Affective neuroscience: the emergence of a discipline

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This past year has seen significant advances in our understanding of the physiology of emotion. Attention continues to focus on the amygdala and its interconnections with prefrontal cortical regions. New evidence underscores the importance of lateralization for emotion. There are also new findings on the physiological predictors of individual differences in emotional behavior and experience, and on the role of autonomic arousal in emotional memory.

Introduction

Knowledge about the neural substrates of emotion has grown exponentially over the past several years and is derived from diverse sources, including basic studies in animals, research with normal humans (using a variety of physiological measures and biological probes), and studies of human neuropathology and psychopathology. As research progresses in this area, it is clear that the study of emotion, just like cognition, will require a dissection of emotional processes into more elementary mental operations, such as the perception of emotional information and the production of expressive behavior and autonomic activity, whose neural substrates can be better understood.

This review will focus on the most important recent research on the neurobiology of emotion, with an emphasis on work at the human level. There are three themes that we wish to highlight. First, as noted above, the critical need to dissect emotion into more elementary constituents. Second, the important interaction between cortical and subcortical structures in the regulation of emotion. Third, the preponderance of individual differences in emotional processes. There are dramatic differences in the way individuals respond to emotionally challenging events, and these individual differences may form the basis of adult personality and vulnerability to psychopathology (see e.g. [1]).

The infra-human foundation: animal studies on emotion

Although emotion can be quite complex and is elicited by stimuli requiring semantic analysis, it is also an ubiquitous phenomenon that occurs throughout the animal kingdom. Inferences about emotion can be made on the basis of changes in behavior and physiology, and need not rely upon conscious introspective report. Recognition of this fact has enabled investigators to begin to delineate the circuitry required for simple emotional responses in animals.

Using a classical fear-conditioning paradigm (for reviews, see [2,3]), LeDoux and his colleagues (see [3,4]) have demonstrated that lesions of the amygdala reduce or abolish conditioned fear. They have also observed that lesions of structures afferent to the amygdala will differentially affect aversive conditioning to sensory-specific stimuli. For example, lesions of the medial geniculate nucleus, which sends auditory input directly to the amygdala, blocks the formation of a tone-shock association [5], but not a light-shock association [6].

Learning about the emotional significance of more general, contextual cues involves projections between the hippocampus and the amygdala [3,4]. Within the amygdala, the lateral nucleus is the sensory interface between the afferent projections from sensory-specific thalamic and cortical sites, and the central nucleus. The central nucleus is the primary output, with projections to a wide range of brain circuits concerned with different aspects of the emotional response, including behavioral and autonomic manifestations (for review, see [7•]). The connections to and from the amygdala that have been implicated in fear conditioning are illustrated in Figure 1. The critical importance of the amygdala and the structures with which it is interconnected is also highlighted in experiments that use c-*fos* immunoreactivity as a marker for local neuronal activation [8]: following a 15 minute period of electrical stimulation of either the periaqueductal gray or medial hypothalamus sufficient to produce a defensive reaction, the brains of sacrificed animals were immunostained against the c-*fos* protein; dense labelling was observed in the amygdala, the bed nucleus of the stria terminalis, the anterior hypothalamic area, and both paraventricular thalamic nuclei.

Whereas the neurochemical substrates within the amygdala are complex, two neuropeptides have been identified as playing a particularly significant role: corticotropin-releasing factor (CRF) and neuropeptide Y

Abbreviations

CRF—corticotropin-releasing factor; GABA—γ-aminobutyric acid; NPY—neuropeptide Y; PET—positron emission tomography.
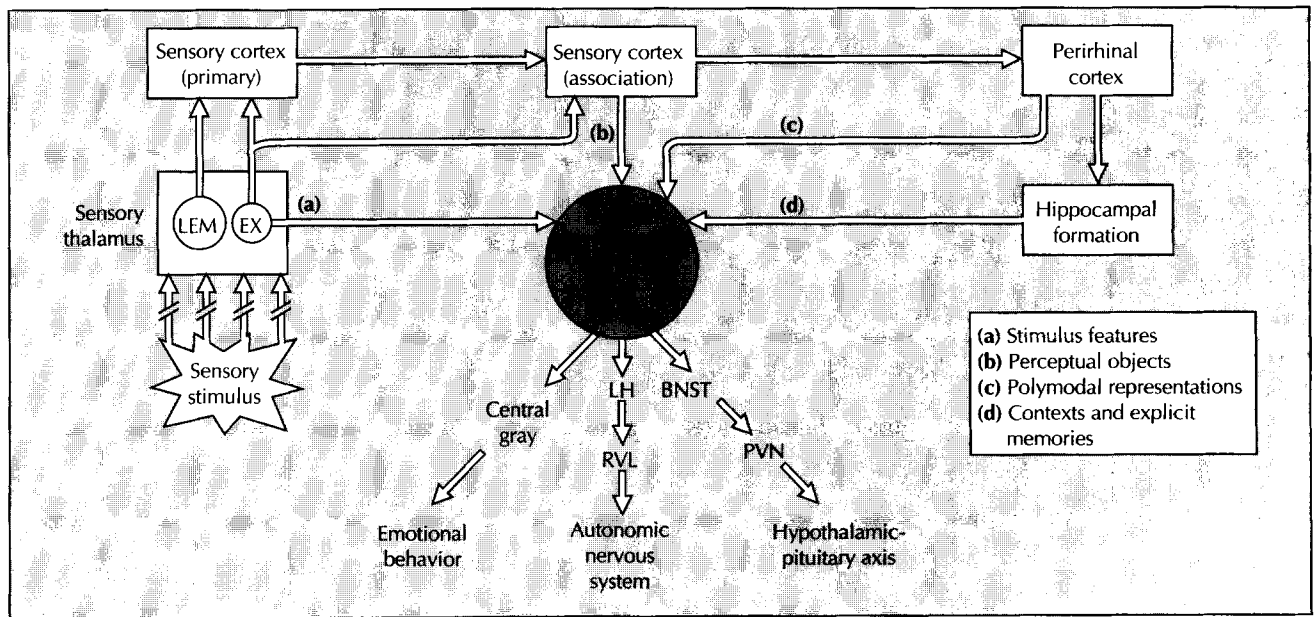
Fig. 1. Neural circuits of fear conditioning. The neural pathways by which a sensory conditioned stimulus elicits emotional responses involve the relay of sensory inputs to the thalamus. Whereas the lemniscal nuclei (LEM) transmit only to the primary sensory cortex, the extralemniscal areas (EX) transmit to primary sensory and association regions of the cortex, as well as to the lateral nucleus of the amygdala. This region of the amygdala also receives inputs from sensory association areas of the neocortex, as well as from polymodal areas, such as the perirhinal cortex and the hippocampal formation. (a) The thalamo-amygdala sensory projection has been implicated in simple fear conditioning: one conditioned stimulus (CS) paired with an unconditioned stimulus (US). (b) The cortico-amygdala sensory projection has been linked to differential fear conditioning: one CS paired with US, another not paired. And (d) the hippocampo-amygdala projection has been linked to contextual conditioning: conditioning to situational cues other than the CS. The hippocampal projection (d) may also be involved in conditioning of fear to explicit or declarative memories that occur in the presence of an US, but this has not yet been studied. (c) The role of the perirhinal projection to amygdala is not known, but it may have something to do with the elicitation of fear by complex polymodal stimulus representations. The central nucleus of the amygdala is the interface with motor systems, as it connects with various brainstem areas involved in the regulation of specific defense response networks. Projections to the central gray control freezing and other defensive behaviors; projections to the lateral hypothalamus (LH) and from there to the rostral ventral lateral medulla (RVL) control sympathetic autonomic nervous system responses; and projections to the bed nucleus of the stria terminalis (BNST) and paraventricular hypothalamus (PVN) control stress reactions involving the pituitary–adrenal axis. The amygdala nuclei are the sensory- and motor-independent parts of the circuitry and probably play important integrative roles in fear conditioning. Reprinted with permission from LeDoux [3].

(NPY) [9]. CRF release is thought to increase anxiety whereas NPY is hypothesized to play an antagonistic role, as in an opponent process. In fetal rat primary neuronal cultures of the amygdala, depolarization evokes CRF release [10]. One hour of restraint stress has been found to increase CRF mRNA in the amygdala within the first hour following the stress [11]. By 48 hours post-stress, CRF mRNA returns to baseline. Systemically administered corticosterone has been found to facilitate CRF mRNA expression in the central nucleus [12]. Individual differences in cortisol in infant rhesus monkeys predicts fearful reactions to the presence of a human intruder [13••]. Collectively, these findings imply that CRF release is associated with activation of the amygdala and further establish that both corticosterone administration and psychological stress evokes a CRF response in the amygdala. Individual differences in fearfulness may be associated with differences in amygdala CRF, given that such differences are associated with variations in cortisol levels.

Most animal studies have not investigated possible hemispheric differences at either subcortical or cortical levels, although human research (see below) has implicated such hemispheric differences in the regulation of emotion [14••]. An important exception is a report by Adamec

and Morgan [15], who kindled the left or right amygdala in rats. Kindling of the left medial or basolateral amygdala decreased behavioral measures of anxiety for at least one week after the last kindled seizure, whereas kindling homologous regions in the right amygdala tended to increase anxiety. In another study [16], rhesus monkeys showing the least right and most left prefrontal desynchronization of brain electrical activity in response to an acute dose of diazepam had the longest duration of freezing in response to a standardized challenge. This implies that stable differences in fearfulness may be associated with an asymmetric organization of the benzodiazepine system. These findings underscore the importance of the amygdala and the prefrontal cortex in emotion, highlight the role of particular neurochemical systems in modulating activity in these regions, and raise the possibility of functional differences between the left/right amygdala and left/right prefrontal cortex in non-human mammals.

Other studies have also investigated the contribution of prefrontal activity in the regulation of emotional responses, which may occur via interaction with the amygdala. The amygdala receives afferent input from a number of cortical regions, including the inferior temporal lobe, temporal pole, superior temporal sulcus and frontal cortex. Most of these regions, in turn, receive projections

back from the amygdala (for review, see [17•]). The research on prefrontal–amygdala interaction is important for understanding failures of adaptive emotional responding and may be key to developing mechanistic analyses of affective psychopathology and individual differences in affective reactivity. Lesions of medial prefrontal cortex in rats interfere with the normal process of extinction of a classically conditioned aversive response [18•]. Pharmacological dissection of the cardiovascular component of conditioned fear revealed that lesions of medial prefrontal cortex increased the tachycardic response to the 'conditioned' stimulus, suggesting that this brain region may normally act to decrease heart rate during stress [19]. These findings raise the possibility that prefrontal cortex may modulate emotional reactivity via inhibitory influences on the amygdala. Recent human data (see below) are consistent with this view.

Human emotions

Central substrates

Research on humans underscores the increased complexity of emotion-related phenomena and the corresponding emphasis on the role of the cortex in different features of emotion.

Amygdala
A particularly compelling example that questions the exclusive role of the amygdala in the formation of stimulus–reward associations in humans is the case of patient Boswell, a 63-year old man who has been severely amnesic following herpes simplex encephalitis (see [20]). This encephalitis resulted in bilateral destruction of the mesial temporal region, including the amygdala, entorhinal cortex and hippocampus. In addition, both insular cortices, along with both posterior orbital cortices and basal forebrain regions were destroyed. All primary and most early sensory association cortices in occipital, temporal and parietal cortices were left intact. Most of the prefrontal cortex, including the entire expanse of the dorsolateral prefrontal cortex on both sides, was left intact. This patient presents with a severe anterograde amnesia for all types of factual knowledge, including faces [20]. Despite this amnesia, patient Boswell is able to acquire non-conscious associations between entirely new persons and the affective valence they display [21••].

Using a very clever procedure, patient Boswell was introduced to three new stimulus persons who were instructed to behave in consistently different ways over a six day period. The 'good guy' was always especially kind to Boswell, gave him numerous compliments and granted all of his (frequent) requests for treats such as gum, soda, and coffee. The 'bad guy' behaved in a systematically negative manner toward Boswell. He never complimented Boswell and actively refused his requests for treats. The 'neutral guy' behaved in manner between these two extremes. After six days of exposure to these three individuals, Boswell was tested in two conditions. In the 'overt' condition, he was presented with eight faces, three of which were those of the three stimulus persons to which he had just been exposed. He was asked to identify the individual shown in the picture. In the 'covert' condition, the face of each familiar person was presented along with an unfamiliar face and for each pair, Boswell was asked to "choose the person that you would go to for a treat". Although Boswell could not identify any of the faces in the overt condition, in the covert condition, he chose the good guy on 83% of the pairings, the neutral guy on 56% of the pairings, and the bad guy on 22% of the pairings. These findings indicate that the medial temporal lobe structures are not required for the formation of associations between novel exteroceptive stimuli and their positive and negative affective consequences.

Though the findings on patient Boswell question the necessity of an intact amygdala for the formation of stimulus–reward associations, other recent findings from patient S.M. introduce additional complexities [22]. This patient is afflicted with Urbach–Wiethe disease, a condition that caused a nearly complete bilateral destruction of the amygdala, while sparing the hippocampus and all neocortical structures. In a series of experiments with this patient, impairments in the recognition of facial expressions of fear and in the recognition of multiple emotions in a single facial expression were demonstrated [22]. In studies with another patient (D.R.), who has partial bilateral lesions of the amygdala subsequent to surgery for intractable epilepsy [23], poor identification was obtained for facial expressions of emotion. In both of these studies, explicit conscious procedures were used to test for expression recognition. While the amygdala may be required for such overt discrimination, the earlier study on patient Boswell suggests that covert identification might not require an intact amygdala. This hypothesis requires further testing and could be evaluated using modern neuroimaging procedures and normals.

Neocortex
The role of the neocortex in emotional processing has been underscored by findings which indicate that left-sided lesions, particularly those close to the frontal pole, are more likely to be associated with depression than lesions in the homologous location in the contralateral hemisphere [24•]. Mania secondary to brain injury is much more prevalent following right-sided lesions [25]. The deactivation of a whole hemisphere with intra-carotid injections of sodium amytal in epileptic patients before neurosurgery results in mood changes consistent with the lesion data (e.g. [26]). Christianson et al. [26] found that left-sided inactivation led to a significant decrease in self-reported positive affect compared with right-sided deactivation. Damasio and colleagues [27] demonstrated that patients with bilateral lesions of ventromedial prefrontal cortex cannot anticipate the future positive or negative consequences of their actions, although immediately available rewards and punishments do influence their behavior.
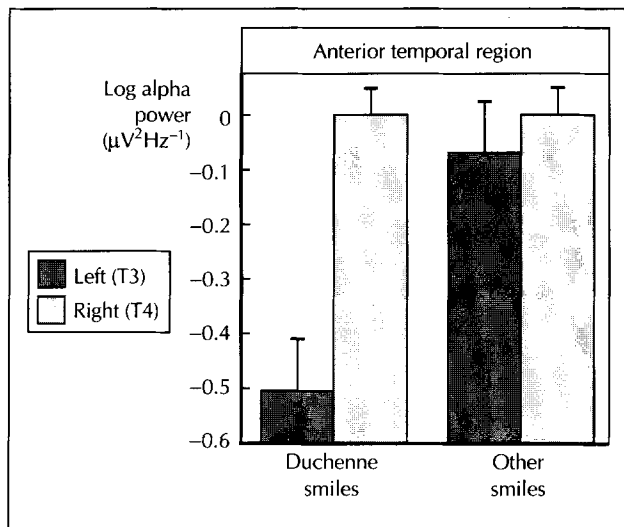
Fig. 2. Mean log-transformed alpha (8–13 Hz) power density in the left (T3) and right (T4) anterior temporal regions during the voluntary production of Duchenne smiles (requiring the contraction of both orbicularis oculi and zygomatic major muscles) and other smiles (requiring the contraction of only zygomatic major muscles). Power density measures have been residualized to remove the contribution of power in an electromyographic band (75–125 Hz). Power density in the alpha band is inversely related to activation so that lower values on this measure reflect higher levels of activation. Error bars represent standard errors of the mean. The findings indicate that only Duchenne smiles are associated with left-sided activation, a pattern similar, but not identical, to that found during elicited happiness [14••]. From Ekman and Davidson [28••].

These findings in brain-damaged patients have provided the foundation for examining similar questions in normal subjects and neurologically intact psychiatric patients using non-invasive methods. Our laboratory has used quantitative scalp-recorded electrophysiological methods to examine asymmetric hemispheric activation produced by stimuli designed to induce positive and negative affect. In general, negative affect (e.g. disgust or fear) accompanied by withdrawal reactions, such as turning away from the stimulus or fleeing, has been found to increase right-sided anterior activation (in both prefrontal and anterior temporal scalp regions), whereas positive affect associated with approach reactions, such as reaching out toward another person, increases left-sided activation in these regions [14••]. The voluntary production of facial signs of enjoyment elicits asymmetric changes that are similar to, but not identical with, those found during the spontaneous display of these expressions [28••] (Fig. 2). Individual differences in baseline levels of asymmetric activation in the prefrontal region predict responsivity to positive and negative emotion elicitors. Higher levels of left-sided prefrontal activation at baseline were associated with more intense positive emotion to a positive film clip, whereas higher levels of right-sided prefrontal activation were associated with more intense negative emotion to a negative film clip ([29••]; see also [30•]).

Such individual differences in baseline asymmetric prefrontal activation have also been associated with dispositional mood. Left-activated subjects report greater

positive and less negative affect than their right-activated counterparts [31]. Among depressed psychiatric patients, decreased blood flow in left inferior and dorsolateral prefrontal cortex has been found to be strongly associated with intensity of depressed mood and psychomotor retardation [32]. Patients with obsessive-compulsive disorder, who report significant anxiety, show increased cerebral perfusion in medial and right middle frontal cortex regions on single photon emission computed tomography (SPECT) [33]. Individual differences in mood have also been related to the functioning of the dopamine system, with greater response to the dopamine D_2 receptor agonist bromocriptine associated with higher levels of positive affect [34••]. Some evidence has been interpreted to suggest greater left-sided lateralization of dopamine [35].

Activation in the left prefrontal region may be part of a mechanism that inhibits negative affect. Individuals who habitually utilize a coping strategy that minimizes negative affect are characterized by left-sided prefrontal electrophysiological activation [36•]. If individuals with accentuated left-sided prefrontal activation are more adept at inhibiting negative affect, they should show more rapid extinction of a classically conditioned aversive response. This hypothesis was supported in a recent study showing that individuals with greater left-sided prefrontal activation extinguished a classically conditioned aversive response more rapidly than did subjects with less left-sided prefrontal activation (RJ Davidson, abstract S7, 34th Annual Meeting of the Society for Psychophysiological Research, Atlanta, November 1994). As noted above, lesions of the rat prefrontal cortex led to delayed extinction of a classically conditioned aversive response [18•], possibly indicating that the amygdala is tonically inhibited by prefrontal activation. Consistent with this finding, depressed patients exhibited a negative correlation between left prefrontal blood flow and blood flow in the amygdala [37]. A similar inverse relation between glucose metabolic activity (as measured with positron emisson tomography, i.e. PET) in the left prefrontal cortex and in the amygdala has also been found (RJ Davidson, abstract S7, 34th Annual Meeting of the Society for Psychophysiological Research, Atlanta, November 1994).

Several PET studies have utilized experimental procedures to induce emotion while regional cerebral blood flow was measured using the short half-life tracer O^{15}. Self-generated sadness compared with a resting, eyes-closed control condition, produced increased blood flow in inferior and orbitofrontal regions, particularly on the left side [38]. Unfortunately, the control condition was inadequate because the blood flow changes could have been due to the act of self-generated recall itself. In a study using simple phobics, the presentation of visual phobic stimuli led to bilateral increases in blood flow in secondary visual cortex compared with the presentation of aversive and neutral visual stimuli, despite the matching of the stimuli for basic sensory properties [39]. Another study with simple phobics utilized a tactile method of presenting phobic and control stimuli. In

this study, increased blood flow was found in response to the phobic compared with control stimuli in the anterior cingulate cortex, the insular cortex, the anterior temporal cortex, the somatosensory cortex, the posterior medial orbitofrontal cortex and the thalamus [40].

Peripheral correlates
Affect-modulated startle experiments
The fear-potentiated startle paradigm used with rodents [7•] has been usefully adapted to humans by examining the modulation of the acoustic startle by a foreground visual stimulus using electromyographic measures of the eyeblink reflex as the dependent variable (see e.g. [41•,42]). The amplitude of the eyeblink reflex is potentiated when viewing unpleasant pictures (e.g. mutilated bodies) and attenuated when viewing pleasant pictures (e.g. appetizing food), relative to viewing neutral pictures (e.g. a table). Similar effects were found when pleasant and unpleasant odors [43], and when fear-inducing and sexually arousing film clips [44] were used as foreground stimuli. Research has also shown that initially neutral stimuli paired with an aversive stimulus in a classical conditioning paradigm potentiate the eyeblink reflex [45•], an important parallel with the animal data.

The time course of affect-modulated startle has also been investigated. In one study, subjects viewed pictures that differed in affective tone for 6 seconds with acoustic startle probes occurring at various times following the onset (or offset) of the picture [41•]. The results suggest that the influence of affect on the eyeblink reflex develops over time. Subjects exhibited an attenuated eyeblink reflex when probes were presented 300 ms after the onset of pleasant, neutral, and unpleasant pictures. It is thought that this attenuation of the eyeblink reflex is attention-based, due to picture-onset. When a startle probe is delivered at 1300 and 3800 ms post-onset, as well as at 300 ms post-offset, there is affect-based modulation of the eyeblink reflex [41•]. Using a different paradigm where subjects were exposed to a signaled, 45 s threat condition in which an aversive shock might occur in the last 10 s of the period (alternated with a signaled, 50 s non-threat 'safe' period), startle potentiation was greatest at times immediately preceding the potential shock (i.e. the end of the signal period) [46].

The 'anticipatory anxiety' paradigm and the 'foreground visual stimulus' paradigm have also been used to assess the influence of state and trait variables on affect-modulated startle. Subjects reporting greater fear of the shock exhibited greater startle potentiation in the signaled threat period, but not during baseline, relative to subjects reporting less fear of the shock [47]. In a related study, subjects under the age of 40 diagnosed with panic disorder exhibited greater startle potentiation under the signaled threat and 'safe' periods than did age-matched controls [48]. These groups did not differ in startle reflex during signal-free periods. Using the foreground visual stimulus paradigm, incarcerated psychopaths exhibited startle reflex attenuation during the presentation of both pleasant and unpleasant pictures relative to neu-

tral pictures; whereas control subjects exhibited potentiated reflexes during unpleasant pictures and attenuated reflexes during pleasant pictures [49].

Autonomic acitivity and emotion
One primary and long-standing area of-interest and debate concerns the role of autonomic activity in emotion. One of the most exciting new advances has been made by examining the cognitive consequences of autonomic arousal [50••]. Randomly assigned subjects were given either propranolol, a β-adrenergic receptor antagonist, or placebo an hour before presenting a series of slides and narrative. The two versions of the narrative differed primarily in terms of emotional valence: neutral or negative. Subjects receiving propranolol exhibited, on average, the expected decreases in heart rate and blood pressure. One week later, memory for the neutral stories did not differ for subjects receiving propranolol or placebo. However, memory for the negatively valenced stories was poorer for the subjects receiving propranolol than those who received placebo. This deficit was clearest for the portion of the story that contained the emotionally laden content. These data suggest that cardiovascular arousal may facilitate the encoding of negative affective information, though the precise mechanism by which this occurs requires additional study.

The extent to which different patterns of autonomic activity differentiate among emotions continues to receive attention. Whereas there is some evidence of emotion-specific autonomic activity (e.g. [51]), recent reviews [52•,53•] suggest substantial variability in the patterns of activity across studies assessing the autonomic activation that accompanies discrete emotions. The paradigm that has been used to amass the most support for autonomic differentiation among emotions is the directed facial action task [51]. In this task, subjects are requested to move specific facial muscles in combinations that constitute facial expressions of emotion. A recent study [54] found that effort-related respiratory changes that accompany such facial productions account for a substantial amount of variance in heart rate that are produced by this task, thus calling into question the interpretation of such autonomic patterns as being emotion-specific.

Independent of the emotion-specific autonomic activity issue, recent studies relating autonomic activity and emotion have produced four findings of note. First, subjects with specific fears exhibit larger skin conductance responses to fear-relevant stimuli relative to neutral stimuli, and relative to responses of non-fearful subjects to these stimuli [55]. This occurs when the pictures are presented normally and when presented using a backward mask (i.e. a brief presentation of the target stimulus followed by a neutral non-target stimulus, such that the target stimulus is outside of conscious awareness). Second, subjects viewing pleasant, unpleasant, and neutral pictures exhibited a positive relation between self-reports of arousal (none to extreme) and skin conductance response magnitude. However, self-reports of valence (negative to positive) were not correlated with skin

conductance magnitude [56]. Third, low-psychopathy, relative to high-psychopathy, subjects exhibited greater autonomic activity when imagining fearful situations, even though self-reports of fearfulness and imagery effectiveness were comparable for both groups [57]. Fourth, voluntary suppression of emotional expressive behavior in response to disgust-oriented film clips was associated with decreased heart rate and increases in several indices of sympathetic activation [58], although it is not possible to separate which effects are a function of changes in the intensity of the emotion per se, in overall level of somatic activity, or as a result of the process of suppression itself.

Conclusions

Considerable progress has been made over the past year in understanding the neural substrates of emotion. A number of observations have helped to parse emotion into separable constituents, such as perceptual and expressive components. From work at the animal level, we know that different sensory and contextual inputs are conveyed by separate pathways to the amygdala and that the output of the central nucleus of the amygdala projects to different brain stem regions that control diverse autonomic and behavioral manifestations of emotion. Research has also identified the prefrontal cortex as an important site for the inhibition of emotion, with lesions or naturally occurring decreases of activation in portions of the prefrontal cortex associated with failures to inhibit affect. This work also highlights the importance of cortical–subcortical interactions. The amygdala receives input from and projects to prefrontal and anterior temporal cortex. These interactions probably play an important role in the modulation of emotion by higher cortical processes and in the modulation of cognition by upstream influences from the amygdala and, possibly, other structures. The study of individual differences in specific parameters of emotion is increasing, with work at both the animal and human levels. A particularly promising line of research indicates that individual differences in prefrontal electrophysiological asymmetries predict both dispositional mood and reactivity to emotion elicitors. Future research in affective neuroscience will benefit from the use of new neuroimaging modalities, such as functional magnetic resonance imaging (fMRI), which promises to provide better temporal and spatial resolution than is available with any of the older technologies ([59]; see also Le Bihan and Karni, pp 231–237, in this issue).

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