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The emotional brain

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Preface

The discipline of affective neuroscience is concerned with the underlying 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 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 recording, animal and human lesion studies, and animal and human behavioural experiments in seeking 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 James¹ and Charles Darwin². This is followed by discussion of the early functional neuroanatomical models of emotion of Cannon and Bard, Papez and MacLean. The review then briefly outlines our current knowledge of the contribution of key brain regions, including the prefrontal cortex, amygdala, hypothalamus and anterior cingulate cortex, 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 ground-breaking 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 evolution³. 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 (see Figure 1). He also proposed that many emotion 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 substrates⁴.

Ten years later, William James, in his seminal paper *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 in the world. 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 1885⁵, providing us with the James-Lange theory of emotions.

The James-Lange theory was challenged in the 1920s by Walter Cannon^{6,7}, 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 activity⁸; 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 attacks⁹.

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. Indeed, most contemporary affective neuroscientists would endorse a

modified James-Lange view in which bodily feedback modulates the experience of emotion (see below).

Early theories of affective neuroanatomy

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. The fact that removal of the cortex did not eliminate emotions, they proposed, 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^{10,11}. 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. Firstly, the use of animal emotions as human homologues, as proposed by Darwin². Secondly, 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 proposed a scheme for the central neural circuitry of emotion - now known as the "Papez circuit" (see Figure 2)¹². 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. Via this route sensations were turned into perceptions, thoughts and memories. Papez proposed that this stream continued beyond the cingulate cortex via the cingulum pathway to the hippocampus and, via 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 thence, 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 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 involved in emotion was proposed by Paul MacLean in 1949¹³ (see Figure 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 Bucy¹⁴ 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 coprophagia (eating of faeces). These studies suggested a key role for temporal lobe structures in emotion — a centrepiece in MacLean's theory.

MacLean viewed the brain as a triune architecture¹⁵ consisting of: 1) 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; 2) 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 prefrontal cortex; and, 3) the “new” mammalian brain consisting mostly of the neocortex, which interfaces emotion with cognition and exerts top-down control over the emotional responses 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 emotion 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 brain¹⁶.

MacLean's limbic system concept survives to the current day as the dominant conceptualisation 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 criticised on both empirical¹⁷ and theoretical grounds¹⁸. A number of the limbic system structures– the hippocampus, the mammillary bodies, and the anterior thalamus – seem to play a much smaller role than MacLean imagined. Some of 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 prefrontal cortex. In the next four sections, I examine how research on these four limbic regions has developed since MacLean’s original paper (see Figure 4). Other brain regions (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 insula cortex and its potential involvement in disgust).

The amygdala

The original work on Kluver-Bucy syndrome¹⁴ involved surgical removal of almost the entire temporal lobes in monkeys. However, Weiskrantz¹⁹ 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 standing²⁰. 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 signs²³. A Kluver-Bucy-like syndrome only becomes apparent in humans after more extensive bilateral damage, including the rostral temporal neocortex²⁴. 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 signals²⁵. This finding builds on single-unit recording studies in animals that

have shown that amygdala neurons can respond differently to different faces²⁶ and can respond selectively to dynamic social stimuli such as approach behaviour²⁷. Later studies^{28,29} indicated that the processing of emotional facial expressions, especially fear, was particularly impaired in humans with amygdala lesions³⁰. This involvement of the amygdala in the processing of facial expression has been supported by functional neuroimaging studies. Morris and colleagues using Positron Emission Topography (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 expressions³³. Such amygdala activation 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 blindsight³⁶. 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 control³⁷.

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 (e.g. heart rate and blood pressure), endocrine, and motor (e.g. 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 Blanchard³⁸, and more recently and extensively by Joseph LeDoux and his colleagues³⁹⁻⁴³, among many others. This body of research has highlighted the role played by 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 a very 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 cognition⁴⁴. 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, a number of important findings exist. First, Angrilli and colleagues⁴⁵ 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. Second, Bechara and colleagues⁴⁶ described a patient with bilateral amygdala damage who again failed to fear-condition to aversive stimuli but could nevertheless report the facts about the conditioning experience. In 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. Third, Morris and colleagues showed differential amygdala activation for fear-conditioned angry faces that had been previously paired with an aversive noise, compared to angry faces that had not been paired with noise³⁵. Fourth, in line with LeDoux's ideas⁴⁷, there is evidence from functional neuroimaging that such conditioning to faces operates via a subcortical thalamo-amygdala route. Finally, as well as its role in fear conditioning, the amygdala has also been implicated in appetitive conditioning⁴⁸.

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 damage⁵⁰. 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 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 perception⁵³.

The prefrontal cortex (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 noted⁵⁴ "he was no longer Gage". 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 Phineas Gage represent an early human lesion study of the effects of PFC damage on emotions. Since Gage's time, the prefrontal cortex 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' work on the orbitofrontal region of the PFC⁵⁵⁻⁵⁷ 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 response 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 1960s⁵⁸. I will return briefly to Roll's conceptualisation of emotions in terms of reward later.

The PFC and bodily signals

As discussed above, the James-Lange theory of the embodiment of emotions was heavily criticised 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 Singer⁵⁹ 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 1975⁶⁰. 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 ventro-medial PFC), with their presentation of the somatic marker hypothesis (SMH)⁶¹⁻⁶⁴. The SMH builds on the earlier work of Nauta⁶⁵ who used the term "interoceptive" markers rather than somatic markers, and Pribram⁶⁶, who used the phrase "feelings as monitors", and reflects the original ideas of James-Lange. Basically, somatic markers are physiological reactions, such as shifts in autonomic nervous system activity, that tag previously emotionally significant events. Somatic markers therefore provide a signal delineating which current events have had emotion-related consequences in the past. Damasio argues that these somatic codes are processed in the ventromedial PFC, thus

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 have used human lesion studies to support these arguments. In 1991⁶⁷ 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) - a state of affairs that Nauta termed “interoceptive blindness”⁶⁵. They propose that EVR is unable to utilise somatic markers due to his ventro-medial 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 colleagues⁶⁸ asked patients with ventro-medial 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 evidenced bodily responses (elevated skin conductance) in anticipation of poor card choices. In contrast, patients with damage to the ventro-medial 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 are unaware of these signals but can act on them – making intuitive or hunch decisions that “feel” right. However, the patients lack the brain regions to process these somatic markers. They cannot use such information and so cannot 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 anterior cingulate cortex, see below) send 'bias signals' to other parts of the brain to guide behaviour towards the most adaptive current goals⁷⁰⁻⁷⁴. 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 linked to immediate emotional consequences⁷⁵. 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 anterior cingulate cortex (ACC)

Contemporary affective neuroscientists view the ACC as a point of integration of visceral, attentional and emotional information that is critically 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 experience⁷⁸ (as suggested by Papez) and of the central representation of autonomic arousal⁷⁹.

The ACC has generally been conceptualised in terms of a dorsal "cognitive" subdivision and a more rostral, ventral "affective" subdivision⁷⁶. The affective subdivision of the ACC is routinely activated in functional imaging studies involving all types of emotional stimuli^{76,80,81}. Present thinking suggests that it monitors conflict between the current 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 PFC where adjudications among response options can occur⁷⁶.

The Hypothalamus

In the 1920s, Walter Hess conducted a series of experiments in which he implanted electrodes into the hypothalamic region of cats⁸². Electrical stimulation of one part of the hypothalamus led to an “affective defence reaction” 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 co-ordinated and sophisticated, recognisable 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 1954⁸³ 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 1972⁸⁴ in studies investigating self-stimulation via electrodes in human subjects. The hypothalamus therefore seems to be part of an extensive reward network in the brain also involving the prefrontal cortex⁵⁶, amygdala⁸⁵, and ventral striatum⁸⁶. Numerous other electrical stimulation studies have identified further roles for the hypothalamus in motivations such as sex and hunger^{87,88}.

Single, dual and multiple 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 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 (see Figure 2), MacLean (see Figure 3) and, to some extent, Damasio, are all good examples of single-system models. A further example, alluded to in the discussion of Davidson's work above⁷¹, is the "right-hemisphere hypothesis" originally proposed by Mills in 1912⁸⁹ and expanded by Sackeim and Gur^{90,91} and others^{92,93}. In its simplest form, this hypothesis emphasised a specialised role of the right hemisphere in all aspects of emotion processing^{90,91}, though more refined views have proposed that hemispheric specialisation is restricted to the perception and expression of emotion, rather than its experience⁹⁴.

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 1959⁹⁵, have proposed that 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 systems⁷³; and appetitive and aversive systems⁹⁸. Finally, Rolls proposed a dual-system approach that conceptualises 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 Darwin², 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 above a number of studies linking 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 cortex¹⁰⁶. This is consistent with early work by Penfield and Faulk in 1955¹⁰⁷ indicating that electrical stimulation of the insula in humans produced sensations of nausea and unpleasant tastes and sensation 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 recognising both facial and vocal signals of disgust, and impaired experience of disgust¹⁰⁸. Similar findings have been reported in patients with Huntington's disease¹⁰⁹ - a condition that affects the striatum - and in carriers of the Huntington's disease gene¹¹⁰. There has been relatively little work to 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/basal ganglia 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 circumstances¹¹³⁻¹¹⁵. 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 clearly 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 Lane⁷⁸, and this is likely to be a focus of future efforts.

Future progress in affective neuroscience will be depend on the emergence of new technologies and methods. The advent of functional brain imaging has transformed the field in the last ten years and new forms of imaging such as diffusion tensor imaging (DTI), 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 activate or deactivate specific regions of cortex and to observe the behavioural or neural consequences. These advances will be complemented by more research utilising multiple methodologies, integrating functional imaging, pharmacology, TMS,

psychophysiology, cognitive psychology, as well as the emerging field of behavioural genetics¹¹⁸.

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 emotion states¹¹⁹ and of psychiatric disorders such as depression¹²⁰, 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.

Figures and text box

Figure 1 - Drawings and photographs used by Darwin (2) to illustrate cross-species similarities in emotion expression - in this case anger/aggression.

Figure 2 The Papez circuit theory of the functional neuroanatomy of emotion (12)

Papez argued that sensory messages concerning emotional stimuli arriving at the thalamus get 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 (a) and on to the cingulate cortex (b). 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 (c) and thence the hypothalamus (d) allow top-down cortical control of emotional responses. Reproduced from LeDoux (1996)(17).

Figure 3 - MacLean's limbic system theory of the functional neuroanatomy of emotion (13)

The core feature of MacLean's limbic system theory 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

Figure reprinted from MacLean (1949)(13).

Figure 4 - Key structures within a generalised 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. Figure adapted from Berridge (2003)¹²¹.

Timeline

- 1868 - Harlow describes the effects of prefrontal cortex damage to Phineas Gage⁵⁴
- 1872 - Charles Darwin publishes *The expression of emotions in man and animals*²
- 1884 - William James proposes his bodily theory of emotion¹
- 1885- Lange proposes a similar theory to James⁵
- 1912 - Mills first proposes a right hemisphere hypothesis of emotion⁸⁹
- 1931 - The Cannon-Bard theory of emotion is outlined⁶
- 1937 - Kluver and Bucy publish their work on temporal lobectomy¹⁴
- 1937 - Papez outlines his theory of emotion¹²
- 1943 - Hess and Brugger describe their work on single cell recording in the hypothalamus⁸²
- 1949 - MacLean proposes his tripartite 'limbic' model of emotion¹³
- 1956 - Weiskrantz describes the effects of amygdala ablation in monkeys¹⁹
- 1956 - Schneirla outlines an approach-withdrawal model of emotion⁹⁵
- 1962 - Schachter & Singer describe experiments indicating the importance of cognitive factors in determining the nature of emotion experience⁵⁹
- 1970/1971 – Pribram and Nauta propose early versions of the somatic marker hypothesis^{65,66}
- 1975 - Mandler publishes *Mind and emotion*⁶⁰
- 1980 - Zajonc argues the case for emotion in the absence of cognition⁴⁴
- 1982 - Lazarus argues the case for emotions requiring cognition¹²²
- 1982 - Gray publishes *The neuropsychology of anxiety*⁹⁷
- 1983 - Ekman and colleagues propose that different basic emotions can be distinguished autonomically⁸
- 1986 - LeDoux proposes multiple amygdala pathways for fear conditioning⁴³
- 1991 - Antonio Damasio outlines his somatic marker hypothesis⁶¹

1992 - Panksepp coins the term Affective Neuroscience¹²³

1994 - Adolphs et al. describe impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala²⁸

1995 - Bechara et al. show that the amygdala is necessary for fear conditioning but not for explicit memory of the conditioning experience⁴⁶

1996 - Cahill et al. reveal how the amygdala is important in the consolidation of emotional memories⁵¹

1997 - Phillips et al. propose the insula as a specific neural substrate for perceiving facial expressions of disgust¹⁰⁶

2000 - Damasio et al. publish work indicating different brain regions underlying different emotions¹⁰³

2000 - Calder et al. describe a patient with impaired insula and basal ganglia damage who showed impaired recognition and experience of disgust¹⁰⁸

2002 - Lawrence et al. show how sulpiride selectively impairs facial recognition of anger¹¹²

2002 - Lambie and Marcel publish their theory of conscious emotion experience¹¹⁷

2002 - Hariri et al. show that amygdala response to emotive stimuli varies as a function of serotonin transporter gene variation¹¹⁸

References

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 University Press, Chicago, 1872/1965).
3. Darwin, C. *On the origin of species by means of natural selection* (Murray, London, 1859).
4. Ekman, P. (ed.) *Darwin and facial expression: A century of research in review* (Academic Press, New York, 1973).
5. Lange, C. in *The emotions* (ed. Dunlap, E.) (Williams & Wilkins, Baltimore, MD, 1885).
6. Cannon, W. B. The James-Lange theory of emotions: A critical examination and an alternative theory. *American Journal of Psychology* **39**, 106-124 (1927).
7. Cannon, W. B. Again the James-Lange and the thalamic theories of emotions. *Psychological Review* **38**, 281-295 (1931).
8. Ekman, P., Levenson, R. W. & Friesen, W. Autonomic nervous system activity distinguishes among emotions. *Science* **221**, 1208-1210 (1983).
9. Harro, J. & Vasar, E. Cholecystokinin-induced anxiety: How is it reflected in studies on exploratory behavior. *Neuroscience and Biobehavioural Reviews* **15**, 473-477 (1991).
10. Bard, P. A diencephalic mechanism for the expression of rage with special reference to the central nervous system. *American Journal of Physiology* **84**, 490-513 (1928).
11. Bard, P. & Riach, D. M. A study of four cats deprived of neocortex and additional portions of the forebrain. *Johns Hopkins Medical Journal* **60**, 73-153 (1937).
12. Papez, J. W. A proposed mechanism of emotion. *Archives of Neurology and Psychiatry* **38**, 725-743 (1937).
13. MacLean, P. D. Psychosomatic disease and the "visceral brain": Recent developments bearing on the Papez theory of emotion. *Psychosomatic Medicine* **11**, 338-353 (1949).
14. Kluver, H. & Bucy, P. C. 'Psychic blindness' and other symptoms following bilateral temporal lobectomy. *American Journal of Physiology* **119**, 254-284 (1937).
15. MacLean, P. D. in *The neurosciences. Second study program* (ed. Schmidt, F. O.) 336-349 (Rockefeller University Press, New York, 1970).
16. MacLean, P. D. Some psychiatric implications of physiological studies on frontotemporal of limbic system (visceral brain). *Electroencephalography and Clinical Neurophysiology* **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 Reviews Neuroscience* **2**, 352-363 (2001).

19. Weiskrantz, L. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *Journal of Comparative and Physiological Psychology* **49**, 381-391 (1956).
20. Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D. & Beck, L. H. A continuous performance test of brain damage. *Journal of Consulting Psychology* **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. *Behavioural Neuroscience* **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. *Society for Neuroscience Abstract* **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. *Psychological Medicine* **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. *Behavioural Brain Research* **15**, 159-176 (1985).
27. Brothers, L., Ring, B. & Kling, A. Response of neurons in the macaque amygdala to complex social stimuli. *Behavioural Brain Research* **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. *Cognitive Neuropsychology* **13**, 699-745 (1996).
31. Morris, J. S. et al. A differential neural response in the human amygdala to 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. *The Journal of Neuroscience* **18**, 411-418 (1998).
35. Morris, J., 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** (2001).
37. Pessoa, L., McKenna, M., Gutierrez, E. & Ungerleider, L. G. Neural processing of emotional faces requires attention. *Proceedings of the National Academy of Sciences* **99**, 11458-11463 (2002).
38. Blanchard, D. C. & Blanchard, R. J. Innate and conditioned reactions to threat in rats with amygdaloid lesions. *Journal of Comparative and Physiological Psychology* **81**, 281-290 (1972).
39. LeDoux, J. E. Emotion: Clues from the brain. *Annual Review of Psychology* **46**, 209-235 (1995).
40. LeDoux, J. E. in *Handbook of Emotions* (eds. Lewis, M. & Haviland, J. M.) (The Guilford Press, New York, 1993).
41. LeDoux, J. E. Cognitive-emotional interactions in the brain. *Cognition and Emotion* **3**, 267-289 (1989).
42. LeDoux, J. E. in *Handbook of physiology, Nervous system. Volume 5, Higher function* (eds. Mountcastle, V. & Plum, F.) 419-459 (American Physiological Society, Washington, D.C., 1987).
43. LeDoux, J. E. Sensory systems and emotion: A model of affective processing. *Integrative Psychiatry* **4**, 237-248 (1986).
44. Zajonc, R. B. Feeling and thinking: Preferences need no inferences. *American Psychologist* **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. *Proceedings of the National Academy of Sciences* **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. *Journal of Neuroscience* **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. *Learning & Memory* **4**, 291-300 (1997).
51. Cahill, L. et al. Amygdala activity at encoding correlated with long-term free recall of emotional information. *Proceedings of the National Academy of Sciences* **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 Neuroscience* **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. *Reprinted in History of Psychiatry* (1993) **4**, 271-281 (1868).

55. Rolls, E. T. The orbitofrontal cortex. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences* **351**, 1433-1443 (1996).
56. Rolls, E. T. *The Brain and emotion* (Oxford University Press, Oxford, 1999).
57. Rolls, E. T. A theory of emotion, and its application to understanding the neural basis of emotion. Special Issue: Development of relationships between emotion and cognition. *Cognition and 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. *Psychological Review* **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 University 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. *Journal of Psychiatric Research* **8**, 167-187 (1971).
66. Pribram, K. H. in *Feelings and emotions: The Loyola Symposium* (ed. Arnold, M. B.) 41-53 (Academic Press, 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 University Press, Cambridge/New York, 1984).
71. Davidson, R. J. in *Approaches to emotion* (eds. Scherer, K. R. & Ekman, P.) 39-58 (Erlbaum, Hillsdale, N.J., 1984).
72. Davidson, R. J. in *Handbook of emotions* (eds. Lewis, M. & Haviland, J. M.) 143-154 (Guilford Press, New York/London, 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. *Journal of Personality and Social Psychology* **58**, 330-341 (1990).
74. Davidson, R. J. & Irwin, W. The functional neuroanatomy of affective style. *Trends in Cognitive Sciences* **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. *Journal of Cognitive Neuroscience* **14**, 1215-1219 (2002).
76. Bush, G., Luu, P. & Posner, M. I. Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences* **4**, 215-222 (2000).
77. Davidson, R. J. et al. Neural and Behavioral substrates of mood and mood regulation. *Biological 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. *Journal of Cognitive Neuroscience* **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. *Journal of Neuroscience* **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. *Cognitive, Affective, & Behavioural Neuroscience* **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-Verlag (current edition 1981), Berlin, 1943).
83. Olds, J. & Milner, P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology* **47**, 419-427 (1954).
84. Heath, R. G. Pleasure and brain activity in man. *Journal of Nervous and Mental Disease* **154**, 3-18 (1972).
85. Baxter, M. G. & Murray, E. A. The amygdala and reward. *Nature Reviews Neuroscience* **3**, 563-573 (2002).
86. Robbins, T., Cador, M., Taylor, J. R. & Everitt, B. J. Limbic-striatal interactions in reward-related processes. *Neuroscience and Biobehavioural Reviews* **13**, 155-162 (1989).
87. Teitelbaum, P. & Epstein, A. N. The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. *Psychological Review* **69**, 74-90 (1962).
88. Stellar, E. The physiology of motivation. *Psychological Review* **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. *Proceedings of the American Medico-Psychological Association* **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. *Journal of Neuroscience* **16**, 7678-7687 (1996).
95. Schneirla, T. C. in *Nebraska Symposium on Motivation* (ed. Jones, M. R.) 1 - 42 (University of Nebraska Press, Lincoln, 1959).
96. Cloninger, C. A systematic method for clinical description and classification of personality variants. *Archives of 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 Press, Oxford, 1982).
98. Lang, P. J., Bradley, M. M. & Cuthbert, B. N. Emotion, attention, and the startle reflex. *Psychological Review* **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. *Behavioral and Brain Sciences* **5**, 407-467 (1982).
101. Tomkins, S. S. in *Approaches to emotion* (eds. Scherer, K. R. & Ekman, P.) 163-196 (Erlbaum, Hillsdale, N.J., 1982).
102. Ekman, P. An argument for basic emotions. *Cognition and Emotion* **6**, 169-200 (1992).
103. Damasio, A. R. et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience* **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 Neuroscience* **3**, 1077-1078 (2000).
109. Sprengelmayer, R. et al. Loss of disgust: Perception of faces and emotions in Huntington'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 Huntington'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 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. *Psychological Review* **100**, 68-90 (1993).
114. Power, M. J. & Dalgleish, T. *Cognition and emotion: From order to disorder* (Psychology Press, Hove, U.K., 1997).
115. Dalgleish, T. Cognitive approaches to Posttraumatic Stress Disorder (PTSD): The evolution of multi-representational theorizing. *Psychological Bulletin* **130**, 228-260 (2004).
116. Dalgleish, T. & Power, M. J. The I of the storm: relations between self and conscious emotion experience. *Psychological Review* (in press).
117. Lambie, J. A. & Marcel, A. J. Consciousness and the varieties of emotion experience: A theoretical framework. *Psychological Review* **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*, 591-595 (2000).
120. Mayberg, H. S. Limbic-cortical dysregulation: A proposed model of depression. *The Journal of Neuropsychiatry and Clinical Neurosciences* **9**, 471-481 (1997).
121. Berridge, K. C. in *Handbook of affective sciences* (eds. Davidson, R. J., Scherer, K. R. & Hill Goldsmith, H.) 25-51 (Oxford University Press, Oxford, 2003).
122. Lazarus, R. S. Thoughts on the relationship between emotion and cognition. *American Psychologist* **37**, 1019-1024 (1982).
123. Panksepp, J. A critical role for "Affective Neuroscience" in resolving what is basic about emotions. *Psychological Review* **99**, 554-560 (1992).