

Affective Neuroscience: Past, Present, and Future

Tim Dalgleish, Barnaby D. Dunn, and Dean Mobbs

Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK

Abstract

The discipline of affective neuroscience is concerned with the underlying neural substrates of emotion and mood. This review presents an historical overview of the pioneering work in affective neuroscience of James and Lange, Cannon and Bard, and Hess, Papez, and MacLean before summarizing the current state of research on the brain regions identified by these seminal researchers. We also discuss the more recent strides made in the field of affective neuroscience. A final section considers different hypothetical organizations of affective neuroanatomy and highlights future directions for the discipline.

Keywords

affect, brain, emotion, neuroscience

The advent of modern neuroscience methodologies has led to an explosion over the past 15 years in our understanding of brain regions involved in the recognition, generation, experience, and regulation of emotion. In this brief review, we suggest some early historical milestones in the development of what has become known as affective neuroscience, and then consider the extent to which recent findings have advanced understanding in the field (see Table 1). We begin with the pioneering work of James and Lange, go on discuss the early functional neuroanatomical models of Cannon and Bard, then outline the hypothalamic stimulation studies conducted by Hess, and finally, consider Papez and MacLean's development of increasingly sophisticated neuroanatomical frameworks. We evaluate how well these key contributions fit with the current state of knowledge about which brain regions are seemingly central to the representation and processing of affect, including the amygdala, prefrontal cortex, thalamus, insular, anterior cingulate cortex, and midbrain. We next very briefly overview contemporary theoretical frameworks of how these regions might interact. Finally, we offer some thoughts about possible future directions for affective neuroscience.¹

The James-Lange Theory

William James, in his ground-breaking paper *What is an emotion?* (James, 1884), proposed that emotions are no more than the

experience of sets of bodily changes that occur in response to emotive cues 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 and perception of changes in the body “as they occur is the emotion.” Similar ideas were developed in parallel by Carl Lange in 1885 (Lange, 1885), generating the James-Lange theory of emotions.

The James-Lange model was critiqued on several grounds by Cannon in the 1920s (Cannon, 1927, 1931) who cited, in particular, the failure of autonomic activity to differentiate different emotional states, the fact that surgical separation of the viscera from the brain in animals did not impair emotional behaviour, the suggestion that bodily changes are typically too slow to generate emotions, and work showing that artificial hormonal activation of bodily activity is insufficient to generate emotion, all as evidence that the James-Lange conceptualization was incomplete.

Subsequent research has cast doubt on Cannon's bold claims. Emotional responses, it seems, may be distinguishable (at least partly) on the basis of autonomic activity (Ekman, Levenson, & Friesen, 1983). Partial disconnection of the brain from the body can sometimes reduce emotional intensity

Table 1. Key scientific milestones in the development of affective neuroscience

Year	Milestone
1868	Harlow describes the effects of prefrontal cortex damage to Phineas Gage
1872	Charles Darwin publishes <i>The Expression of Emotions in Man and Animals</i>
1878	Broca outlines the architecture of <i>le grand lobe limbique</i>
1884/1885	James and Lange independently propose their bodily theory of emotion
1912	Mills first puts forward a right hemisphere hypothesis of emotion
1931	The Cannon-Bard theory of emotion is outlined
1937	Kluver and Bucy publish their work on temporal lobectomy
1937	Papez outlines his theory of emotion
1943	Hess and Brugger describe their earlier work on single cell recording in the hypothalamus
1949	MacLean proposes his tripartite "limbic" model of emotion
1956	Weiskrantz describes the effects of amygdala ablation in monkeys
1956	Schneirla outlines an approach-withdrawal model of emotion
1962	Schachter and Singer describe experiments indicating the importance of cognitive factors in determining the nature of emotion experience
1970/1971	Pribram and Nauta propose precursors of the somatic marker hypothesis
1980	Zajonc argues the case for emotion in the absence of cognition
1982	Lazarus argues the case for emotions requiring cognition
1983	Ekman and colleagues propose that different basic emotions can be distinguished autonomically
1986	LeDoux proposes multiple amygdala pathways for fear conditioning
1991	Antonio Damasio outlines his somatic marker hypothesis
1994	Adolphs et al. describe impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala
1995	Bechara et al. show that the amygdala is necessary for fear conditioning but not for explicit memory of the conditioning experience
1996	Cahill et al. reveal how the amygdala is important in the consolidation of emotional memories
1996	Using PET, Phillips and colleagues reveal the involvement of the insula in disgust
2000	Calder et al. describe a patient with insula and basal ganglia damage who showed selective impaired recognition and experience of disgust
2002	Hariri et al. show that amygdala response to emotive stimuli varies as a function of serotonin transporter gene variation
2003	The first study on the neural basis of social pain is published by Eisenberger and colleagues
2004	Singer and colleagues describe the sensory and affective systems that underlie pain and empathy for pain
2005	Mayberg and coworkers show that deep brain stimulation of the subgenual ACC results in remission of depression
2007	Mobbs et al. reveal the role of PAG in fear responses to proximal danger in humans

(e.g., following spinal injury; Hohmann, 1966; Montoya & Schandry, 1994). Some artificial manipulations of organ activity can induce emotions—for instance, intravenous administration of cholecystokinin (a gastric peptide) can provoke panic attacks (Harro & Vasar, 1991). A postulated ability to simulate in the somatosensory regions of the brain the activity that is expected in the body, the so-called ‘as-if’ loop, may also allow for more rapid and flexible responses (Damasio, 1994). Furthermore, in support of the James-Lange theory, there is some, albeit inconsistent, evidence that those with superior ability to perceive changes in the body (“interoception”) report more intense emotion experience (see Barrett, Quigley, Bliss-Moreau, & Aronson, 2004, for a review). Finally, even if null findings have emerged from some studies examining emotion processing following partial separation of brain and body, these are difficult to unambiguously interpret. It is not possible to safely isolate the brain from all aspects of bodily feedback, meaning that emotion experience may still be driven by remaining peripheral feedback mechanisms in these separation designs (e.g., Heims, Critchley, Dolan, Mathias, & Cipolotti, 2004).

These points notwithstanding, the claim that patterns of bodily response are sufficient to *fully* differentiate between emotional states is no longer widely accepted. A hybrid position, whereby the body contributes to a crude sense of emotional intensity which is then centrally cognitively appraised to lead to more nuanced emotional experience, is generally adopted (two factor theory). Key evidence for this position comes from studies showing that similar patterns of bodily arousal could be experienced as anger or happiness depending on the social and cognitive context (Schachter & Singer, 1962).

Overall, the James-Lange theory has remained remarkably influential on contemporary thinking and is indeed enjoying something of a renaissance by virtue of the emphasis it places on the embodiment of emotions, which sits well with broader frameworks of embodied cognition (Niedenthal, 2007).

From Theory to Anatomy

The Cannon-Bard Theory

As part of his critique of the James-Lange theory Cannon developed the first substantive neuroanatomical theory of emotion (Cannon, 1927), which was later elaborated by Bard (Bard, 1928; Bard & Rioch, 1937). This argued that the thalamus and hypothalamus are critically involved in the emotion response to stimuli and that such responses are inhibited by evolutionarily more recent neocortical regions. Removal of the cortex frees the thalamic circuitry from top-down control, allowing uncontrolled emotion displays.

This account was influenced by work conducted by Henry Head showing that unilateral thalamic lesions led to excessive reactions to painful stimuli (e.g., a pinprick or excessive heat) on the damaged side of the body (Head, 1921). Similarly, the hypothalamus was implicated by studies conducted in the 1920s by Walter Hess where he implanted electrodes into the hypothalamic region of cats (Hess & Brugger, 1943/1981). 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 coordinated and sophisticated, 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. Supporting the contention that the cortex inhibits these thalamic functions, Bard went on to show that following decortication cats were liable to make sudden, inappropriate anger attacks that were labelled as “sham rage” (Bard & Rioch, 1937). Together these findings support Cannon and Bard’s contention that thalamic regions are a central component of the emotional brain.

Subsequent research has revealed a wider role for the hypothalamus in the processing of affect. Olds and Milner (1954) 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 four hours a day. Similar arguments concerning the hypothalamus and reward were made by Heath (1972) 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 that has since been shown to also involve the prefrontal cortex (Rolls, 1999), amygdala (Baxter & Murray, 2002), and ventral striatum (Garnefski, Teerds, Kraaij, Legerstee, & van den Kommer, 2004). Numerous other electrical stimulation studies have identified further roles for the hypothalamus in motivations such as sex and hunger (Stellar, 1954; Teitelbaum & Epstein, 1962).

The Papez Circuit

Following on from the thalamic-centred proposals of Cannon and Bard, in 1937 James Papez outlined an anatomically broader scheme for the central neural circuitry of emotion—now known as the “Papez circuit” (Papez, 1937). Papez proposed that sensory input into the thalamus diverged into an upstream “thought” and a downstream “feeling” pathway. The thought stream linked 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, in contrast, 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 *feelings* were a function of cingulate activity generated through either stream. Echoing Cannon and Bard’s ideas, downward projections from the cingulate to the hypothalamus also permitted top-down cortical regulation of emotional responses. Papez’s paper was a seminal achievement

and subsequent research has revealed that many of the pathways that he 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 1949 (MacLean, 1949). MacLean’s model built on Papez’s and Cannon and Bard’s original ideas and integrated them with the seminal findings of Kluver and Bucy (Kluver & Bucy, 1937) who had shown that bilateral removal of the temporal lobes in monkeys led to a characteristic set of behaviours (the “Kluver-Bucy syndrome”) that included increased exploratory behaviour, a loss of emotional reactivity, hypersexuality, a tendency to examine objects with the mouth, and abnormal dietary changes including coprophagia (eating of faeces). These studies suggested a key role for temporal lobe structures in emotion and this was to become a cornerstone of MacLean’s theory.

MacLean viewed the brain as a triune architecture (MacLean, 1970) consisting of three interacting systems. First, the evolutionarily ancient reptilian brain (striatal complex and basal ganglia) which he saw as the seat of primitive emotions such as aggression and fear. Second, the “old” mammalian brain (originally called the “visceral brain”) which MacLean proposed augments primitive reptilian emotional responses such as aggression but also elaborates the social emotions. This brain system incorporates key components of the Papez circuit—the hypothalamus, thalamus, hippocampus and cingulate cortex—along with important additional structures, most notably the amygdala and the prefrontal cortex. Third, the “new” mammalian brain consisting primarily of the neocortex, which represents the interface of emotion with cognition and is the seat of top-down control over emotional responses originating within other systems.

MacLean’s key proposition was that emotion experiences involve the integration of sensations from the world with information from the body. In this 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” to describe this circuitry (MacLean, 1952; see Figure 1), based on the original terminology of Broca—*Le grand lobe limbique* (Broca, 1878).

MacLean’s limbic system concept remains the dominant conceptualization of the “emotional brain” today, and the structures that he identified as central have been the focus of the majority of the research in affective neuroscience since his original publication. The notion of the limbic system remains controversial and has been criticized on both empirical (LeDoux, 1996) and theoretical grounds (Calder, Lawrence, & Young, 2001). A number of the limbic system structures—the hippocampus,

The Limbic System

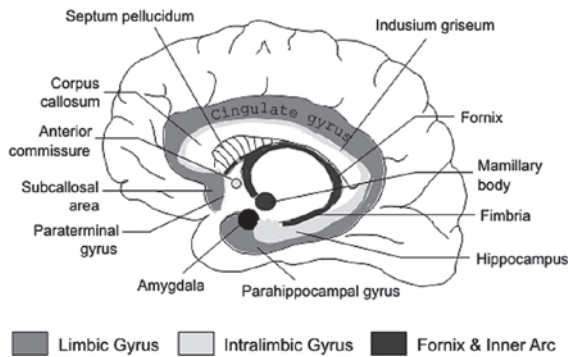


Figure 1. MacLean's limbic system.

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, insular and prefrontal cortex, and the notion of a limbic system thus retains its influence (Morgane & Mokler, 2006).

Findings from Contemporary Affective Neuroscience

Next, we focus on subsequent research investigating five key limbic regions implicated in MacLean's original paper (MacLean, 1949). We also consider recent work on midbrain structures. Other brain regions (nucleus accumbens, ventral pallidum, hippocampus, septum, and the somatosensory cortices) have also been implicated in the processing of emotion; however, detailed discussion of these areas is beyond the scope of this review.

The Amygdala

The amygdala (see Figure 2) is embedded in the medial temporal lobe and rests on the anterior tip of the hippocampus. The amygdala consists of functionally distinct nuclei (i.e., 13 main nuclei, each having further subdivisions), which have extensive internuclear and intranuclear connections. The nuclei also project extensively to cortical and subcortical locations associated mainly with affective or salience processing.

The beginning of our understanding of amygdala functioning has its origins in the work on Kluver-Bucy syndrome (Kluver & Bucy, 1937) which involved surgical removal of almost the entire temporal lobes, including the amygdala, in monkeys. Building on this work, Weiskrantz (1956) 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 (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956). 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 (e.g., Meunier, Bachevalier, Murray, Malkova, & Mishkin, 1996; Murray, Gaffan, & Flint, 1996). 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 learning, and in the consolidation of emotional memories. We consider these different functions next.

The amygdala and social signals of emotion. Selective amygdala damage in humans is rare but seems not to lead to many Kluver-Bucy signs (Aggleton, 1992). A Kluver-Bucy-like syndrome only becomes apparent in humans after more extensive bilateral damage, including the rostral temporal neocortex (Terzian & Ore, 1955). However, 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 (Jacobson, 1986). This finding builds on single-unit recording studies in animals that have shown that amygdala neurons can respond differently to different faces (Leonard, Rolls, Wilson, & Baylis, 1985) and can respond selectively to dynamic social stimuli such as approach behaviour (Brothers, Ring, & Kling, 1990). Later studies (Adolphs, Tranel, Damasio, & Damasio, 1994; Young et al., 1995) indicated that the processing of emotional facial expressions,

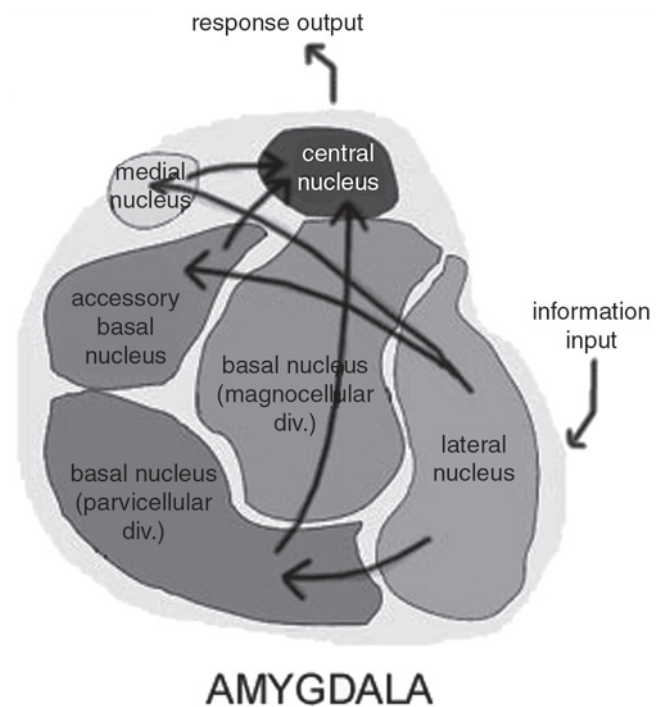


Figure 2. The human amygdala.

especially fear, was particularly impaired in humans with amygdala lesions (e.g., Calder et al., 1996), although facial expressions of other emotions seem to more closely implicate other circuits (Calder, Keane, Lawrence, & Manes, 2004; Calder, Keane, Manes, Antoun, & Young, 2000).

The 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) (Morris et al., 1996) and Breiter and colleagues using functional magnetic resonance imaging (fMRI) (Breiter et al., 1996) showed selective brain activation in the amygdala in response to the presentation of fearful faces. The amygdala is also selective for fear communicated in other ways such as in vocal expressions (Scott et al., 1997) or bodily movements (Hadjikhani & de Gelder, 2003). Such amygdala activation by fearful faces occurs even when the faces are presented so quickly that the subject is unaware of them (Morris, Ohman, & Dolan, 1998; Whalen et al., 1998), or are presented in the blind hemifield of patients with blindsight (Morris, DeGelder, Weiskrantz, & Dolan, 2001). Activation also seems to be more robust in response to subliminal presentation of the eyes alone (Whalen et al., 2004). There is emerging but controversial evidence that activation to fearful faces is greater in individuals possessing particular genetic attributes, for example individuals characterized by the short allele variant in the human serotonin transporter gene (*SLC6A4*) (Hariri et al., 2005). Finally, 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 (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002).

The amygdala and emotional learning. 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 Blanchard (1972), and more recently and extensively by Joseph LeDoux and his colleagues (LeDoux, 1986, 1987, 1989, 1993, 1995), 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 cognition (Zajonc, 1980). The second route

is a thalamo-cortico-amygdala pathway that allows more complex analysis of the incoming stimulus and delivers a slower conditioned emotion response.

Fear conditioning in humans has been less extensively studied. However, a number of important findings exist. First, Angrilli et al. (1996) 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, Tranel, Damasio, and Adolphs (1995) 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 noise (Morris, Ohman, & Dolan, 1998). Fourth, in line with LeDoux's ideas, Morris, Ohman, and Dolan (1999) provided 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 conditioning (Gallagher, Graham, & Holland, 1990).

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 nonemotional aspects; Cahill, Babinsky, Markowitsch, & McGaugh, 1995). This was confirmed in another patient with nearly selective amygdala damage (Adolphs, Cahill, Schul, & Babinsky, 1997). 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 (Cahill et al., 1996; Hamann, Ely, Grafton, & Kilts, 1999). Moreover, administration of the anaesthetic sevoflurane has been found to impair emotional memory at higher doses and this effect appears to be modulated by virtue of the drug suppressing amygdala to hippocampus effective connectivity (Alkire et al., 2008). 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 perception (Fitzgerald et al., 2003).

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 noted (Harlow, 1869/1993) “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 (Macmillan, 2002).

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 PFC has been implicated in emotion in many ways, but there is still no consensus as to its exact functions. In the next section, we consider four aspects of PFC functioning and their historical antecedents.

The PFC and reward processing. Rolls’ work on the orbitofrontal region of the PFC (Rolls, 1990, 1996, 1999) proposes that it is involved in learning the emotional and motivational value of stimuli (Rolls, 1999). 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 1960s (Mowrer, 1960).

The PFC and bodily signals. As discussed above, the James-Lange theory emphasizes how emotions are in part embodied phenomena. Damasio and colleagues have argued in the influential somatic marker hypothesis (SMH) (Damasio, 1994, 1996, 1997) that regions of the PFC, particularly the ventromedial PFC (vmPFC), use this emotional bodily feedback to guide decision-making in situations of complexity and uncertainty (see also the section on the insula below).

The SMH builds on the earlier work of Nauta (1971) who used the term “interoceptive” markers rather than somatic markers, and Pribram (1970) 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 or muscular activity, which tag previous 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 1991 Saver and Damasio described the patient EVR—a “modern day Phineas Gage” (Damasio, 1994)—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” (Nauta, 1971). They propose that EVR is unable to utilize 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, Damasio, and Anderson (1994) asked patients with vmPFC damage, including EVR, to play a card game (the Iowa Gambling Task) 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 vmPFC 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 participants, somatic markers develop in the early trials of the task which then provide signals to guide later card choices (Bechara, Damasio, & Damasio, 2000; Bechara et al., 1994). The healthy participants 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. Despite recent criticism of the Iowa task methodology there is no doubt that the SMH remains the most influential theory of the relationship between bodily feedback and decision making (Dunn, Dalgleish, & Lawrence, 2006).

The PFC and ‘top-down’ regulation. The dorsolateral regions of the PFC (dlPFC), comprising Broca’s Areas 46 and 9 which lie in the middle and superior frontal gyrus respectively (Petrides, 2005), have been implicated in numerous cognitive operations including behavioural selection, maintenance of attentional demands, top-down control of memory, and counterfactual “what if” thinking (Baird & Fugelsang, 2004; Bechara, 2005). The dlPFC is an important component of a proposed cortical behavioural inhibition circuit and is an integral part of the striatal-thalamo-cortical loop (Masterman & Cummings, 1997).

Also implicated in the control circuit is the ventrolateral prefrontal cortex (vlPFC). This circuit is thought to extend to the subthalamic nucleus (STN) and pre-supplementary motor area (pre-SMA) (Aron, Behrens, Smith, Frank, & Poldrack, 2007). The core of the vlPFC is located in BA 47/44/45 and is segregated into several functional distinct regions. Regions encompassing the right inferior frontal gyrus (IFG) are thought to mediate the wilful suppression of actions and thoughts (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). The right IFG is a core node in the inhibition network and acquired lesions to this region cause dramatic deficits in behavioural inhibition (Aron et al., 2003; Mobbs, Eckert, et al., 2007). This differs substantially from

the left IFG which is critical to the language network. Others have implicated the vlPFC in social-norm violation and punishment (Berthoz, Grèzes, Armony, Passingham, & Dolan, 2006).

In related work on top-down regulation, Amat and coworkers have shown that the rodent infralimbic and prelimbic sectors of the vmPFC are associated with detection of whether a stressor is controllable. If the stressor is controllable, the vmPFC inhibits the dorsal raphe nuclei (DRN)—a core region of the stress and serotonergic system in the midbrain (Amat et al., 2005). More recently, Pascucci and colleagues showed that the mPFC modulates nucleus accumbens dopamine responses to stress (Pascucci, Ventura, Latagliata, Cabib, & Puglisi-Allegra, in press) and Phelps and coworkers showed that both the vmPFC and amygdala are involved in fear extinction (Phelps, Delgado, Nearing, & LeDoux, 2004). Others have pointed to the mPFC's role in controlling the hypothalamic-pituitary-adrenal axis (HPA axis) and harmful corticoid steroids (Figueiredo, Bruestle, Bodie, Dolgas, & Herman, 2003). The mPFC has been implicated in higher top-down processes such as predictive coding or predicted perception. Summerfield and coworkers recently used fMRI to show that the mPFC is involved in the resolution of perceptual ambiguity by anticipating forthcoming stimuli. In addition, Summerfield et al. showed increased top-down connectivity from the PFC to the fusiform gyrus, which fits with a putative role in matching of predicted and observed faces (Summerfield et al., 2006).

Related to this broad involvement of the PFC in top-down modulation, there has been increasing interest in links to emotion regulation, defined as automatic or effortful attempts to up- or down-regulate emotion experience and expression (Gross & Levenson, 1997). A range of behavioural studies (for a review see Gross, 2002) have contrasted the effects of different forms of emotion regulation, generally reaching the conclusion that antecedent strategies that happen in advance of an emotional reaction (e.g., reappraisal, whereby the meaning of an emotion-eliciting event is altered) are more effective forms of emotion regulation than response-focused strategies (e.g., expression suppression, whereby any outward sign of an affective reaction is hidden). At a neural level, findings generally support the conclusion that prefrontal control systems, along with orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), are involved in emotion regulation (e.g., Ochsner, Bunge, Gross, & Gabrieli, 2002), although these results are more robust for attempts at cognitive rather than attentional control (Ochsner & Gross, 2005). Activation of these regions is often associated with deactivation in limbic regions such as the amygdala, consistent with successful emotional down-regulation (e.g., Kalisch, in press; Ochsner et al., 2002; Schaefer et al., 2002).

The PFC and social processing. The mPFC has also been implicated in person perception, mentalizing, and outcome monitoring (Amodio & Frith, 2006). It is likely that other regions also support these functions, including the temporoparietal junction, superior temporal sulcus (STS), and temporal poles. One recent study implicated the dorsal mPFC in the perception of people dissimilar to oneself, while more ventral

regions were related to similarity to oneself and with self-referential thought (Mitchell, Macrae, & Banaji, 2006). More broadly, recent brain-imaging and lesion studies have shown that these regions are explicitly involved in social behaviour including regret (Coricelli et al., 2005), and moral decision-making (Koenigs et al., 2007).

The Anterior Cingulate Cortex (ACC)

Contemporary affective neuroscientists view the ACC as a point of integration of visceral, attentional, and emotional information that, along with regions of the PFC discussed above, is critically involved in the regulation of affect and other forms of top-down control (Bush, Luu, & Posner, 2000; Davidson et al., 2002). It has also been suggested that the ACC is a key substrate of conscious emotion experience (Lane et al., 1998), as suggested by Papez, and of the central representation of autonomic arousal (Critchley, Elliot, Mathias, & Dolan, 2000). These regions are also involved in generating autonomic changes. For example, the dACC activates during increased heart rate, blood pressure, and pupil size (Critchley, Mathias, & Dolan, 2001).

The ACC encompasses Broca's Areas 32, 25, and 24, and has been functionally segregated into dorsal "cognitive" and ventral "affective" systems (Bush et al., 2000). The affective subdivision of the ACC is routinely activated in functional imaging studies involving all types of emotional stimuli (Bush et al., 2000; Murphy, Nimmo-Smith, & Lawrence, 2003; Phan, Wager, Taylor, & Liberzon, 2002). Present thinking suggests that the ACC is involved in the monitoring of 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 occur (Bush et al., 2000; Carter & van Veen, 2007). In addition to connections between the thalamus, pallidum, striatum, and ACC are thought to form an "anterior cingulate circuit" (Alexander, DeLong, & Strick, 1986). This circuit is partially closed by projections to ACC from medial and posterior regions of the mediodorsal nucleus (Baleydier & Mauguier, 1980).

It is known that in humans pain anticipation and analgesia also engage the ACC (Wager et al., 2004), which interacts with brainstem nuclei including the periaqueductal grey (see below); both are regions with a high-density of opioid receptors (Petrovic, Kalso, Petersson, & Ingvar, 2002). More posterior portions of the dorsal ACC and pregenual ACC (pgACC) have been implicated in pain control (Petrovic et al., 2002; Salomons, Johnstone, Backonja, & Davidson, 2004). This region also activates to more subjective elements of pain including empathy for pain (i.e., seeing a loved one in pain) (Singer et al., 2004) and social ostracism (Eisenberger, Lieberman, & Williams, 2003). The ventral portions of the ACC, which include the pgACC and subgenual ACC (sgACC), have been implicated in mood. In one study, deep brain stimulation of the sgACC (BA 25) in patients with treatment-resistant depression resulted in remission of depression in the majority of the sample (four out of six) (Mayberg et al., 2005).

The Insular Cortex or Insula

As discussed above, MacLean originally postulated that the hippocampus was essential in the integration of bodily responses with perception of the external world. Recent theorists, however, suggest that the insular rather than the hippocampus may be the crucial region involved in the perception of bodily changes. Interoception ability (Craig, 2003), measured by asking participants to judge if a tone is simultaneous or delayed relative to the heartbeat, has been shown to activate right anterior insular, along with somatosensory and ACC regions as noted above (Critchley, Wiens, Rotshtein, Öhman, & Dolan, 2004). Further, individual differences in interoception correlate with right anterior insular size measured using voxel based morphometry (VBM) (Critchley et al., 2004).

There is a considerable body of work implicating the insula in a range of emotional processes, including recognition (Calder et al., 2001), experience (Simmons, Matthews, Stein, & Paulus, 2004; Stein, Simmons, Feinstein, & Paulus, 2007), and empathy (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003). It has also been shown that the insula is involved in the generation of a risk prediction error that guides decision-making in risky situations and can facilitate learning about uncertain rewards (Preusschoff, Quartz, & Bossaerts, 2008), supporting the role for bodily feedback in decision-making proposed by the somatic marker hypothesis (Damasio, 1994). Along similar lines, the proposal has been put forward that the insula may provide information about anticipated body states associated with conditioned stimuli (Paulus & Stein, 2006), which can be used to inform attention allocation and action execution.

The Midbrain

William James proposed that while the lower centres of the brain “act from present sensational stimuli alone” the cortex acts from perceptions and considerations (James, 1890). These lower centres, which we now know include the midbrain and below, seem to be involved in such reflexive processes as fight/flight/freeze behaviours. The midbrain has several important neuronal assemblies notably the locus coeruleus and the dorsal raphe nuclei. Comprehensive discussion of the research implicating these regions in the processing of affect is beyond our purview here. Instead, in illustration of the exciting developments involving these brain regions, we focus on one region which recent findings from our own work and that of others suggest is critical to affective behaviour and related reflexive processes—the periaqueductal grey matter (PAG).

Periaqueductal Gray (PAG). The PAG is a thin long mid-brain structure located around the cerebral aqueduct (Bandler, Keay, Floyd, & Price, 2000). Comparative studies suggest that the PAG is functionally segregated. For example, while fight processes are mediated by the rostral PAG, flight processes are modulated by the caudal PAG. Neuroanatomical studies support this conjecture, showing that exposure to a predator increases Fos expression (i.e., immediate gene expression) in the rostral dorsomedial/dorsolateral PAG (dm/dlPAG). Freezing behaviour is thought to be mediated by the central nucleus of the amygdala

(CeA; see Figure 2) through its projections to the ventral PAG (Blanchard & Blanchard, 1990a, 1990b; Comoli, Ribeiro-Barbosa, & Canteras, 2003; Fanselow, 1991, 1994). Evidence also shows that a microinjection of excitatory amino acids in the lateral or dorsal PAG results in heightened threat perception and opioid dependent analgesia (see Comoli et al., 2003). During the so-called *circa-strike* phase (i.e., direct interaction between predator and prey), increased activity is also seen in the dorsal PAG and superior colliculus (Fanselow, 1994). These systems are increasingly activated with predatory imminence (Blanchard & Blanchard, 1990a, 1990b; Fanselow, 1994; Mobbs, Petrovic, et al., 2007).

In addition to its role in the detection of threat in predation, research is starting to emerge suggesting that the PAG is also involved in predatory behaviour itself. Predation is characterized by activity in several distinct regions, including the rostral lateral PAG, amygdala, prefrontal cortex, and striatum. Recent empirical work suggests that inhibition of the rat rostralateral PAG via injections of morphine results in decreased maternal behaviour and increased predatory hunting of live cockroaches (Sukikara et al., 2006). Others have shown decreased Fos expression in the rostral dm/dlPAG to be associated with predation (Comoli et al., 2003), while lesions, and injections of Naloxone, an opioid antagonist, to the rostral lateral PAG impair predatory hunting (Sukikara et al., 2006). One theory is that the PAG is involved in adaptive behavioural responses, although the amygdala and orbital prefrontal cortex are likely to play a key role in integration of pre-motivational values. Importantly, predation is exciting, arousing, and highly rewarding. Given its hedonic nature, predation is likely characterized by activity in reward-seeking systems.

These different fear and hedonic states have not been described in detail in humans although some theoretical attempts have been made (Lang, Davis, & Ohman, 2000). What is known in humans is that pain anticipation and analgesia are likely to engage the ACC (Wager et al., 2004) which in turn interacts with brainstem nuclei including the PAG; both are regions with high-densities of opioid receptors (Petrovic et al., 2002). Previous studies have also shown how the PAG is evoked during the anticipation of pain (Berns et al., 2006).

With animal models in mind, Deakin and Graeff—and later, McNaughton and Corr—proposed that the intensity of threat is associated with a cascade of neural systems which begin in the PFC when the threat is distant, and as the threat increases (e.g., grows closer) a shift to subcortical regions is made (Deakin & Graeff, 1991; McNaughton & Corr, 2004).

Overview

In summary, contemporary neuroscience has offered reasonable support for MacLean’s claims about brain regions crucially involved in emotion; in particular, the amygdala, hypothalamus, cingulate cortex, insular, and the prefrontal cortex. However, it is increasingly apparent that affect cannot be cleanly separated from other cognitive processes and that a range of other regions not originally envisaged in the limbic system framework are also importantly involved in emotion. The pervasiveness of the brain’s involvement with the processing of affect interfaces with the increasing need to understand how the different brain

regions interact. We consider aspects of this question in the next section on affective systems in the brain.

Single, Dual, or Multiple Emotion Systems?

Frameworks of the functional neuroanatomy of emotion range from single-system models, in which the same neural system underlies all emotions, to multiple-system models, which 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.

Single-System Models

The accounts discussed earlier proposed by Cannon and Bard, Papez, MacLean and, to some extent, Damasio, are all good examples of single-system models. A further example is the “right-hemisphere hypothesis” originally proposed by Mills in (1912) and expanded by Sackeim and Gur (1978; Sackeim, Gur, & Saucy, 1978) and others (Schwartz, Ahern, & Brown, 1979; Schwartz, Davidson, & Maer, 1975). In its simplest form, this hypothesis emphasized a specialized role of the right hemisphere in all aspects of emotion processing (Sackeim & Gur, 1978; Sackeim et al., 1978), though more refined views have proposed that hemispheric specialization is restricted to the perception and expression of emotion, rather than its experience (Adolphs, Damasio, Tranel, & Damasio, 1996).

Dual-System Models

Davidson’s approach/withdrawal 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 approach and withdrawal emotions, respectively (Davidson, 1984a, 1984b). Other dual-system theorists, beginning with Schneirla in 1959, 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 (Cloninger, 1987; Gray, 1982); approach and withdrawal systems (Davidson, Ekman, Saron, Senulis, & Friesen, 1990); and appetitive and aversive systems (Lang, Bradley, & Cuthbert, 1990). 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 (Rolls, 1990, 1999).

Multiple-Systems Models

Other theorists, inspired by the prototypical work of Darwin (Darwin, 1872/1965), have proposed that a small set of discrete emotions are underpinned by relatively separable neural systems in the brain (Adolphs et al., 1994, 1999; Bechara et al., 1995; Calder et al., 1996; Schmolck & Squire, 2001; Scott et al., 1997). Some of the key research in support of this multi-system view has come from human lesion studies and from functional neuroimaging. We have mentioned above a number of studies

linking the processing of fear to the amygdala. Similar studies have emerged 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 (Phillips et al., 1997). This is consistent with early work by Penfield and Faulk in 1955 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 recognizing both facial and vocal signals of disgust, and impaired experience of disgust (Calder et al., 2000). Similar findings have been reported in patients with Huntington’s disease (Sprengelmeyer et al., 1996)—a condition that affects the striatum—and in carriers of the Huntington’s disease gene (Gray, Young, Barker, Curtis, & Gibson, 1997).

There has been relatively little work on the neural substrates of other emotions (Calder et al., 2004) 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 (Murphy et al., 2003; Phan et al., 2002), with other brain regions, notably the PFC and ACC, being activated for all emotions (see above). However, these proposals concerning separable neural regions underpinning different basic emotions remain the focus of considerable debate (Barrett, 2006a).

Possible Future Directions in 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. This has led some to question whether classic distinctions between cognition and emotion should be retained within both psychology and neuroscience (Pessoa, 2008). This notwithstanding, 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 (Dalgleish, 2004; Izard, 1993). 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 recent influential theoretical papers (Barrett, 2006b; Dalgleish & Power, 2004; Lambie & Marcel, 2002; Panksepp, 2005). There has been little theory or research on the underlying neural substrates of emotion experience, with the exception of the work of Richard Lane discussed earlier, and this is likely to be a focus of ongoing efforts.

The interaction of affect with other domains of psychology, as well as other disciplines, is also likely to feature significantly on the future research agenda; for example, the interplay of affective neuroscience and social psychology—so-called social affective neuroscience (Ochsner & Lieberman, 2001)—and the dialogue between affective neuroscience and economics (Glimcher & Rustichini, 2004).

Future progress in affective neuroscience will depend on the emergence of new technologies and methods. Functional brain imaging has transformed the field in the last 10 years and the advent of high-field MRI (up to 11 Teslas) will provide far greater spatial resolution, for example allowing for better discrimination between nuclei in the midbrain, striatum and amygdala. Relatively new forms of imaging such as diffusion tensor imaging (DTI), enabling noninvasive tracing of white matter tracts, and Magnetoencephalography (MEG), providing millisecond accuracy in examining the timing of affective processes, will lead to further leaps in our understanding. Similarly, real time brain imaging (Posse et al., 2003) that permits examination of brain activity concurrently with behaviour has exciting potential providing the possibility of real time feedback from the brain as a stimulus for behaviour regulation (Caria et al., 2007). Another relatively recent methodology with considerable 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 utilizing multiple methodologies, integrating functional imaging, pharmacology, TMS, psychophysiology, and cognitive psychology. In particular, the emerging field of behavioural genetics is likely to greatly enhance our understanding of mechanisms involved in the generation and regulation of affect (Hariri et al., 2002). For example, genetic variations in COMT and the serotonin transporter gene have already been linked to activation in the key neural circuitry for affect regulation when processing aversive stimuli (e.g. Hariri et al., 2002; Montag et al., 2008; Smolka et al., 2005; Smolka et al., 2007), particularly fearful material. Similarly, variations in CREB1 have been linked to activation of the insular in response to negative stimuli (Perlis et al., 2008). The combination of neuroimaging with such genetic measures seems a particularly fruitful avenue for more clearly accounting for individual differences in affective responding.

Beyond technical advances, affective neuroscience has been at the forefront of recent neuroethical arguments associated with the legal system. Affective neuroscience may have important implications for both how we understand the multiple influences on violent behaviour and how the legal system may better

engage with violent criminals (Mobbs, Lau, Jones, & Frith, 2007). Indeed, studies are beginning to show that different types of crimes are associated with different parts of the brain's emotion systems (Markowitsch, 2008).

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 states (Davidson, Putnam, & Larson, 2000) and of psychiatric disorders such as depression (Mayberg, 1997), as well as the neural correlates of individual differences in normal emotions, for example, variations in “affective style” (Davidson, 1993). Similarly, there is also an increasing recognition of the need to better understand the generation and regulation of positive, as well as negative, affect (for reviews see Berridge & Kringelbach, 2008; Burgdorf & Panksepp, 2006). These issues will surely come further into the spotlight in the decades to come.

Note

- 1 A review of this kind inevitably focuses on selective aspects of the literature. We mention only in passing neurochemistry and molecular biology studies relevant to affective neuroscience. We also do not consider the extensive literature on the relationship between emotion, stress, and the neuro-immuno axis that has emerged from Selye's pioneering work (for a recent review see Goldstein & Kopin, 2007). Similarly, while we have concentrated on contemporary studies on human samples, we acknowledge it continues to be important to integrate findings across species to fully account for emotional phenomena (e.g., Panksepp, 1998).

References

- Adolphs, R., Cahill, L., Schul, R., & Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learning & Memory*, *4*, 291–300.
- Adolphs, R., Damasio, H., Tranel, D., & Damasio, A. R. (1996). Cortical systems for the recognition of emotion in facial expression. *Journal of Neuroscience*, *16*, 7678–7687.
- Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, *372*, 669–672.
- Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E., et al. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*, *37*, 1111–1117.
- Aggleton, J. P. (1992). The functional effects of amygdaloid lesions in humans: A comparison with findings from monkeys. In J. P. Aggleton (Ed.), *The amygdala* (pp. 485–503). New York/Chichester: Wiley-Liss.
- Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Reviews of Neuroscience*, *9*, 357–381.
- Alkire, M. T., Gruver, R., Miller, J., McReynolds, J. R., Hahn, E. L., & Cahill, L. (2008). Neuroimaging analysis of an anesthetic gas that blocks human emotional memory. *Proceedings of the National Academy of Sciences*, *105*(5), 1722.
- Amat, J., Baratta, M. V., Paul, E., Bland, S. T., Watkins, L. R., & Maier, S. F. (2005). Medial prefrontal cortex determines how stressor controllability affects behavior and dorsal raphe nucleus. *Nature Neuroscience*, *8*, 365–371.
- Amodio, D. M., & Frith, C. D. (2006). Meeting of minds: The medial frontal cortex and social cognition. *Nature Reviews Neuroscience*, *7*(4), 268.
- Angrilli, A., Mauri, A., Palomba, D., Flor, H., Birbaumer, N., Sartori, G., et al. (1996). Startle reflex and emotion modulation impairment after right amygdala lesion. *Brain*, *119*, 1991–2000.

- Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J., & Poldrack, R. A. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *Journal of Neuroscience*, 27(14), 3743.
- Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nature Neuroscience*, 6(2), 115–116.
- Baird, A. A., & Fugelsang, J. A. (2004). The emergence of consequential thought: Evidence from neuroscience. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 359(1451), 1797–1804.
- Baleydier, C., & Mauguier, F. (1980). The duality of the cingulate gyrus in monkey. *Brain*, 103, 525–554.
- Bandler, A., Keay, K. A., Floyd, N., & Price, J. (2000). Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. *Brain Research Bulletin*, 53(1), 95–104.
- Bard, P. (1928). A diencephalic mechanism for the expression of rage with special reference to the central nervous system. *American Journal of Physiology*, 84, 490–513.
- Bard, P., & Rioch, D. M. (1937). A study of four cats deprived of neocortex and additional portions of the forebrain. *Johns Hopkins Medical Journal*, 60, 73–153.
- Barrett, L. F. (2006a). Are emotions natural kinds? *Perspectives on Psychological Science*, 1(1), 28–58.
- Barrett, L. F. (2006b). Solving the emotion paradox: Categorization and the experience of emotion. *Personality and Social Psychology Review*, 10(1), 20–46.
- Barrett, L. F., Quigley, K. S., Bliss-Moreau, E., & Aronson, K. R. (2004). Interoceptive sensitivity and self-reports of emotional experience. *Journal of Personality and Social Psychology*, 87(5), 684–697.
- Baxter, M. G., & Murray, E. A. (2002). The amygdala and reward. *Nature Reviews Neuroscience*, 3, 563–573.
- Bechara, A. (2005). Decision making, impulse control and loss of will-power to resist drugs: A neurocognitive perspective. *Nature Neuroscience*, 8, 1458–1463.
- Bechara, A., Damasio, H., & Damasio, A. R. (2000). Emotion, decision making, and the orbitofrontal cortex. *Cerebral Cortex*, 10, 295–307.
- Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50(1–3), 7–15.
- Bechara, A., Tranel, D., Damasio, H., & Adolphs, R. (1995). Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*, 269, 1115–1118.
- Berns, G. S., Chappelow, J., Cekic, M., Zink, C. F., Pagnoni, G., & Martin-Skurski, M. E. (2006). Neurobiological substrates of dread. *Science*, 312, 754–758.
- Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: Reward in humans and animals. *Psychopharmacology*, 199, 457–480.
- Berthoz, S., Grèzes, J., Armony, J. L., Passingham, R. E., & Dolan, R. J. (2006). Affective response to one's own moral violations. *NeuroImage*, 31(2), 945–950.
- Blanchard, D. C., & Blanchard, R. J. (1972). Innate and conditioned reactions to threat in rats with amygdaloid lesions. *Journal of Comparative and Physiological Psychology*, 81, 281–290.
- Blanchard, R. J., & Blanchard, D. C. (1990a). Anti-predator defence as models of animal fear and anxiety: Fear and defence. In P. F. Brain, S. Parmigiani, R. J. Blanchard & D. Mainardi (Eds.), *Fear and defence* (pp. 89–108). London: Harwood Academic Publishers.
- Blanchard, R. J., & Blanchard, D. C. (1990b). An ethoexperimental analysis of defence, fear and anxiety. In N. McNaughton & G. Andrews (Eds.), *Anxiety* (pp. 24–33). Dunedin: Otago University Press.
- Breiter, H. C., Etcoff, N. L., Whalen, P. J., Kennedy, W. A., Rauch, S. L., Buckner, R. L., et al. (1996). Response and habituation of the human amygdala during visual processing of facial emotion. *Neuron*, 17, 875–887.
- Broca, P. (1878). Anatomie comparée des circonvolutions cérébrales. *Revue d'Anthropologie*, 1, 385–498.
- Brothers, L., Ring, B., & Kling, A. (1990). Response of neurons in the macaque amygdala to complex social stimuli. *Behavioural Brain Research*, 41, 199–213.
- Burgdorf, J., & Panksepp, J. (2006). The neurobiology of positive emotions. *Neuroscience and Biobehavioral Reviews*, 30, 173–187.
- Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, 4(6), 215–222.
- Cahill, L., Babinsky, R., Markowitsch, H. J., & McGaugh, J. L. (1995). The amygdala and emotional memory. *Nature*, 377, 295–296.
- Cahill, L., Haier, R., Fallon, J., Alkire, M., Tang, C., Keator, D., et al. (1996). Amygdala activity at encoding correlated with long-term free recall of emotional information. *Proceedings of the National Academy of Sciences*, 93, 8016–8021.
- Calder, A. J., Keane, J., Lawrence, A. D., & Manes, F. (2004). Impaired recognition of anger following damage to the ventral striatum. *Brain*, 127(9), 1958.
- Calder, A. J., Keane, J., Manes, F., Antoun, N., & Young, A. W. (2000). Impaired recognition and experience of disgust following brain injury. *Nature Neuroscience*, 3(11), 1077–1078.
- Calder, A. J., Lawrence, A. D., & Young, A. W. (2001). Neuropsychology of fear and loathing. *Nature Reviews Neuroscience*, 2, 352–363.
- Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., & Etcoff, N. L. (1996). Facial emotion recognition after bilateral amygdala damage: Differentially severe impairment of fear. *Cognitive Neuropsychology*, 13(5), 699–745.
- Cannon, W. B. (1927). The James-Lange theory of emotions: A critical examination and an alternative theory. *American Journal of Psychology*, 39, 106–124.
- Cannon, W. B. (1931). Again the James-Lange and the thalamic theories of emotions. *Psychological Review*, 38, 281–295.
- Caria, A., Veit, R., Sitaram, R., Lotze, M., Weiskopf, N., Grodd, W., et al. (2007). Regulation of anterior insular cortex activity using real-time fMRI. *NeuroImage*, 35(3), 1238–1246.
- Carr, L., Iacoboni, M., Dubeau, M. C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: A relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences*, 100(9), 5497–5502.
- Carter, C. S., & van Veen, V. (2007). Anterior cingulate cortex and conflict detection: An update of theory and data. *Cognitive, Affective, & Behavioural Neuroscience*, 7(4), 367–379.
- Cloninger, C. (1987). A systematic method for clinical description and classification of personality variants. *Archives of General Psychiatry*, 44, 573–588.
- Comoli, E., Ribeiro-Barbosa, E. R., & Canteras, N. S. (2003). Predatory hunting and exposure to live predator induce opposite patterns of Fos immunoreactivity in the PAG. *Behavioural Brain Research*, 138, 17–28.
- Coricelli, G., Critchley, H. D., Joffily, M. O., Doherty, J. P., Sirigu, A., & Dolan, R. J. (2005). Regret and its avoidance: A neuroimaging study of choice behavior. *Nature Neuroscience*, 8(9), 1255.
- Craig, A. D. (2003). Interoception: The sense of the physiological condition of the body. *Current Opinion in Neurobiology*, 13(4), 500–505.
- Critchley, H. D., Elliot, R., Mathias, C. J., & Dolan, R. J. (2000). Neural activity relating to generation and representation of galvanic skin responses: A functional magnetic resonance imaging study. *Journal of Neuroscience*, 20(8), 3033–3040.
- Critchley, H. D., Mathias, C. J., & Dolan, R. J. (2001). Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron*, 29, 537–545.
- Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, 7, 189–195.

- Dalgleish, T. (2004). Cognitive approaches to Post-traumatic Stress Disorder (PTSD): The evolution of multi-representational theorizing. *Psychological Bulletin*, *130*, 228–260.
- Dalgleish, T., & Power, M. J. (2004). The I of the storm: Relations between self and conscious emotion experience. *Psychological Review*, *111*, 812–819.
- Damasio, A. R. (1994). *Descartes' error*. New York: Putnam.
- Damasio, A. R. (1996). The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philosophical Transactions of the Royal Society London B*, *351*, 1413–1420.
- Damasio, A. R. (1997). Towards a neuropathology of emotion and mood. *Nature*, *386*, 769–770.
- Darwin, C. (1965). *The expression of the emotions in man and animals*. Chicago, IL: Chicago University Press. (Original work published 1872)
- Davidson, R. J. (1984a). Affect, cognition, and hemispheric specialization. In J. Kagan, C. E. Izard & R. B. Zajonc (Eds.), *Emotions, cognition, and behavior* (pp. 320–365). Cambridge/New York: Cambridge University Press.
- Davidson, R. J. (1984b). Hemispheric asymmetry and emotion. In K. R. Scherer & P. Ekman (Eds.), *Approaches to emotion* (pp. 39–58). Hillsdale, NJ: Erlbaum.
- Davidson, R. J. (1993). The neuropsychology of emotion and affective style. In M. Lewis & J. M. Haviland (Eds.), *Handbook of emotions* (pp. 143–154). New York/London: Guilford Press.
- Davidson, R. J., Ekman, P., Saron, C., Senulis, J., & Friesen, W. V. (1990). Approach-withdrawal and cerebral asymmetry: Emotional expression and brain physiology I. *Journal of Personality and Social Psychology*, *58*, 330–341.
- Davidson, R. J., Lewis, D. A., Alloy, L. B., Amaral, D. G., Bush, G., Cohen, J. D., et al. (2002). Neural and behavioral substrates of mood and mood regulation. *Biological Psychiatry*, *52*(6), 478–502.
- Davidson, R. J., Putnam, K. M., & Larson, C. L. (2000). Dysfunction in the neural circuitry of emotion regulation: A possible prelude to violence. *Science*, *289*, 591–595.
- Deakin, J. F. W., & Graeff, F. G. (1991). 5-HT and mechanisms of defence. *Journal of Psychopharmacology*, *5*, 305–315.
- Dunn, B. D., Dalgleish, T., & Lawrence, A. D. (2006). The somatic marker hypothesis: A critical evaluation. *Neuroscience and Biobehavioral Reviews*, *30*(2), 239–271.
- Eisenberger, N. I., Lieberman, M. D., & Williams, K. D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science*, *302*, 290–292.
- Ekman, P., Levenson, R. W., & Friesen, W. (1983). Autonomic nervous system activity distinguishes among emotions. *Science*, *221*, 1208–1210.
- Fanselow, M. S. (1991). The midbrain periaqueductal gray as a coordinator of action in response to fear and anxiety. In A. Depaulis & R. Bandler (Eds.), *The midbrain periaqueductal gray matter: Functional, anatomical and immunohistochemical organization* (pp. 151–173). New York: Plenum Publishing Corporation.
- Fanselow, M. S. (1994). Neural organization of the defensive behavior system responsible for fear. *Psychonomic Bulletin & Review*, *1*, 429–438.
- Figueiredo, H. F., Brustle, A., Bodie, B., Dolgas, C. M., & Herman, J. P. (2003). The medial prefrontal cortex differentially regulates stress-induced c-fos expression in the forebrain depending on type of stressor. *European Journal of Neuroscience*, *18*(8), 2357–2364.
- Fitzgerald, P. B., Brown, T. L., Marston, N. A. U., Daskalakis, Z. J., de Castella, A., & Kulkarni, J. (2003). Transcranial magnetic stimulation in the treatment of depression: A double-blind, placebo-controlled trial. *Archives of General Psychiatry*, *60*(10), 1002–1008.
- Gallagher, M., Graham, P. W., & Holland, P. C. (1990). The amygdala central nucleus and appetitive Pavlovian conditioning: Lesions impair one class of conditioned behavior. *Journal of Neuroscience*, *10*(6), 1906–1911.
- Garnefski, N., Teerds, J., Kraaij, V., Legerstee, J., & van den Kommer, T. (2004). Cognitive emotion regulation strategies and depressive symptoms: Differences between males and females. *Personality and Individual Differences*, *36*(2), 267–276.
- Glimcher, P. W., & Rustichini, A. (2004). Neuroeconomics: The consilience of brain and decision. *Science*, *306*, 447–452.
- Goldstein, D. S., & Kopin, I. J. (2007). Evolution of concepts of stress. *Stress*, *10*, 109–120.
- Gray, J. A. (1982). *The neuropsychology of anxiety: An enquiry into the function of the septo-hippocampal system*. Oxford: Clarendon Press.
- Gray, J. M., Young, A. W., Barker, W. A., Curtis, A., & Gibson, D. (1997). Impaired recognition of disgust in Huntington's disease gene carriers. *Brain*, *120*, 2029–2038.
- Gross, J. J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology*, *39*, 281–291.
- Gross, J. J., & Levenson, R. W. (1997). Hiding feelings: The acute effects of inhibiting negative and positive emotion. *Journal of Abnormal Psychology*, *106*, 95–103.
- Hadjikhani, N., & de Gelder, B. (2003). Seeing fearful body expressions activates the fusiform cortex and amygdala. *Current Biology*, *13*(24), 2201–2205.
- Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive material. *Nature Neuroscience*, *2*(3), 289–293.
- Hariri, A. R., Drabant, E. M., Munoz, K. E., Kolachana, B. S., Mattay, V. S., Egan, M. F., et al. (2005). A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry*, *62*, 146–152.
- Hariri, A. R., Mattay, V. S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science*, *297*(5580), 400–403.
- Harlow, J. M. (1993). Recovery of the passage of an iron bar through the head. *History of Psychiatry*, *4*, 271–281. (Original work published 1869)
- Harro, J., & Vasar, E. (1991). Cholecystokinin-induced anxiety: How is it reflected in studies on exploratory behaviour? *Neuroscience and Biobehavioral Reviews*, *15*, 473–477.
- Head, H. (1921). Croonian lecture: Release of function in the nervous system. *Proceedings of the Royal Society of London. Series B, Containing Papers of a Biological Character (1905–1934)*, *92*, 184–209.
- Heath, R. G. (1972). Pleasure and brain activity in man. *Journal of Nervous and Mental Disease*, *154*, 3–18.
- Heims, H. C., Critchley, H. D., Dolan, R. J., Mathias, C. J., & Cipolotti, L. (2004). Social and motivational functioning is not critically dependent on feedback of autonomic responses: Neuropsychological evidence from patients with pure autonomic failure. *Neuropsychologia*, *42*, 1979–1988.
- Hess, W. R., & Brugger, M. (1981). Subcortical center of the affective defence reaction. In K. Akert (Ed.), *Biological order and brain organization: Selected works of W. R. Hess* (pp. 183–202). Berlin: Springer-Verlag. (Original work published 1943)
- Hohmann, G. W. (1966). Some effects of spinal cord lesions on experienced emotional feelings. *Psychophysiology*, *3*(2), 143–156.
- Izard, C. E. (1993). Four systems for emotion activation: Cognitive and noncognitive processes. *Psychological Review*, *100*(1), 68–90.
- Jacobson, R. (1986). 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.
- James, W. (1884). What is an emotion? *Mind*, *9*, 188–205.
- James, W. (1890). *The principles of psychology*. New York: Henry Holt.
- Kalisch, R. (in press). The functional neuroanatomy of reappraisal: Time matters. *Neuroscience and Biobehavioral Reviews* (2009). doi:10.1016/j.neubiorev.2009.06.003
- Kliver, H., & Bucy, P. C. (1937). "Psychic blindness" and other symptoms following bilateral temporal lobectomy. *American Journal of Physiology*, *119*, 254–284.
- Koenigs, M., Young, L., Adolphs, R., Tranel, D., Cushman, F., Hauser, M., et al. (2007). Damage to the prefrontal cortex increases utilitarian moral judgements. *Nature*, *446*(7138), 908.

- Lambie, J. A., & Marcel, A. J. (2002). Consciousness and the varieties of emotion experience: A theoretical framework. *Psychological Review*, *109*(2), 219–259.
- Lane, R. D., Reiman, E. M., Axelrod, B., Yun, L.-S., Holmes, A., & Schwarz, G. E. (1998). 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.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review*, *97*(3), 377–395.
- Lang, P. J., Davis, M., & Ohman, A. (2000). Fear and anxiety: Animal models and human cognitive psychophysiology. *Journal of Affective Disorders*, *61*(3), 137–159.
- Lange, C. (1922). The emotions. In K. Dunlap (Eds.), *The emotions* (I. A. Haupt, Trans., pp. 33–90). Baltimore, MD: Williams & Wilkins. (Original work published 1885)
- LeDoux, J. E. (1986). Sensory systems and emotion: A model of affective processing. *Integrative Psychiatry*, *4*, 237–248.
- LeDoux, J. E. (1987). Emotion. In V. Mountcastle & F. Plum (Eds.), *Handbook of physiology: Nervous system. Volume 5, Higher function* (pp. 419–459). Washington, DC: American Physiological Society.
- LeDoux, J. E. (1989). Cognitive-emotional interactions in the brain. *Cognition & Emotion*, *3*, 267–289.
- LeDoux, J. E. (1993). Emotional networks in the brain. In M. Lewis & J. M. Haviland (Eds.), *Handbook of emotions*. New York: Guilford Press.
- LeDoux, J. E. (1995). Emotion: Clues from the brain. *Annual Review of Psychology*, *46*, 209–235.
- LeDoux, J. E. (1996). *The emotional brain: The mysterious underpinning of emotional life*. New York: Simon & Schuster.
- Leonard, C. M., Rolls, E. T., Wilson, F. A. W., & Baylis, C. G. (1985). Neurons in the amygdala of the monkey with responses selective for faces. *Behavioural Brain Research*, *15*, 159–176.
- MacLean, P. D. (1949). Psychosomatic disease and the “visceral brain”: Recent developments bearing on the Papez theory of emotion. *Psychosomatic Medicine*, *11*, 338–353.
- MacLean, P. D. (1952). Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain). *Electroencephalography and Clinical Neurophysiology*, *4*, 407–418.
- MacLean, P. D. (1970). The triune brain, emotion, and scientific bias. In F. O. Schmidt (Ed.), *The neurosciences. Second study program* (pp. 336–349). New York: Rockefeller University Press.
- Macmillan, M. (2002). *An odd kind of fame: Stories of Phineas Gage*. Boston, MA: MIT Press.
- Markowitsch, H. J. (2008). Neuroscience and crime. *Neurocase*, *14*(1), 1–6.
- Masterman, D. L., & Cummings, J. L. (1997). Frontal-subcortical circuits: The anatomic basis of executive, social and motivated behaviors. *Journal of Psychopharmacology*, *11*(2), 107.
- Mayberg, H. S. (1997). Limbic-cortical dysregulation: A proposed model of depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *9*, 471–481.
- Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., et al. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron*, *45*, 651–660.
- McNaughton, N., & Corr, P. J. (2004). A two-dimensional neuropsychology of defence: Fear/anxiety and defensive distance. *Neuroscience and Biobehavioral Reviews*, *28*(3), 285–305.
- Meunier, M., Bachevalier, J., Murray, E. A., Malkova, L., & Mishkin, M. (1996). Effects of aspiration vs. neurotoxic lesions of the amygdala on emotional reactivity in rhesus monkeys. *Society for Neuroscience Abstract*, *13*, 5418–5432.
- Mills, C. K. (1912). 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.
- Mitchell, J. P., Macrae, C. N., & Banaji, M. R. (2006). Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. *Neuron*, *50*(4), 655–663.
- Mobbs, D., Eckert, M. A., Mills, D., Korenberg, J., Bellugi, U., Galaburda, A. M., et al. (2007). Frontostriatal dysfunction during response inhibition in Williams syndrome. *Biological Psychiatry*, *62*, 256–261.
- Mobbs, D., Lau, H. C., Jones, O. D., & Frith, C. D. (2007). Law, responsibility, and the brain. *PLoS Biology*, *5*(4), 693–700.
- Mobbs, D., Petrovic, P., Marchant, J. L., Hassabis, D., Weiskopf, N., Seymour, B., et al. (2007). When fear is near: Threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science*, *317*(5841), 1079.
- Montag, C., Buckholtz, J. W., Hartmann, P., Merz, M., Burk, C., & Hennig, J. (2008). COMT genetic variation affects fear processing: Psychophysiological evidence. *Behavioural Neuroscience*, *4*, 901–909.
- Montoya, P., & Schandry, R. (1994). Emotional experience and heartbeat perception in patients with spinal cord injury and control subjects. *Journal of Psychophysiology*, *8*, 289–296.
- Morgane, P. J., & Mokler, D. J. (2006). The limbic brain: Continuing resolution. *Neuroscience and Biobehavioral Reviews*, *30*(2), 119–125.
- Morris, J., Ohman, A., & Dolan, R. J. (1998). Modulation of human amygdala activity by emotional learning and conscious awareness. *Nature*, *393*, 467–470.
- Morris, J., Ohman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating unseen fear. *Proceedings of the National Academy of Sciences*, *96*, 1680–1685.
- Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2001). Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain*, *124*(6), 1241.
- Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., et al. (1996). A differential neural response in the human amygdala for fearful and happy facial expressions. *Nature*, *383*, 812–815.
- Mowrer, O. H. (1960). *Learning theory and behavior*. New York: Wiley.
- Murphy, F. C., Nimmo-Smith, I., & Lawrence, A. D. (2003). Functional neuroanatomy of emotions. *Cognitive, Affective, & Behavioural Neuroscience*, *3*, 207–233.
- Murray, E. A., Gaffan, E. A., & Flint, R. W. (1996). Anterior rhinal cortex and amygdala: Dissociation of their contributions to memory and food preference in rhesus monkeys. *Behavioural Neuroscience*, *110*, 30–42.
- Nauta, W. J. H. (1971). The problem of the frontal lobe: A reinterpretation. *Journal of Psychiatric Research*, *8*, 167–187.
- Niedenthal, P. M. (2007). Embodying emotion. *Science*, *316*(5827), 1002.
- Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking feelings: An fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*, 1215–1219.
- Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences*, *9*(5), 242–249.
- Ochsner, K. N., & Lieberman, M. D. (2001). The emergence of social cognitive neuroscience. *American Psychologist*, *56*, 717–734.
- Olds, J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology*, *47*, 419–427.
- Panksepp, J. (1998). *Affective neuroscience: The foundations of human and animal emotions*. New York: Oxford University Press.
- Panksepp, J. (2005). Affective consciousness: Core emotional feelings in animals and humans. *Consciousness and Cognition*, *14*, 30–80.
- Papez, J. W. (1937). A proposed mechanism of emotion. *Archives of Neurology and Psychiatry*, *38*, 725–743.
- Pascucci, T., Ventura, R., Latagliata, E. C., Cabib, S., & Puglisi-Allegra, S. (in press). The medial prefrontal cortex determines the accumbens dopamine response to stress through the opposing influences of norepinephrine and dopamine. *Cerebral Cortex*.
- Paulus, M. P., & Stein, M. B. (2006). An insular view of anxiety. *Biological Psychiatry*, *60*(4), 383–387.

- Penfield, W., & Faulk, M. E. (1955). The insula: Further observations of its function. *Brain*, 78, 445–470.
- Perlis, R. H., Holt, D. J., Smoller, J. W., Blood, A. J., Lee, S., Kim, B. W., et al. (2008). Association of a polymorphism near CREB1 with differential aversion processing in the insula of healthy participants. *Archives of General Psychiatry*, 65, 882–892.
- Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience*, 9(2), 148.
- Pessoa, L., McKenna, M., Gutierrez, E., & Ungerleider, L. G. (2002). Neural processing of emotional faces requires attention. *Proceedings of the National Academy of Sciences*, 99(17), 11458–11463.
- Petrides, M. (2005). Lateral prefrontal cortex: Architectonic and functional organization. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1456), 781–795.
- Petrovic, P., Kalso, E., Petersson, K. M., & Ingvar, M. (2002). Placebo and opioid analgesia: Imaging a shared neuronal network. *Science*, 295(5560), 1737–1740.
- Phan, K. L., Wager, T., Taylor, S. F., & Liberzon, I. (2002). Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage*, 16, 331–348.
- Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, 43(6), 897–905.
- Phillips, M. L., Young, A. W., Senior, C., Brammer, M., Andrew, C., Calder, A. J., et al. (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature*, 389, 495–498.
- Posse, S., Fitzgerald, D., Gao, K., Habel, U., Rosenberg, D., Moore, G. J., et al. (2003). Real-time fMRI of temporolimbic regions detects amygdala activation during single-trial self-induced sadness. *NeuroImage*, 18(3), 760–768.
- Preusschoff, K., Quartz, S. R., & Bossaerts, P. (2008). Human insula activation reflects risk prediction errors as well as risk. *Journal of Neuroscience*, 28(11), 2745.
- Pribram, K. H. (1970). Feelings as monitors. In M. B. Arnold (Ed.), *Feelings and emotions: The Loyola Symposium* (pp. 41–53). New York: Academic Press.
- Rolls, E. T. (1990). A theory of emotion, and its application to understanding the neural basis of emotion. *Cognition & Emotion*, 4(3), 161–190.
- Rolls, E. T. (1996). The orbitofrontal cortex. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences*, 351(1346), 1433–1443.
- Rolls, E. T. (1999). *The brain and emotion*. Oxford: Oxford University Press.
- Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D., & Beck, L. H. (1956). A continuous performance test of brain damage. *Journal of Consulting Psychology*, 20, 343–350.
- Sackeim, H. A., & Gur, R. C. (1978). Lateral asymmetry in intensity of emotional expression. *Neuropsychologia*, 16, 473–481.
- Sackeim, H. A., Gur, R. C., & Saucy, M. C. (1978). Emotions are expressed more intensely on the left side of the face. *Science*, 202, 434–436.
- Salomons, T. V., Johnstone, T., Backonja, M. M., & Davidson, R. J. (2004). Perceived controllability modulates the neural response to pain. *Journal of Neuroscience*, 24, 199–203.
- Saver, J. L., & Damasio, A. R. (1991). Preserved access and processing of social knowledge in a patient with acquired sociopathy due to ventromedial frontal damage. *Neuropsychologia*, 29, 1241–1249.
- Schachter, S., & Singer, J. E. (1962). Cognitive, social, and physiological determinants of emotional state. *Psychological Review*, 69, 379–399.
- Schaefer, S. M., Jackson, D. C., Davidson, R. J., Aguirre, G. K., Kimberg, D. Y., & Thompson-Schill, S. L. (2002). Modulation of amygdala activity by the conscious regulation of negative emotion. *Journal of Cognitive Neuroscience*, 14(6), 913–921.
- Schmolck, H., & Squire, L. R. (2001). Impaired perception of facial emotions following bilateral damage to the anterior temporal lobe. *Neuropsychologia*, 15, 30–38.
- Schneirla, T. C. (1959). An evolutionary and developmental theory of biphasic processes underlying approach and withdrawal. In M. R. Jones (Ed.), *Nebraska Symposium on Motivation* (Vol. 7, pp. 1–42). Lincoln: University of Nebraska Press.
- Schwartz, G. E., Ahern, G. L., & Brown, S. L. (1979). Lateralized facial muscle response to positive and negative emotional stimuli. *Psychophysiology*, 16, 561–571.
- Schwartz, G. E., Davidson, R. J., & Maer, F. (1975). Right hemisphere lateralization from emotion in the human brain: Interactions with cognition. *Science*, 190, 286–288.
- Scott, S. K., Young, A. W., Calder, A. J., Hellawell, D. J., Aggleton, J. P., & Johnson, M. (1997). Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature*, 385, 254–257.
- Simmons, A., Matthews, S. C., Stein, M. B., & Paulus, M. P. (2004). Anticipation of emotionally aversive visual stimuli activates right insula. *NeuroReport*, 15(14), 2261.
- Singer, T., Seymour, B., O’Doherty, J., Kaube, H., Dolan, R. J., & Frith, C. D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, 303, 1157–1162.
- Smolka, M. N., Bühler, M., Schumann, G., Klein, S., Hu, X. Z., Moayer, M., et al. (2007). Gene-gene effects on central processing of aversive stimuli. *Molecular Psychiatry*, 12, 307–317.
- Smolka, M. N., Schumann, G., Wrase, J., Grusser, S. M., Flor, H., Mann, K., et al. (2005). Catechol-O-Methyltransferase val158met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. *Journal of Neuroscience*, 25, 836–842.
- Sprengelmeyer, R., Young, A. W., Calder, A. J., Karnat, A., Lange, H., Homborg, V., et al. (1996). Loss of disgust: Perception of faces and emotions in Huntington’s disease. *Brain*, 119, 1647–1665.
- Stein, M. B., Simmons, A. N., Feinstein, J. S., & Paulus, M. P. (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*, 164(2), 318.
- Stellar, E. (1954). The physiology of motivation. *Psychological Review*, 61, 5–22.
- Sukikara, M. H., Mota-Ortiz, S. R., Baldo, M. V., Felicio, L. F., & Canteras, N. S. (2006). A role for the periaqueductal gray in switching adaptive behavioral responses. *Journal of Neuroscience*, 26(9), 2583–2589.
- Summerfield, C., Egner, T., Greene, M., Koechlin, E., Mangels, J., & Hirsch, J. (2006). Predictive codes for forthcoming perception in the frontal cortex. *Science*, 314(5803), 1311–1314.
- Teitelbaum, P., & Epstein, A. N. (1962). The lateral hypothalamic syndrome: Recovery of feeding and drinking after lateral hypothalamic lesions. *Psychological Review*, 69, 74–90.
- Terzian, H., & Ore, G. D. (1955). Syndrome of Kluver-Bucy reproduced in man by bilateral removal of temporal lobes. *Neurology*, 5, 373–380.
- Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., et al. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*, 303, 1162–1167.
- Weiskrantz, L. (1956). Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *Journal of Comparative and Physiological Psychology*, 49, 381–391.
- Whalen, P. J., Kagan, J., Cook, R. G., Davis, F. C., Kim, H., Polis, S., et al. (2004). Human amygdala responsivity to masked fearful eye whites. *Science*, 306(5704), 2061.
- Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *The Journal of Neuroscience*, 18(1), 411–418.
- Young, A. W., Aggleton, J. P., Hellawell, D. J., Johnson, M., Brooks, P., & Hanley, J. R. (1995). Face processing impairments after amygdalotomy. *Brain*, 118, 15–24.
- Zajonc, R. B. (1980). Feeling and thinking: Preferences need no inferences. *American Psychologist*, 35, 151–175.