next four sections, I examine how research on these four limbic regions has

developed since MacLean's original paper (FIG. 4). Other brain regions (the thalamus, nucleus accumbens, ventral pallidum, hippocampus, septum, insula, somatosensory cortices and brain stem) have also been implicated in the processing of emotion; however, detailed discussion of these areas is beyond the scope of this review (but see below for a discussion of the insular cortex and its potential involvement in disgust).
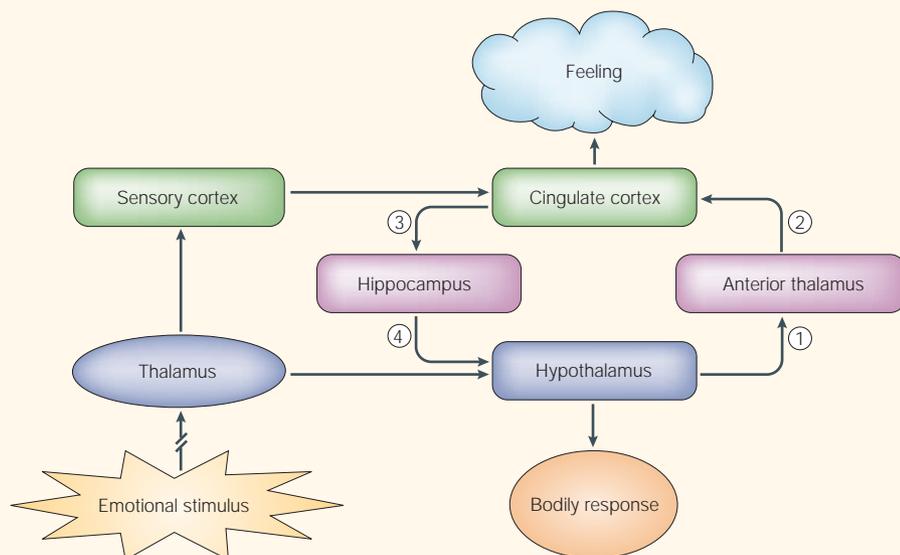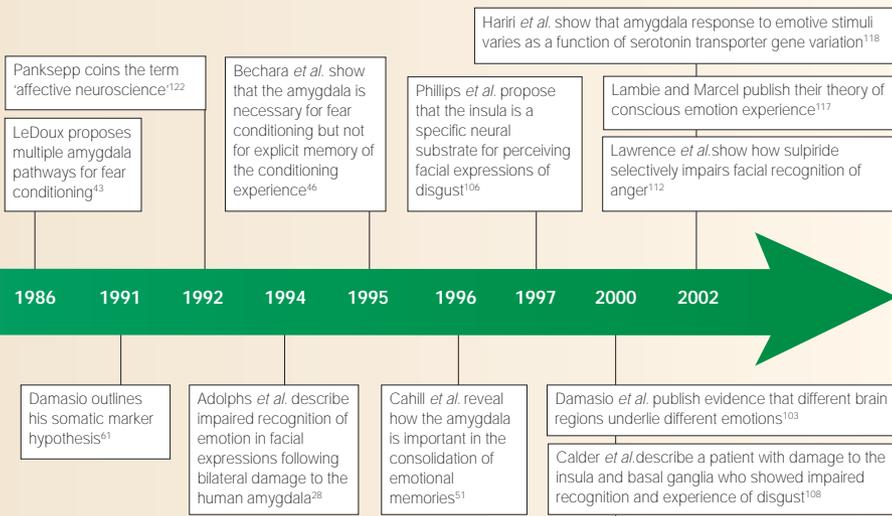

Figure 2 | **The Papez circuit theory of the functional neuroanatomy of emotion.** Papez[7] argued that sensory messages concerning emotional stimuli that arrive at the thalamus are then directed to both the cortex (stream of thinking) and the hypothalamus (stream of feeling). Papez proposed a series of connections from the hypothalamus to the anterior thalamus (1) and on to the cingulate cortex (2). Emotional experiences or feelings occur when the cingulate cortex integrates these signals from the hypothalamus with information from the sensory cortex. Output from the cingulate cortex to the hippocampus (3) and then to the hypothalamus (4) allows top–down cortical control of emotional responses. Modified, with permission, from REF. 17 © (1996) Joseph Ledoux. Used by permission of Simon and Schuster.

The amygdala

The original work on Kluver–Bucy syndrome[14] involved surgical removal of almost the entire temporal lobes in monkeys. However, Weiskrantz[19] showed that bilateral lesions of the amygdala were sufficient to induce the orality, passivity, strange dietary behaviour and increased exploratory tendencies of the syndrome. Removal of the amygdala also permanently disrupted the social behaviour of monkeys, usually resulting in a fall in social standing[20]. The aspiration lesions used in these early studies were anatomically inexact. However, more recent studies involving ibotenic acid lesions have provided similar results, albeit with less severe Kluver–Bucy behaviours[21,22]. This line of research established the amygdala as one of the most important brain regions for emotion, with a key role in processing social signals of emotion (particularly involving fear), in emotional conditioning and in the consolidation of emotional memories.

The amygdala and social signals of emotion. Selective amygdala damage in humans is rare but seems not to lead to many Kluver–Bucy signs[23]. A Kluver–Bucy-like syndrome becomes apparent in humans only after more extensive bilateral damage, including the rostral temporal neocortex[24]. One of the first studies of human amygdala lesions showed that amygdala damage can lead to impairments in the processing of faces and other social signals[25]. This finding builds on single-unit recording studies in animals that have shown that amygdala neurons can respond differently to different faces[26] and can respond selectively to dynamic social stimuli such as approach

Panksepp coins the term 'affective neuroscience'[122]

LeDoux proposes multiple amygdala pathways for fear conditioning[43]

Bechara et al. show that the amygdala is necessary for fear conditioning but not for explicit memory of the conditioning experience[46]

Phillips et al. propose that the insula is a specific neural substrate for perceiving facial expressions of disgust[106]

Hariri et al. show that amygdala response to emotive stimuli varies as a function of serotonin transporter gene variation[118]

Lambie and Marcel publish their theory of conscious emotion experience[117]

Lawrence et al. show how sulpiride selectively impairs facial recognition of anger[112]

1986   1991   1992   1994   1995   1996   1997   2000   2002

Damasio outlines his somatic marker hypothesis[61]

Adolphs et al. describe impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala[28]

Cahill et al. reveal how the amygdala is important in the consolidation of emotional memories[51]

Damasio et al. publish evidence that different brain regions underlie different emotions[103]

Calder et al. describe a patient with damage to the insula and basal ganglia who showed impaired recognition and experience of disgust[108]

behaviour[27]. Later studies[28,29] indicated that the processing of emotional facial expressions, especially fear, was particularly impaired in humans with amygdala lesions[30]. This involvement of the amygdala in the processing of facial expression has been supported by functional neuroimaging studies. Morris and colleagues, using positron emission tomography (PET)[31], and Breiter and colleagues, using functional magnetic resonance imaging (fMRI)[32], showed selective brain activation in the amygdala in response to the presentation of fearful faces. The amygdala is also selective for certain emotions, especially fear, in vocal expressions[33]. Such activation of the amygdala by fearful faces occurs even when the faces are presented so quickly that the subject is unaware of them[34,35], or are presented in the blind hemifield of patients with blindsight[36]. Nevertheless, there is evidence that amygdala activation can be modulated by attention. Pessoa and colleagues, for example, showed that the amygdala
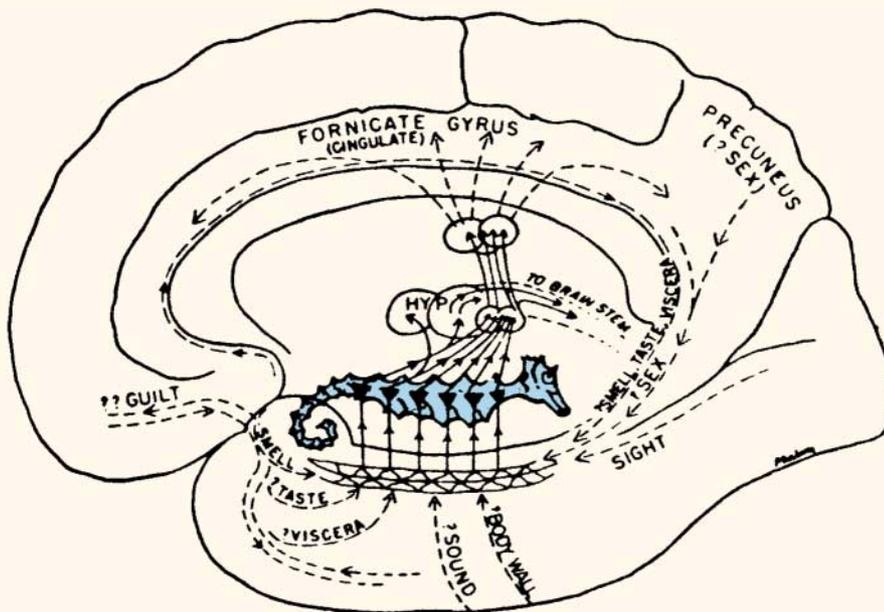
did not respond differentially to emotional faces when attentional resources were recruited elsewhere, indicating that emotional processing in the amygdala is susceptible to top–down control[37].

The amygdala and fear conditioning. In fear conditioning, meaningless stimuli come to acquire fear-inducing properties when they occur in conjunction with a naturally threatening event such as an electric shock. For example, if a rat hears a tone followed by a shock, after a few such pairings it will respond fearfully to the tone, showing alterations in autonomic (heart rate and blood pressure), endocrine and motor (for example, freezing) behaviour, along with analgesia and somatic reflexes such as a potentiated startle response. Fear conditioning has been extensively studied (mostly in animals), prototypically by Blanchard and Blanchard[38], and more recently and extensively by LeDoux and colleagues[39–43], among many others. This body of research has highlighted the roles of two afferent routes involving the amygdala that can mediate such conditioning. The first is a direct thalamo–amygdala route that can process crude sensory aspects of incoming stimuli and directly relay this information to the amygdala, allowing an early conditioned fear response if any of these crude sensory elements are signals of threat. This echoes psychological ideas about emotion activation, notably Zajonc's position regarding emotions without cognition[44]. The second route is a thalamo–cortico–amygdala pathway that allows more complex analysis of the incoming stimulus and delivers a slower, conditioned emotional response.

Fear conditioning in humans has been less extensively studied. However, there have been a number of important findings. One study, by Angrilli and colleagues[45], described a man with extensive right amygdala damage who showed a reduced startle response to a sudden burst of white noise. The patient also seemed relatively immune to fear conditioning, as this startle response was not potentiated by the presence of aversive slides to provide an emotional backdrop — a technique that reliably potentiates startle in healthy subjects. Another study, by Bechara and colleagues[46], described a patient with bilateral amygdala damage who again failed to fear-condition to aversive stimuli, but who could nevertheless report the facts about the conditioning experience. By contrast, another patient with hippocampal damage successfully acquired a conditioned fear response but had no explicit memory of the conditioning procedure — indicating that fear conditioning depends on the amygdala.

Figure 3 | **MacLean's limbic system theory of the functional neuroanatomy of emotion**. The core feature of MacLean's limbic system theory[8] was the hippocampus, illustrated here as a seahorse. According to MacLean, the hippocampus received sensory inputs from the outside world as well as information from the internal bodily environment (viscera and body wall). Emotional experience was a function of integrating these internal and external information streams. HYP, hypothalamus. Reproduced, with permission, from REF. 8 © (1949) Lippincott Williams and Wilkins.
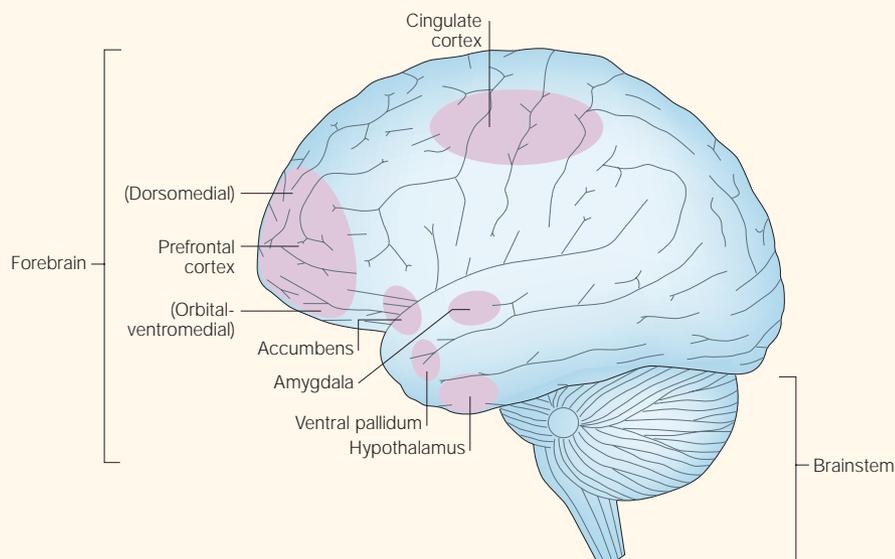
Figure 4 | **Key structures within a generalized emotional brain.** The figure does not show the relative depths of the various structures, merely their two-dimensional location within the brain schematic. As this is a lateral view, only one member of bilateral pairs of structures can be seen. Anatomical image adapted, with permission, from REF. 123 © (1996) Appleton & Lange.

Morris and colleagues showed that the amygdala was activated differentially in response to fear-conditioned angry faces that had been previously paired with an aversive noise, compared with angry faces that had not been paired with noise[35]. In line with LeDoux's ideas[47], there is also evidence from functional neuroimaging that such conditioning to faces operates by a subcortical thalamo–amygdala route. Finally, as well as its role in fear conditioning, the amygdala has also been implicated in appetitive conditioning[48].

The amygdala and memory consolidation. In a seminal study, Cahill and colleagues reported on a patient with amygdala damage who did not show the usual enhanced memory for emotional aspects of stories (compared with non-emotional aspects)[49]. This was confirmed in another patient with nearly selective amygdala damage[50]. Subsequent PET studies showed that levels of glucose metabolism in the right amygdala during encoding could predict the recall of complex negative or positive emotional stimuli up to several weeks later[51,52]. These studies indicate that the amygdala is involved in the consolidation of long-term emotional memories. As well as its role in memory, the amygdala has been associated with the modulation of other cognitive processes, such as visual perception[53].

The PFC
In 1848, Phineas Gage, a construction site foreman, was tamping down gunpowder in a blast hole with a 1-metre-long iron rod when the powder exploded, propelling the rod straight through his head. It entered just under his left eyebrow and exited through the top of his skull, before landing 20 metres away. Miraculously, Gage recovered, but as his physician Harlow noted, "he was no longer Gage"[54]. The previously amiable and efficient man had become someone for whom the "balance, so to speak, between his intellectual faculties and his animal propensities seems to have been destroyed." He was now irreverent, impatient, quick to anger and unreliable.

The radical changes in personality and emotional behaviour of Gage represent an early human lesion study of the effects of PFC damage on emotions. Since Gage's time, the PFC has been implicated in emotion in many ways, but there is no consensus as to its exact functions. In this section, I consider three contemporary views of PFC functioning and their historical antecedents.

The PFC and reward processing. Rolls's work on the orbitofrontal region of the PFC[55–57] proposes that it is "involved in learning the emotional and motivational value of stimuli"[56]. Specifically, he suggests that PFC regions work together with the amygdala to learn and represent relationships between new stimuli (secondary reinforcers) and primary reinforcers such as food, drink and sex. Importantly, according to Rolls, neurons in the PFC can detect changes or reversals in the reward value of learned stimuli and change their responses accordingly. These ideas have been based on 30 years of electrophysiological

and brain imaging studies of humans and animals and derive from the pioneering work of Mowrer in the 1950s and 1960s (REF. 58). (For Rolls's conceptualization of emotions in terms of reward, see later in text.)

The PFC and bodily signals. As discussed above, the James–Lange theory of the embodiment of emotions was heavily criticized by Cannon. However, since the mid-twentieth century there has been a revival of a modified version of the James–Lange approach, which proposes that bodily signals interact with other forms of information to modulate emotional intensity, rather than being the single determining factor. In 1962, Schachter and Singer[59] showed that similar patterns of bodily arousal could be experienced as anger or happiness depending on the social and cognitive context. Such studies on the interaction of bodily information and cognition to generate emotional experience provided the substrate for one of the more influential cognitive theories of emotion, as outlined by Mandler in 1975 (REF. 60). More recently, Damasio and colleagues have continued this tradition of promoting a key role for bodily feedback in emotion, this time implicating the PFC (especially the ventromedial PFC), with their presentation of the somatic marker hypothesis[61–64]. The somatic marker hypothesis builds on the earlier work of Nauta[65], who used the term 'interoceptive' markers rather than somatic markers, and Pribram[66], who used the phrase 'feelings as monitors', and reflects the original ideas of James and Lange. Basically, somatic markers are physiological reactions, such as shifts in autonomic nervous system activity, that tag previous emotionally significant events. Somatic markers therefore provide a signal delineating those current events that have had emotion-related consequences in the past. Damasio argues that these somatic codes are processed in the ventromedial PFC, thereby enabling individuals to navigate themselves through situations of uncertainty where decisions need to be made on the basis of the emotional properties of the present stimulus array. In particular, somatic markers allow decisions to be made in situations where a logical analysis of the available choices proves insufficient.

Damasio's group has used human lesion studies to support these arguments. In 1991 (REF. 67), they described the patient 'EVR' — a "modern day Phineas Gage"[62] — whose cognitive functioning and explicit emotional knowledge were more or less intact but who had great difficulty with situations of uncertainty where the subtle emotional values of multiple stimuli need to be processed (for

example, social situations). Nauta termed this state of affairs 'interoceptive blindness'[65]. They propose that EVR cannot use somatic markers because of his ventromedial PFC damage and therefore tries, and fails, to deal with complex situations of uncertainty using logical reasoning alone.

In a famous study, Bechara, Damasio and colleagues[68] asked patients with ventromedial PFC damage (including EVR) to play a card game in which they could win or lose a reward and for which they had to figure out the best strategy as they went along. The trick to winning on the card task was to ignore the immediate rewards on offer and become sensitive to the delayed rewards. Control participants could do this based on 'hunches', which they could not articulate, about which cards to choose. Furthermore, these healthy controls showed bodily responses (elevated skin conductance) in anticipation of poor card choices. By contrast, patients with damage to the ventromedial PFC did not learn to perform the task in this way and did not show the skin conductance response. The argument was that for the healthy subjects, somatic markers develop in the early trials of the task, which then provide signals to guide later card choices[68,69]. The subjects were unaware of these signals but could act on them — making intuitive or hunch decisions that 'feel' right. However, the patients lacked the brain regions to process these somatic markers. They could not use such information and so could not perform the task.

The PFC and 'top-down' regulation. Davidson and colleagues have proposed a different function for the PFC. They argue that prefrontal regions (as well as the ACC, see below) send 'bias signals' to other parts of the brain to guide behaviour towards the most adaptive current goals[70–74]. Often behavioural choices are in danger of being heavily influenced by the immediate affective consequences of a situation (for example, immediate reward), even though the most adaptive response might be, for example, to delay gratification (not unlike the optimal behaviour required on the Bechara gambling task described above). Davidson and colleagues suggest that the PFC promotes adaptive goals in the face of strong competition from behavioural alternatives that are linked to immediate emotional consequences[75]. In this model, left-sided PFC regions are involved in approach-related appetitive (positive) goals and right-sided PFC regions are involved in the maintenance of goals that require behavioural inhibition and withdrawal (negative). This 'valence-asymmetry hypothesis' is discussed in more detail below.

The ACC

Contemporary affective neuroscientists view the ACC as a point of integration of visceral, attentional and emotional information that is crucially involved in the regulation of affect and other forms of top–down control[76,77]. It has also been suggested that the ACC is a key substrate of conscious emotion experience[78] (as suggested by Papez) and of the central representation of autonomic arousal[79].

The ACC has generally been conceptualized in terms of a dorsal 'cognitive' subdivision and a more rostral, ventral 'affective' subdivision[76]. The affective subdivision of the ACC is routinely activated in functional imaging studies involving all types of emotional stimuli[76,80,81]. Current thinking suggests that it monitors conflict between the functional state of the organism and any new information that has potential affective or motivational consequences. When such conflicts are detected, the ACC projects information about the conflict to areas of the PFC where adjudications among response options can occur[76].

The hypothalamus

In the 1920s, Walter Hess conducted a series of experiments in which he implanted electrodes into the hypothalamic region of cats[82]. Electrical stimulation of one part of the hypothalamus led to an 'affective defence reaction' that was associated with increased heart rate, alertness and a propensity to attack. Hess could induce animals to act angry, fearful, curious or lethargic as a function of which brain regions were stimulated. These results showed that a simple train of electrical impulses can bring about a coordinated, sophisticated and recognizable emotional response. Furthermore, the response is not stereotyped but can be made in a skilfully targeted manner. In addition, different brain regions seemed to be associated with pleasure–approach and distress–avoidance responses.

Olds and Milner in 1954 (REF. 83) performed electrical stimulation studies in rats to show that the hypothalamus was also involved in the processing of rewarding stimuli. The rats would press a lever to deliver electrical 'self-stimulation' to the hypothalamus continuously for 75% of the time for up to 4 hours a day. Similar arguments concerning the hypothalamus and reward were made by Heath in 1972 (REF. 84) in studies investigating self-stimulation through electrodes in human subjects. The hypothalamus therefore seems to be part of an extensive reward network in the brain, also involving the PFC[56], amygdala[85] and ventral striatum[86]. Numerous other electrical stimulation studies have identified further roles for the hypothalamus in motivations such as sex and hunger[87,88].

How many emotion systems?

How do the different brain regions that have been implicated in emotion interact with each other? What are the emotion systems in the brain? Theories of how the functional neuroanatomy of emotion operates systemically range from single-system models, in which the same neural system underlies all emotions, to views that propose a combination of some common brain systems across all emotions, allied with separable regions that are dedicated more closely to the processing of certain individual emotions such as fear, disgust and anger (multiple-system models).

Single-system models. The proposals of Cannon and Bard, Papez (FIG. 2), MacLean (FIG. 3) and, to some extent, Damasio, are all examples of single-system models. A further example, alluded to in the discussion of Davidson's work above[71], is the 'right-hemisphere hypothesis', which was originally proposed by Mills in 1912 (REF. 89) and expanded by Sackeim and Gur[90,91] and others[92,93]. In its simplest form, this hypothesis emphasized a specialized role of the right hemisphere in all aspects of emotion processing[90,91], though more refined views have proposed that hemispheric specialization is restricted to the perception and expression of emotion, rather than its experience[94].

Dual-system models. Davidson's valence asymmetry model is related to the right-hemisphere hypothesis, with the emphasis in this case being on differential contributions of the left and right hemispheres to positive and negative emotions, respectively[70,71]. Other dual-system theorists, beginning with Schneirla in 1959 (REF. 95), have proposed that the emotions can be broken down into approach and withdrawal components, and have used different terminology and proposed different neuroanatomical substrates for each component; for example, behavioural activation and behavioural inhibition systems[96,97], approach and withdrawal systems[73], and appetitive and aversive systems[98]. Finally, Rolls proposed a dual-system approach that conceptualizes emotions in terms of states elicited by positive (rewarding) and negative (punishing) instrumental reinforcers, within a dimensional space[56,57].

Multiple-systems models. Other theorists, inspired by the prototypical work of Darwin[2], have proposed that a small set of discrete emotions are underpinned by relatively separable neural systems in the brain[18,99–103]. Some of the

key research in support of this multi-system view has come from human lesion studies and from functional neuroimaging. I have mentioned a number of studies that have linked the processing of fear to the amygdala[28,30,33,46,104,105]. Similar studies are beginning to emerge with respect to disgust. Phillips and colleagues used fMRI to show that perception of facial expressions of disgust was associated with activation in the anterior insular cortex[106]. This is consistent with early work by Penfield and Faulk in 1955 (REF. 107) that indicated that electrical stimulation of the insula in humans produced sensations of nausea and unpleasant tastes and sensations in the stomach. Following this up, Calder and colleagues reported a patient with left hemisphere damage affecting the insula and basal ganglia, including the striatum. The patient showed a clear selective impairment in recognizing both facial and vocal signals of disgust, and impaired experience of disgust[108]. Similar findings have been reported in patients with Huntington's disease[109] — a condition that affects the insula and the striatum — and in carriers of the Huntington's disease gene[110]. There has been relatively little work on the neural substrates of other emotions[111,112], and recent meta-analyses show that the clearest support is for separable neural substrates for fear and disgust, focusing on the amygdala and insula, respectively[80,81], with other brain regions, notably the PFC and ACC, being activated for all emotions (see above).

The future of affective neuroscience

A historical analysis of the development of affective neuroscience reveals that many more brain regions than initially supposed are involved in the processing of emotion and mood. In many ways this mirrors developments at the psychological level of explanation, where there is an increasing understanding of the pervasive influence of emotions on all forms of psychological processing. An impressive body of knowledge is accumulating about the roles of individual regions of the brain, such as the amygdala, in emotion processing. However, there is less consistency, and little hard empirical data, about the detailed interactions of these regions as part of a broader emotion system. A key challenge for the future is to address these issues.

Related to this is the challenge of integrating psychological models of emotion with neuroscientific models. At the psychological level of explanation, there are multiple routes to the generation of emotion — some reflecting 'automatic' or conditioned emotional responses, and some representing emotions derived from online appraisals of current circumstances[113–115]. There is a relative paucity of discussion and research on the underlying neural basis of appraisal-driven emotions, and this is an important research question if any rapprochement between neural and psychological levels of explanation is to be achieved.

The conscious experience of emotion is a crucial feature and has been the focus of a recent influential theoretical paper by Lambie and Marcel[116,117]. There has been little theory or research on the underlying neural substrates of emotion experience, with the exception of the work of Richard Lane[78], and this is likely to be a focus of future efforts.

Future progress in affective neuroscience will depend on the emergence of new technologies and methods. The advent of functional brain imaging has transformed the field in the last 10 years, and new forms of imaging such as diffusion tensor imaging, which enables non-invasive tracing of white matter tracts, will lead to further leaps in our understanding. Another recent methodology with enormous potential is transcranial magnetic stimulation (TMS) — a technique that enables a researcher or clinician to temporarily and non-invasively activate or deactivate specific regions of cortex and to observe the behavioural or neural consequences in humans. These advances will be complemented by more research that uses multiple methodologies, integrating functional imaging, pharmacology, TMS, psychophysiology, cognitive psychology and the emerging field of behavioural genetics[118].

The main focus of this review has been on so-called 'normal' emotions. However, there is an increasing interest in the neural substrates of abnormal emotional states[119] and of psychiatric disorders such as depression[120], as well as the neural correlates of individual differences in normal emotions, for example, variations in 'affective style'[72]. These issues will surely come further into the spotlight in the decades to come.

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1. James, W. What is an emotion? *Mind* **9**, 188–205 (1884).
2. Darwin, C. *The Expression of the Emotions in Man and Animals* (Chicago Univ. Press, Chicago, 1872/1965).
3. Cannon, W. B. The James–Lange theory of emotions: a critical examination and an alternative theory. *Am. J. Psychol.* **39**, 106–124 (1927).
4. Cannon, W. B. Against the James–Lange and the thalamic theories of emotions. *Psychol. Rev.* **38**, 281–295 (1931).
5. Bard, P. A diencephalic mechanism for the expression of rage with special reference to the central nervous system. *Am. J. Physiol.* **84**, 490–513 (1928).
6. Bard, P. & Rioch, D. M. A study of four cats deprived of neocortex and additional portions of the forebrain. *John Hopkins Med. J.* **60**, 73–153 (1937).
7. Papez, J. W. A proposed mechanism of emotion. *Arch. Neurol. Psychiatry* **38**, 725–743 (1937).
8. MacLean, P. D. Psychosomatic disease and the 'visceral brain': recent developments bearing on the Papez theory of emotion. *Psychosom. Med.* **11**, 338–353 (1949).
9. Darwin, C. *On the Origin of Species by Means of Natural Selection* (Murray, London, 1859).
10. Ekman, P. (ed.) *Darwin and Facial Expression: a Century of Research in Review* (Academic, New York, 1973).
11. Lange, C. in *The Emotions* (ed. Dunlap, E.) 33–90 (Williams & Wilkins, Baltimore, Maryland, 1885).
12. Ekman, P., Levenson, R. W. & Friesen, W. Autonomic nervous system activity distinguishes among emotions. *Science* **221**, 1208–1210 (1983).
13. Harro, J. & Vasar, E. Cholecystokinin-induced anxiety: how is it reflected in studies on exploratory behavior? *Neurosci. Biobehav. Rev.* **15**, 473–477 (1991).
14. Kluver, H. & Bucy, P. C. 'Psychic blindness' and other symptoms following bilateral temporal lobectomy. *Am. J. Physiol.* **119**, 254–284 (1937).
15. MacLean, P. D. in *The Neurosciences. Second Study Program* (ed. Schmidt, F. O.) 336–349 (Rockefeller Univ. Press, New York, 1970).
16. MacLean, P. D. Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain). *Electroencephalogr. Clin. Neurophysiol.* **4**, 407–418 (1952).
17. LeDoux, J. E. *The Emotional Brain: the Mysterious Underpinning of Emotional Life* (Simon & Schuster, New York, 1996).
18. Calder, A. J., Lawrence, A. D. & Young, A. W. Neuropsychology of fear and loathing. *Nature Rev. Neurosci.* **2**, 352–363 (2001).
19. Weiskrantz, L. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *J. Comp. Physiol. Psychol.* **49**, 381–391 (1956).
20. Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D. & Beck, L. H. A continious performance test of brain damage. *J. Consult. Psychol.* **20**, 343–350 (1956).
21. Murray, E. A., Gaffan, E. A. & Flint, R. W. Anterior rhinal cortex and amygdala: dissociation of their contributions to memory and food preference in rhesus monkeys. *Behav. Neurosci.* **110**, 30–42 (1996).
22. Meunier, M., Bachevalier, J., Murray, E. A., Malkova, L. & Mishkin, M. Effects of aspiration vs neurotoxic lesions of the amygdala on emotional reactivity in rhesus monkeys. *Soc. Neurosci. Abstr.* **13**, 5418–5432 (1996).
23. Aggleton, J. P. in *The Amygdala* (ed. Aggleton, J. P.) 485–503 (Wiley-Liss, New York/Chichester, 1992).
24. Terzian, H. & Ore, G. D. Syndrome of Kluver-Bucy reproduced in man by bilateral removal of temporal lobes. *Neurology* **5**, 373–380 (1955).
25. Jacobson, R. Disorders of facial recognition, social behaviour and affect after combined bilateral amygdalotomy and subcaudate tractotomy — a clinical and experimental study. *Psychol. Med.* **16**, 439–450 (1986).
26. Leonard, C. M., Rolls, E. T., Wilson, F. A. W. & Baylis, C. G. Neurons in the amygdala of the monkey with responses selective for faces. *Behav. Brain Res.* **15**, 159–176 (1985).
27. Brothers, L., Ring, B. & Kling, A. Response of neurons in the macaque amygdala to complex social stimuli. *Behav. Brain Res.* **41**, 199–213 (1990).
28. Adolphs, R., Tranel, D., Damasio, H. & Damasio, A. Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* **372**, 669–672 (1994).
29. Young, A. W. *et al.* Face processing impairments after amygdalotomy. *Brain* **118**, 15–24 (1995).
30. Calder, A. J. *et al.* Facial emotion recognition after bilateral amygdala damage: Differentially severe impairment of fear. *Cognit. Neuropsychol.* **13**, 699–745 (1996).
31. Morris, J. S. *et al.* A differential neural response in the human amygdala of fearful and happy facial expressions. *Nature* **383**, 812–815 (1996).
32. Breiter, H. C. *et al.* Response and habituation of the human amygdala during visual processing of facial emotion. *Neuron* **17**, 875–887 (1996).
33. Scott, S. K. *et al.* Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature* **385**, 254–257 (1997).
34. Whalen, P. J. *et al.* Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J. Neurosci.* **18**, 411–418 (1998).
35. Morris, J. S., Ohman, A. & Dolan, R. J. Modulation of human amygdala activity by emotional learning and conscious awareness. *Nature* **393**, 467–470 (1998).
36. Morris, J. S., DeGelder, B., Weiskrantz, L. & Dolan, R. J. Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain* **124**, 1241–1252 (2001).

37. Pessoa, L., McKenna, M., Gutierrez, E. & Ungerleider, L. G. Neural processing of emotional faces requires attention. *Proc. Natl Acad. Sci. USA* **99**, 11458–11463 (2002).
38. Blanchard, D. C. & Blanchard, R. J. Innate and conditioned reactions to threat in rats with amygdaloid lesions. *J. Comp. Physiol. Psychol.* **81**, 281–290 (1972).
39. LeDoux, J. E. Emotion: clues from the brain. *Annu. Rev. Psychol.* **46**, 209–235 (1995).
40. LeDoux, J. E. in *Handbook of Emotions* (eds Lewis, M. & Haviland, J. M.) 109–118 (The Guilford Press, New York, 1993).
41. LeDoux, J. E. Cognitive–emotional interactions in the brain. *Cognit. Emotion* **3**, 267–289 (1989).
42. LeDoux, J. E. in *Handbook of Physiology, Nervous System.* Vol. 5 (eds Mountcastle, V. & Plum, F.) 419–459 (American Physiological Society, Washington DC, 1987).
43. LeDoux, J. E. Sensory systems and emotion: a model of affective processing. *Integr. Psychiatry* **4**, 237–248 (1986).
44. Zajonc, R. B. Feeling and thinking: preferences need no inferences. *Am. Psychol.* **35**, 151–175 (1980).
45. Angrilli, A. *et al.* Startle reflex and emotion modulation impairment after right amygdala lesion. *Brain* **119**, 1991–2000 (1996).
46. Bechara, A., Tranel, D., Damasio, H. & Adolphs, R. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science* **269**, 1115–1118 (1995).
47. Morris, J., Ohman, A. & Dolan, R. J. A subcortical pathway to the right amygdala mediating unseen fear. *Proc. Natl Acad. Sci. USA* **96**, 1680–1685 (1999).
48. Gallagher, M. S., Graham, P. W. & Holland, P. C. The amygdala central nucleus and appetitive Pavlovian conditioning: lesions impair one class of conditioned behaviour. *J. Neurosci.* **10**, 1906–1911 (1990).
49. Cahill, L., Babinsky, R., Markowitsch, H. J. & McGaugh, J. L. The amygdala and emotional memory. *Nature* **377**, 295–296 (1995).
50. Adolphs, R., Cahill, L., Schul, R. & Babinsky, R. Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learn. Mem.* **4**, 291–300 (1997).
51. Cahill, L. *et al.* Amygdala activity at encoding correlated with long-term free recall of emotional information. *Proc. Natl Acad. Sci. USA* **93**, 8016–8021 (1996).
52. Hamann, S. B., Ely, T. D., Grafton, S. T. & Kilts, C. D. Amygdala activity related to enhanced memory for pleasant and aversive material. *Nature Neurosci.* **2**, 289–293 (1999).
53. Anderson, A. & Phelps, E. A. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* **411**, 305–309 (2001).
54. Harlow, J. M. Recovery of the passage of an iron bar through the head. *Publ. Mass. Med. Soc.* **2**, 327–334 (1868).
55. Rolls, E. T. The orbitofrontal cortex. *Phil. Trans. R. Soc. Lond. B* **351**, 1433–1443 (1996).
56. Rolls, E. T. *The Brain and Emotion* (Oxford Univ. Press, Oxford, 1999).
57. Rolls, E. T. A theory of emotion, and its application to understanding the neural basis of emotion. *Cognit. Emotion* **4**, 161–190 (1990).
58. Mowrer, O. H. *Learning Theory and Behavior* (Wiley, New York, 1960).
59. Schachter, S. & Singer, J. E. Cognitive, social, and physiological determinants of emotional state. *Psychol. Rev.* **69**, 379–399 (1962).
60. Mandler, G. *Mind and Emotion* (Wiley, New York, 1975).
61. Damasio, A. R., Tranel, D. & Damasio, H. in *Frontal Lobe Function and Dysfunction* (eds Levin, H. S., Eisenberg, H. M. & Bemton, A. L.) 217–219 (Oxford Univ. Press, New York, 1991).
62. Damasio, A. R. *Descartes' Error* (Putnam, New York, 1994).
63. Damasio, A. R. The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Phil. Trans. R. Soc. Lond. B* **351**, 1413–1420 (1996).
64. Damasio, A. R. Towards a neuropathology of emotion and mood. *Nature* **386**, 769–770 (1997).
65. Nauta, W. J. H. The problem of the frontal lobe: a reinterpretation. *J. Psychiatr. Res.* **8**, 167–187 (1971).
66. Pribram, K. H. in *Feelings and Emotions: The Loyola Symposium* (ed. Arnold, M. B.) 41–53 (Academic, New York, 1970).
67. Saver, J. L. & Damasio, A. R. Preserved access and processing of social knowledge in a patient with acquired sociopathy due to ventromedial frontal damage. *Neuropsychologia* **29**, 1241–1249 (1991).
68. Bechara, A., Damasio, A. R., Damasio, H. & Anderson, S. W. Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* **50**, 7–15 (1994).

69. Bechara, A., Tranel, D. & Damasio, H. Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain* **123**, 2189–2202 (2000).
70. Davidson, R. J. in *Emotions, Cognition and Behavior* (eds Kagan, J., Izard, C. E. & Zajonc, R. B.) 320–365 (Cambridge Univ. Press, Cambridge/New York, 1984).
71. Davidson, R. J. in *Approaches to Emotion* (eds Scherer, K. R. & Ekman, P.) 39–58 (Erlbaum, Hillsdale, New Jersey, 1984).
72. Davidson, R. J. in *Handbook of Emotions* (eds Lewis, M. & Haviland, J. M.) 143–154 (The Guilford Press, New York, 1993).
73. Davidson, R. J., Ekman, P., Saron, C., Senulis, J. & Friesen, W. V. Approach-withdrawal and cerebral asymmetry: emotional expression and brain physiology I. *J. Pers. Soc. Psychol.* **58**, 330–341 (1990).
74. Davidson, R. J. & Irwin, W. The functional neuroanatomy of affective style. *Trends Cognit. Sci.* **3**, 11–21 (1999).
75. Ochsner, K. N., Bunge, S. A., Gross, J. J. & Gabrieli, J. D. E. Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *J. Cognit. Neurosci.* **14**, 1215–1219 (2002).
76. Bush, G., Luu, P. & Posner, M. I. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cognit. Sci.* **4**, 215–222 (2000).
77. Davidson, R. J. *et al.* Neural and behavioral substrates of mood and mood regulation. *Biol. Psychiatry* **52**, 478–502 (2002).
78. Lane, R. D. *et al.* Neural correlates of levels of emotional awareness: evidence of an interaction between emotion and attention in the anterior cingulate cortex. *J. Cognit. Neurosci.* **10**, 525–535 (1998).
79. Critchley, H. D., Elliot, R., Mathias, C. J. & Dolan, R. J. Neural activity relating to generation and representation of galvanic skin responses: a functional magnetic resonance imaging study. *J. Neurosci.* **20**, 3033–3040 (2000).
80. Phan, K. L., Wager, T., Taylor, S. F. & Liberzon, I. Functional neuroanatomy of emotion: a metaanalysis of emotion activation studies in PET and fMRI. *Neuroimage* **16**, 331–348 (2002).
81. Murphy, F. C., Nimmo-Smith, I. & Lawrence, A. D. Functional neuroanatomy of emotions. *Cognit. Affect. Behav. Neurosci.* **3**, 207–233 (2003).
82. Hess, W. R. & Brugger, M. in *Biological Order and Brain Organization: Selected Works of W. R. Hess* (ed. Akert, K.) 183–202 (Springer, Berlin, 1943/1981).
83. Olds, J. & Milner, P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol.* **47**, 419–427 (1954).
84. Heath, R. G. Pleasure and brain activity in man. *J. Nerv. Ment. Dis.* **154**, 3–18 (1972).
85. Baxter, M. G. & Murray, E. A. The amygdala and reward. *Nature Rev. Neurosci.* **3**, 563–573 (2002).
86. Robbins, T., Cador, M., Taylor, J. R. & Everitt, B. J. Limbic-striatal interactions in reward-related processes. *Neurosci. Biobehav. Rev.* **13**, 155–162 (1989).
87. Teitelbaum, P. & Epstein, A. N. The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. *Psychol. Rev.* **69**, 74–90 (1962).
88. Stellar, E. The physiology of motivation. *Psychol. Rev.* **61**, 5–22 (1954).
89. Mills, C. K. The cortical representation of emotion, with a discussion of some points in the general nervous system mechanism of expression in its relation to organic nervous disease and insanity. *Proc. Am. Medico-Psychol. Assoc.* **19**, 297–300 (1912).
90. Sackeim, H. A. & Gur, R. C. Lateral asymmetry in intensity of emotional expression. *Neuropsychologia* **16**, 473–481 (1978).
91. Sackheim, H. A., Gur, R. C. & Saucy, M. C. Emotions are expressed more intensely on the left side of the face. *Science* **202**, 434–436 (1978).
92. Schwartz, G. E., Davidson, R. J. & Maer, F. Right hemisphere lateralization from emotion in the human brain: interactions with cognition. *Science* **190**, 286–288 (1975).
93. Schwartz, G. E., Ahern, G. L. & Brown, S. L. Lateralized facial muscle response to positive and negative emotional stimuli. *Psychophysiology* **16**, 561–571 (1979).
94. Adolphs, R., Damasio, H., Tranel, D. & Damasio, A. R. Cortical systems for the recognition of emotion in facial expression. *J. Neurosci.* **16**, 7678–7687 (1996).
95. Schneirla, T. C. in *Nebraska Symposium on Motivation* (ed. Jones, M. R.) 1–42 (Univ. Nebraska Press, Lincoln, 1959).
96. Cloninger, C. A systematic method for clinical description and classification of personality variants. *Arch. General Psychiatry* **44**, 573–588 (1987).
97. Gray, J. A. *The Neuropsychology of Anxiety: an Enquiry into the Function of the Septo–Hippocampal System* (Clarendon, Oxford, 1982).

98. Lang, P. J., Bradley, M. M. & Cuthbert, B. N. Emotion, attention, and the startle reflex. *Psychol. Rev.* **97**, 377–395 (1990).
99. Izard, C. E. *The Face of Emotion* (Appleton-Century-Crofts, New York, 1971).
100. Panksepp, J. Toward a general psychobiological theory of emotions. *Behav. Brain Sci.* **5**, 407–467 (1982).
101. Tomkins, S. S. in *Approaches to Emotion* (eds Scherer, K. R. & Ekman, P.) 163–196 (Erlbaum, Hillsdale, New Jersey, 1982).
102. Ekman, P. An argument for basic emotions. *Cogn. Emotion* **6**, 169–200 (1992).
103. Damasio, A. R. *et al.* Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neurosci.* **3**, 1049–1056 (2000).
104. Schmolck, H. & Squire, L. R. Impaired perception of facial emotions following bilateral damage to the anterior temporal lobe. *Neuropsychology* **15**, 30–38 (2001).
105. Adolphs, R. *et al.* Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia* **37**, 1111–1117 (1999).
106. Phillips, M. L. *et al.* A specific neural substrate for perceiving facial expressions of disgust. *Nature* **389**, 495–498 (1997).
107. Penfield, W. & Faulk, M. E. The insula: further observations of its function. *Brain* **78**, 445–470 (1955).
108. Calder, A. J., Keane, J., Manes, F., Antoun, N. & Young, A. W. Impaired recognition and experience of disgust following brain injury. *Nature Neurosci.* **3**, 1077–1078 (2000).
109. Sprengelmayer, R. *et al.* Loss of disgust: perception of faces and emotions in Huntingdon's disease. *Brain* **119**, 1647–1665 (1996).
110. Gray, J. M., Young, A. W., Barker, W. A., Curtis, A. & Gibson, D. Impaired recognition of disgust in Huntingdon's disease gene carriers. *Brain* **120**, 2029–2038 (1997).
111. Calder, A. J., Keane, J., Lawrence, A. D. & Manes, F. Impaired recognition of anger following damage to the ventral striatum. *Brain* (in the press).
112. Lawrence, A. D., Calder, A. J., McGowan, S. V. & Grasby, P. M. Selective disruption of the recognition of facial expressions of anger. *Neuroreport* **13**, 881–884 (2002).
113. Izard, C. E. Four systems for emotion activation: cognitive and noncognitive processes. *Psychol. Rev.* **100**, 68–90 (1993).
114. Power, M. J. & Dalgleish, T. *Cognition and Emotion: From Order to Disorder* (Psychology, Hove, 1997).
115. Dalgleish, T. Cognitive approaches to posttraumatic stress disorder (PTSD): the evolution of multi-representational theorizing. *Psychol. Bull.* **130**, 228–260 (2004).
116. Dalgleish, T. & Power, M. J. The I of the storm: relations between self and conscious emotion experience. *Psychol. Rev.* (in the press).
117. Lambie, J. A. & Marcel, A. J. Consciousness and the varieties of emotion experience: a theoretical framework. *Psychol. Rev.* **109**, 219–259 (2002).
118. Hariri, A. R. *et al.* Serotonin transporter genetic variation and the response of the human amygdala. *Science* **297**, 400–403 (2002).
119. Davidson, R. J., Putnam, K. M. & Larson, C. L. Dysfunction in the neural circuitry of emotion regulation — a possible prelude to violence. *Science* **289**, 591–595 (2000).
120. Mayberg, H. S. Limbic-cortical dysregulation: a proposed model of depression. *J. Neuropsychiatry Clin. Neurosci.* **9**, 471–481 (1997).
121. Lazarus, R. S. Thoughts on the relationship between emotion and cognition. *Am. Psychol.* **37**, 1019–1024 (1982).
122. Panksepp, J. A critical role for 'affective neuroscience' in resolving what is basic about emotions. *Psychol. Rev.* **99**, 554–560 (1992).
123. Martin, J. H. *Neuroanatomy: Text and Atlas* 2nd edn (Appleton & Lange, Stamford, Connecticut, 1996).

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