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The neural basis of emotion can be found in both the neural computation and the neuromodulation of the neural substrate that mediates behavior. I review the experimental evidence showing the involvement of the hypothalamus, the amygdala, and the prefrontal cortex in emotion. For each of these structures, I show the important role of various neuromodulatory systems in mediating emotional behavior. Generalizing, I suggest that behavioral complexity is caused partly by the diversity and intensity of neuromodulation and hence depends on emotional contexts. Rooting the emotional state in neuromodulatory phenomena allows for its quantitative and scientific study and possibly its characterization. NEUROSCIENTIST 5:283–294, 1999

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The scientific study of the neural basis of emotion is an active field of experimental and theoretical research (1, 2). Partly because of a lack of a clear definition (if it exists) of emotion, and probably because of its complexity, it has been difficult to offer a neuroscience framework in which the influence of emotion on behavior can be studied in a comprehensive manner. Most of the current work focuses on identifying neural structures responsible for the experience or expression of particular emotions. The purpose of this article is to propose an alternative approach, rooting emotion not in particular structures, but in a set of neural mechanisms that operate in many structures simultaneously.

I will suggest that the experience and expression of emotion are neither the result of the activity of some specific brain structures ('emotional centers') nor the diffuse (nonlocalized) effect of some chemical substances. Rather, emotion can be seen as (and possibly characterized by) continuous patterns of neuromodulation of certain sets (systems) of brain structures. These neuromodulations modify the functions of the neural substrate in a manner compatible with the known influence of emotion on the behavior that this substrate mediates. (In the following, we will consider 'thinking' or cognition to be a behavior.) The neuromodulation of 'cognitive centers' results in phenomena pertaining to emotional influences of cognitive processing. Neuromodulations of memory structures explain the influence of emotion on learning and recall, the neuromodulation of specific reflex pathways explains the influence of the emotional state on elementary motor behaviors, and so forth. The instantaneous pattern of such modulations (i.e., their nature and loci), from cognitive centers to reflex pathways, consequently constitutes the neural basis of the emotional state.

The interest of such a perspective on the neural basis of emotion is fivefold. First, it allows the bypassing of the difficulties of assigning an emotional function to several specialized brain structures that in all cases have other known nonemotional functions. It does not require an explanation for how and why emotional and nonemotional functions coexist in the same substrate. I will argue that such a difficulty is naturally resolved by not considering emotion solely as a neural computation (function) based on neural spiking activities, but as a conjunction of such computations and their neuromodulations.

Second, it provides a natural framework for the study of the emergence of a particular emotional state arising from the use of drugs of abuse (3). Such drugs are known and studied for their neuromodulatory effects of (widespread) neural function, rather than the activation of specific brain structures. Therefore, they directly modify the neuromodulatory pattern and, consequently, the emotional state.

Third, this approach allows for the consideration of the coupling between the emotional state and behavior (such as cognition) in a way that does not presuppose that either the behavior or the emotional state has a predominant or causal role. Neuromodulation of neural function is well known to be dependent on neural computations, and neural computations are modulated in ways that are theoretically quantifiable and experimentally testable.

Fourth, because the emotional state is rooted in the neuromodulatory state of the nervous tissue, the quantitative assessment of the emotional state is possible (4). This assessment depends on the nature of the behavior at hand. It is essential in the conduct of behavioral ex-

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periments involving animals or human subjects insofar as the statistics derived rely on the hypothesized 'homogeneity' of the internal state of subject pool. This quantification may also constitute a basis for the objective characterization of emotional disorders (as quantitatively abnormal patterns of neuromodulations) (5).

Finally, it addresses a large body of existing data and techniques that can be used to specifically address the problem of understanding the neural basis of emotion. Neuromodulation has been studied experimentally at various levels of detail, from synapses (6) to single cells (7) to networks in invertebrates (8) and cortex (9) in vivo or in vitro, and theoretically studied using computer modeling techniques (10). I will not discuss neuromodulation in general; instead, I refer the reader to the references mentioned above. Rather, I will point to specific types of neuromodulation as they relate to an understanding of the neural basis of emotional states.

The view presented here stands as an alternative to the classical 'structure-centered' study of the neural substrate of emotion. The discussion will show that if certain brain structures have been implicated in emotion, it is not because they are a component of an 'emotional circuit.' Rather, it is because they are the locus of the influence of emotion on the specific behaviors that these structures mediate. To limit the discussion, I will consider three structures that have been implicated primarily in emotion research (especially depression and schizophrenia). These structures are known to mediate different levels of behavioral complexity, from reflexes to cognition: the hypothalamus, the amygdala, and the prefrontal cortex. Reviewing experimental evidence, I will show that each of these structures can serve as the seat of known classes of neuromodulations that occur during the experience or expression of an emotionally charged behavior. I will suggest that the interaction between the emotional state and behaviors (yielding emotional behaviors) can be understood as a reciprocal interaction between such neuromodulations and the computations that these brain structures perform. Finally, I will propose a general framework in which other neural structures may be similarly understood.

I will argue that a fruitful scientific study of emotion requires the integration of two sets of theories: those that consider a few brain centers to be the loci of all emotions and those that propose that emotion is a nonlocalized diffuse neurochemical process.

The Hypothalamus: Endocrine and Autonomic Expressions of Emotion

Neuromodulatory Systems

The hypothalamus, because of its preponderant role in neuroendocrine functions, contains a wide variety of neurochemical substances (see refs. 11 and 12 for a recent account of the major issues and ref. 13 for a classic review). Together with the pituitary, thyroid, parathyroid, and pancreas glands, as well as the adrenal cortex, the hypothalamus has been associated with a wide variety of mental disorders, most of which present emotional symptoms (depression in particular). These clinical aspects will not be discussed here (but see refs. 14–16 for reviews). I will simply mention that, for example, there are consistent findings involving the hypothalamic-pituitary-adrenal axis in depression, mainly through the excessive secretion of cortisol caused by the hypersecretion of corticotropin (ACTH) or corticotropin-releasing hormone. These hypersecretions in turn have been shown to be caused by the decrease of secretion of thyroid-stimulating hormone elicited by thyrotropin-releasing hormones and the decreased sensitivity of hypothalamic α2-adrenergic receptors to growth hormone (17). Taken altogether, these findings point to a neuromodulatory pattern characteristic of (but possibly not unique to) depression.

However, since Cannon's work (18), particular attention has been given to the catecholamines (norepinephrine, dopamine, and serotonin). The study of the effects of these neuroactive substances gave rise to the "catecholamine hypothesis of affective disorders" (19) that presented general (brain-wide) catecholamine (norepinephrine [NE]) depletion as a characteristic of depression and catecholamine excess as a characteristic of mania. Further studies suggested more specifically that the activation by the catecholamine systems of the hypothalamus play a major role in the association of drives and reward (20). The "drive reduction theory of reward," indeed, presents norepinephrine (from the pons and medulla) as a neuroactive substance released when rewarding gustatory and visceral inputs are presented to the organism. This release inhibits the hypothalamic neurons that mediate drives (or 'learned drives'), thereby reducing their activity. These hypothalamic drive neurons are conversely excited by nonrewarding visceral and hormonal inputs. More recent studies of the substantia nigra (one of the major sources of dopamine) contributed to a more detailed understanding of the role of this substance in associating a stimulus and a reward (21, 22). These studies argue that such dopamine neurons do not encode information about the stimuli or the reward but merely signal their presence by modulating attentional and motivational processes, such as the ones mediated by the hypothalamus. Computational modeling studies have proposed a mechanism by which dopamine mediates this modulation at the neural level (23). It is clear, however, that drug reward involves a complex circuitry, including the hypothalamus, the ventral pallidum, amygdala, hippocampus, and the tegmental nucleus, and that each of these structures are preferentially modulated by different neuromodulatory systems (24).

Other studies have focused on the neurochemical systems mediating and modulating feeding and drinking behaviors. They identified hypothalamic neurons that are both sensitive to various neuromodulatory substances

and targets of specific behavioral circuits mediating viscerally elicited feeding and drinking behaviors. These neurons possess adrenergic (25) and noradrenergic receptors (26). They are located in the target areas of thirst signals arising from visceral control structures (such as the subfornical organ) (27) known to be involved in blood/water regulation. Hunger visceral sensory signals originate mainly in the gut rather than in the brain and reach the hypothalamus paraventricular nucleus. Because of the known modulatory cellular actions of dopamine and norepinephrine, these results suggest that the catecholaminergic receptors of the hypothalamus modulate the behaviors that arise from a deregulation of body tissues needs or drives ('primary thirst,' hunger, etc.). This regulation might rely on intrinsic visceral signals or be mediated by other cognitive structures, such as when hunger and thirst are controlled by 'social' signals directing when and how such needs should be satisfied.

Neuronal Systems

The first results involving the hypothalamus in emotion were obtained by selective stimulation of various nuclei of this structure in awake and behaving animals. For example, stimulation of the lateral hypothalamus in cats produces typical and integrated motor responses characteristic of 'anger' (higher blood pressure, raising of hair, arching of the back, etc.). This resulting behavior was termed 'sham rage' because of its assumed lack of conscious experience (18, 28). On the other hand, ablation of this region produces placidity. The function of the hypothalamus in the putative neural circuit for emotion is to integrate and carry the autonomic and endocrine responses perceived during emotional expression. It accomplishes this role on the basis of cortical information arriving from the hippocampus (through the fornix) and sensory information arriving from the ventral thalamus (29). This view has been further developed by other researchers, insisting more on the hippocampus as the locus of conscious emotional experience, and on the hypothalamus as the locus of emotional expression (30).

Further work has characterized the set of anatomical structures controlling the autonomic and endocrine expressions of emotions mediated by the hypothalamus (31). These structures include the septal nucleus, the amygdala, the pre-optic areas and the diagonal band of Broca, as well as to the periventricular and central gray areas. These regions project to a specific region of the hypothalamus (defined as comprising the perifornical region and the medial portion of the lateral hypothalamus) which was consequently termed HACER (Hypothalamic Area Controlling Emotional Responses). Efferents of the HACER have in turn been identified (32) and share the common property of sending relatively direct inputs to the intermediolateral column cells of the thoracic cord (major group of autonomic cells) (33). Other studies further suggested that the hypothalamic paraventricular nucleus contained separate but interacting populations of cells mediating different autonomic and endocrine responses, making of this nucleus a locus of endocrine and autonomic integration (34).

Most of the modern work relating the hypothalamus to behavioral expressions of emotions has been completed on the basis of the pioneering studies of self-stimulation drives and reinforcements (20). These studies, greatly based on the catecholamine hypothesis, lead to the construction of maps of the hypothalamus localizing the neural subsets primarily involved in one of several behaviors such as feeding, drinking, or reproduction. Even though these maps are to a large extent plastic, they indicate a somewhat behaviorally dependent topological structure of the hypothalamic substrate. These theories propose that drive states can be triggered in the hypothalamus by the release of peptide hormones via a group of fibers that can also transmit reward information through the release of amines. Subsequent studies, using single-neuron recordings, suggested that the same neurons of the lateral hypothalamus responded differentially to rewarding and aversive stimuli (35). Although not formulated explicitly as follows, these theories propose that the mediation of drives and their assigned values (reward) are mediated by the same neuronal systems and pathways, but by two different transmitter systems: one mediating the drive responses (the peptide hormones) and the other one modulating them (the amines).

The Amygdala: Instinctive Emotions

The first studies involving the amygdala in emotion were actually reported by researchers studying the effects of bilateral lesions of the whole temporal lobe (36). These studies showed 'abnormal' monkey behaviors such as: no expression of anger and fear (unrestricted approach of humans and other animals), increased mouth exploration of objects (including snakes and live rats) and general slowing of movements. Later studies focused on specific ablation of the amygdala (37) and demonstrated that animals showed a marked increase of tameness, loss of motivation, decrease of fear response to aversive stimuli, and a more rapid extinction of conditioned avoidance responses acquired preoperatively (and slower subsequent acquisitions). Guided in part by these pioneering studies, researchers attributed to the amygdala both memory (38, 39) and 'emotional' functions (1, 2).

Neuromodulatory Systems

Studies of the involvement of the neuromodulatory systems of the amygdala in negatively-charged memory formation have pointed to the β-adrenergic system (40). Post-training injection of the β-adrenergic receptor antagonists *dl*-propanolol or *dl*-alprenolol in the amygdala clearly showed a time-dependent and dose-dependent decrease in the retention of a passive avoidance task in rats. In addition, simultaneous injection of *l*-norepinephrine has been shown to reverse this effect. Taken to-

gether, and completed by other studies showing the presence of such receptors and the projection of noradrenergic systems onto the amygdala, these results strongly suggest that long-term memory formation (24 hours in rats) involved in passive avoidance tasks are modulated by the β-adrenergic receptor system of the amygdala. The amount of activation of this system predicts the amount of passive avoidance.

Further pharmacological studies, using heart-rate conditioning, revealed that the opiate system was also involved (41). Pretraining administration of opiate in the central nucleus of the amygdala selectively impaired acquisition of conditioned heart-rate responses in rabbits. This effect is canceled by simultaneous injection of the opiate antagonist naloxone. Other studies suggested that the activation of the opioid system of the central nucleus of the amygdala decrease fear-like responses in rats (42), and that the post-training injection of opiate produced naloxone-reversible and dose-dependent decrease in retention of a passive avoidance task (43). Together with results from similar studies, these results strongly implicate the opiate receptors of the amygdaloid central nucleus in the modulation of cardiovascular functions (such as heart rate) in aversive situations.

Other studies have shown the existence of opiate receptor gradients along anatomical sensory pathways, such as visual, auditory, or somatosensory pathways (44). These gradients peak in or near the amygdaloid complex, which suggests that it is the locus of important opiate influences. This result suggests that as the processing of sensory information becomes more and more complex, it becomes more susceptible to opioid neuromodulation, a notion that will be encountered again with dopamine in the prefrontal cortex. Other studies have suggested similar results for neuropeptides. In particular, substance P and somatostatin have been found to have the highest levels in the amygdala compared with the rest of the neocortex (45), suggesting again that the amygdala is a locus of potent neuromodulations. Interestingly, such amygdaloid neuropeptides have been found colocalized with other neurotransmitters such as GABA, which suggests a rather complex pattern of intrinsic, activity-dependent neuromodulation (46).

Neuronal Systems

Fear conditioning depends on an intact and fully operational amygdala (47–49). Sensory inputs relay in modality-specific nuclei of the thalamus before projecting to the lateral nucleus of the amygdala, which therefore appears as the sensory interface of the amygdala in fear conditioning (50, 51). The lateral nucleus then projects in a very organized manner to other amygdaloid nuclei (52, 53). Amygdaloid computations eventually reach the central nucleus, which then projects to extra-amygdaloid structures mediating motor responses (54). These structures include the hypothalamus for autonomic responses and the periaqueductal gray for skeletal motor responses, to cite only a few. In addition to its thalamic inputs, the lateral amygdala receives projections from various levels of sensory cortical processing.

In this neuroanatomical context, and on the basis of further neurophysiological experiments, it was proposed that the learning process (fear conditioning) mediated by the amygdala involves two separate and necessary information streams, which the amygdala integrates. The thalamo-amygdaloid pathway mediates short-latency and crude stimulus-fear associations (55), whereas the thalamo-cortico-amygdaloid pathway carries slower (multisynaptic) and more processed (possibly multimodal) sensory information destined to complement the previous, 'gut-reaction' information (56, 57). This view has been further substantiated by the observation that amygdala and hippocampus (the 'last stage of sensory cortico-cortical processing') are differentially involved depending on whether the stimuli are 'simple' (in which case the amygdala suffices) or 'complex' (in which case the hippocampus is involved [58, 59]).

Fear conditioning, however, is not only a matter of remembering or not remembering fearful stimuli. It involves graded responses, probably because of a graded amount of retention of the triggering events. My theory proposes that this gradation is related to graded patterns of neuromodulations occurring in the amygdala.

As seen in the previous section, opioid, β-adrenergic, and other peptidergic neuromodulatory systems coexist in the amygdala. How do they interact and how do they relate to fear conditioning?

An interesting and ongoing body of studies has attempted to address this question (60–63). These studies suggest that four different neurochemical systems are involved in the regulation of memory storage assessed using a passive avoidance task (Fig. 1).

The main neuroactive system is β-adrenergic (adrenal epinephrine) and is active during stress-related events (64). Both GABA-ergic and opioid-peptidergic inputs of as-yet-unspecified origin (but coursing through the stria terminalis) inhibit it. Another neurochemical system is cholinergic and carries the influence of the amygdala to other brain structures. In contrast with other theories, this body of research suggests that memory storage is localized in brain structures other than the amygdala (65) and that the amygdala has only the function of 'modulating' memory storage in relation to the internal state of the animal, as measured by endogenous levels of opioids and other hormones. Accordingly, the mediation (by NE) of the amygdaloid modulation of other brain structures (through acteylcholine [ACh]) is modulated by a neurochemical system (opioid peptidergic) that has for a long time been involved in emotional disorders; the excessive and exogenous activation of this system in other brain structures has indisputable emotional dimensions.

In a broader context, I propose that the evaluations of the emotional content of a stimulus follow three parallel

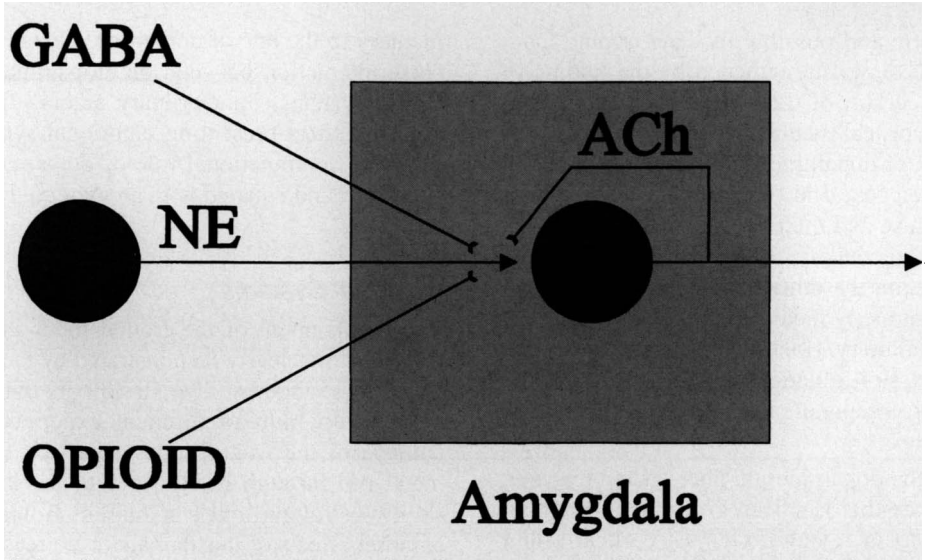

Fig. 1. Neuromodulation of memory storage by the amygdala. Four neurochemical systems are involved: the central and enabling one is mediated by NE (possibly from the nucleus of the solitary tract), the modulating ones are GABA-ergic, opioid peptidergic, and cholinergic (60,62).

pathways. A first, noncognitive route is established in accordance with neuromodulatory mechanisms of the mesencephalic system. A second relies on the amygdala and the hippocampus and is based on the previous experiences of the organism. The third pathway depends on the prefrontal cortex and relies on more cognitive aspects available to the organism (66). A given stimulus is decoded and distributed along several information streams, each reaching one of the structures mentioned above. The decoding depends on the complexity of the stimulus; a simple stimulus strongly activates mesencephalic systems, whereas a more complex one primarily activates frontal cortices. Intermediate levels of complexity would then reach the amygdala and hippocampus (tone or 'context' for example). These structures perform a filtering, or possibly a pattern matching, of the information received; if adequate, they trigger a specific set of actions. In the case of the amygdala, these actions are species-specific and related to the amount of 'danger' that the stimulus carries.

These results suggest that the amygdala is not an 'emotional center,' computing and associating emotional values to sensory stimuli; rather, it is a component of a larger species-specific instinct-mediating system. The amygdala 'filters' its incoming sensory streams of information, looking for those 'dangerous' stimulus features that would require the organism to engage in certain species-specific instincts, such as freezing or startling. These 'filters' are to some extent plastic and modifiable through conditioning, whereas the filtering process itself undergoes neuromodulations, as described above.

The Prefrontal Cortex: Cognitive and Temporal Aspects of Emotion

The neural basis of the involvement of the prefrontal cortex in emotion is less clear than for the hypothalamus or amygdala, because it depends on more cognitive functions that are difficult to assess with the current animal models available. However, clinical data (in humans) are filling this gap and speak clearly for a role of the prefrontal cortex in emotion, as will be reviewed below. I will first point to the richness of the neuromodulatory systems in the prefrontal cortex, each potentially able to modulate its function. I will then focus on the dopaminergic system and its role in emotion.

Neuromodulatory Systems

The prefrontal cortices contain many receptor systems (see ref. 67, chapter III for a review). Norepinephrine-containing fibers originating in the brain stem reticular formation (pontine and medullary reticular formation on the one hand, locus ceruleus on the other hand) are densely found in layers IV and V, whereas they run tangentially in layers I and VI. The selectivity of these projections is higher in the primate than in the rat, which suggests that this system has a diffuse and general neuromodulatory role in the excitability of the prefrontal cortex neurons. In addition, the cholinergic fibers originating from the ascending reticular activating system (medial septum, nuclei of the diagonal band [horizontal and vertical], ventral pallium and nucleus basalis of Meynert) (68), especially from the anterolateral nucleus basalis, have also been found to diffusely project to the prefrontal cortex as well as the amygdala. Neurophysiologically speaking, ACh released from the substantia innominata (nucleus of Meynert) enhances the activity of some excitatory and inhibitory prefrontal cells (69, 70).

Neuropeptides have also been widely found in the prefrontal cortex (45). In particular, substance P is the most common in the prefrontal cortex and the amygdala. These peptides modulate the production and/or release

of neurotransmitters and possibly mediate trophic functions. This hypothesis is strengthened by the finding of colocalization of certain of these peptides in cells containing 'classical cortical' neurotransmitters (71), such as GABA, ACh (72), or dopamine (73). Although serotonin receptors have been found in the prefrontal cortex, their localization is diffuse and their density low and uniform, which suggests a secondary role in neurotransmission (74). Amino acids, on the other hand, are intrinsic transmitters. They presumably mediate inhibitory (for GABA or glycine) or excitatory (for glutamate and aspartate) local neurotransmission functions and, as in most of the cerebral cortex, are preponderant in layers II and IV of the prefrontal cortex.

It is, however, the dopaminergic fiber system reaching the prefrontal cortex that has been given the most attention (see ref. 75 for a review). Of mesocortical origin (ventral tegmental area), this system seems to be one of the highest points of a general rostrocaudal gradient of dopamine projections, peaking in the posterior parietal cortex and ending in the occipital lobe (74). This topology suggests the primary role of this neuromodulatory system in planning and other cognitive and associative (somatic, visual, and motor in the posterior parietal cortex) behavior, although it may be relatively unimportant in primary visual areas. Furthermore, it has been shown that prefrontal dopamine-sensitive neurons are mainly located in layers V and VI. Prefrontal tissue exhibits a higher dopamine turnover rate than other cortical areas (76) and is innervated by cells that have a complex neuromodulatory composition, containing several coexisting additional neuromodulatory substances such as cholecystokinin (73). In turn, these prefrontal cells project to several subcortical dopaminergic cell groups, such as the lateral hypothalamus, the striatum, the substantia nigra, and the ventral tegmental area, which implies their involvement in dopamine regulation at other sites (such as the nucleus accumbens, for example [75]). These projection cells are the locus (to the exclusion of most of the other catecholamine systems) of dopamine increase during stress (76).

Pharmacological and behavioral studies on intracranial self-stimulation further established the important role of the medial prefrontal dopamine system in positively motivated behavior (77). Given the diversity of the nature of the neurotransmitters involved in cells mediating self-stimulation, this study proposed the existence of many subcircuits running to and from the prefrontal cortex and subcortical areas, each involving particular types of neurotransmitters. A dysfunction of these projections leads to an increase in dopamine levels in specific subcortical structures that eventually trigger pathogenic symptoms (both cognitive and affective) associated with schizophrenia (76). Of related interest is the finding that although serotonin seems to be evenly distributed in the prefrontal cortex, its metabolite (5-hydroxytryptophan) presents a gradient exactly complementary to the one of dopamine. This result suggests the close interaction between the dopaminergic and serotonergic systems, both primary actors of several psychiatric disorders presenting emotional symptoms (74, 78, 79). The computational role of dopamine has also been simulated and equated with an increase in signal-to-noise ratio (80).

Neuronal Systems

The involvement of the frontal lobes in affective function was first clearly demonstrated by the case of Phineas Cage, as studied by J.M. Harlow in 1848 (81, 82). This 25-year-old railroad foreman experienced very heavy damage of the frontal lobe caused by the passage of a metal rod through his lower left cheek up through his skull, destroying much of his left frontal lobe. The behavioral effects of this damage were recorded until a few months after Cage's recovery. Aside from obvious cognitive (planning) and social deficits, Harlow noted that Cage exhibited "the animal passions of a strong man," a general inappropriateness of his emotional reactions, together with a marked change of his personality. Subsequent clinical reports confirmed these early findings and led to numerous systematic investigations on animal models. In particular, studies on primates (83) showed that prefrontal lesions could sensitively decrease emotional responsiveness, a result which led Egas Moniz to use, for at least 2 decades, prefrontal lobotomy as a clinical treatment for certain human emotional disorders.

In light of more recent neurophysiological studies, the modern view of the role of the prefrontal cortex is, however, somewhat different. It has been clearly established that the prefrontal cortex serves both cognitive and emotional functions. Ablation of the dorsolateral divisions of this region results in impairment in various delay tasks (delayed-response, delayed-alternation, and delayed-matching tasks [see refs. 67 and 84 for reviews]). Together with electrophysiological data, these results led to the conclusion that the dorsolateral prefrontal cortex mediates cognitive functions related to the crosstemporal contingencies of motor actions and recent sensory information (85). It is therefore the locus of some form of short-term sensory memory related to representations of preparatory motor activities and of their interaction in time (also called 'working memory'). Conversely, the ventromedial division of the prefrontal cortex exerts an inhibitory influence on hypothalamic and other limbic systems, therefore dampening the control of certain instincts and drives (86). This hypothesis is compatible with various clinical observations in humans.

Because of the existence of numerous cases in which lesions of the frontal cortices actually provoked tameness, fearfulness, lack of responsiveness, and abnormal social behaviors (87) in a manner resembling the Klüver-Bücy syndrome, this view had to be modulated in the light of neuroanatomical findings. Although the orbitofrontal cortex has indeed been found to project to the

lateral hypothalamus (88) (which substantiated the hypothesis of cognitive control of hypothalamic function by the frontal cortex [89]), it was also found to have a very tight coupling with the temporal lobe, both directly (90) and via the thalamus (91). In addition, it receives inputs from and projects to the ventral tegmental area, one of the major sources of dopamine in the brain.

These neuroanatomical observations outlined the unique position of the prefrontal cortex in reciprocal sensory motor circuits involving the parietal and temporal cortex (visual, auditory, and somatic areas) and the telencephalon (in particular the hypothalamus and related subcortical structures). Clinical observations in humans show further that frontal lobe damage is strongly associated with oral-affective disorders (92) and that lesion and stimulation of the anterior cingulate cortex have marked emotional consequences (93). More recent studies formed the hypothesis that the orbitofrontal cortex might be involved in the correction of the behavioral response associated with previously reinforced stimuli, when the reinforcement contingencies have changed (94, 95), compatible with other experimental data implicating the medial prefrontal cortex in the extinction of emotional learning (96). These results are also compatible with data from humans suggesting that the frontal lobe is involved in cognitive processing relying on the use of reward contingencies, as in the Wisconsin Card Sorting task (97, 98). The frontal cortex, therefore, can both monitor and modulate limbic mechanisms, in particular emotional and motivational states, by presetting sensory processing mechanisms in accordance to affective landmarks, which, through their temporal arrangement, guide goal-directed behavior in the time domain (99, 100).

I propose that the orbitofrontal divisions of the prefrontal cortex, possibly together with the dorsolateral divisions, are involved in the assessment of the adequacy and control of ongoing and (immediate) future behaviors. This assessment, even though strongly cognitively based, makes use of the emotional state of the organism[1] embedded in prefrontal patterns of neuromodulation (domaninergic and other). This process accounts for environmental (exteroceptive and interoceptive), mnemonic, and social factors and is functionally compatible with the 'somatic marker hypothesis' proposed by others (101).

Other Systems

Many other structures have been implicated in the experience and expression of emotion. They include the Diagonal Band of Broca, the cingulate cortex, the reticular formation, the nucleus of the solitary tract, the nucleus accumbens, the central gray, the periaqueductal gray, and the septohippocampal system (102, 103) (Fig. 2).

[1] The studies of Milner (Wisconsin test and stylus-maze test) show that frontal subjects perceive their mistake but do not make use of this perception to modify their behavior. We attribute this impairment to a lack of evaluation of the (negative) value of the error signal that they perceive. This observation is compatible with clinical data indicating that some frontal patients perceive pain as being a noxious stimulus but ignore its significance.

Summary and Conclusions: Emotion, Behavior, and Neuromodulation

The specificity and adaptability of behaviors are caused partly by the nature and amount of neuromodulation that their underlying neural substrate undergoes. I proposed that the interaction between the emotional state and the ongoing behavior can be understood as continuous patterns of neuromodulation occurring in brain structures that mediate behavior. I illustrated this point by reviewing three structures long thought to be involved in emotion: the hypothalamus, the amygdala, and the prefrontal cortex.

In the hypothalamus, I pointed to the neuromodulatory functions of the catecholamine receptors (NE in particular) in controlling the association between drives and rewards. I reviewed the "catecholamine hypothesis of affective disorders" and the possible additional role of amines and peptide hormones in the registration of rewards. I then presented the amygdala as a site of neuromodulatory control of the memory of instinct-triggering stimuli. I cited studies showing the simultaneous involvement of noradrenergic, opioid peptidergic, and GABA-ergic systems in the modulation of memory storage of aversive events eliciting escape and avoidance. I finally pointed to the role of the dopaminergic system (and to a lesser extent the serotonergic system) in modulating the processing of the prefrontal cortex neurons. I mentioned studies relating dysfunction of these systems with psychiatric emotional disorders such as depression and schizophrenia.

The study of the functional role of neuromodulatory systems in behavior suggests a possible organization of behaviors with respect to the amount and nature of neuromodulation their neural substrate undergoes (Fig. 3) and, consequently, with respect to their potential for being emotionally modulated.

On the one hand, reflexes are motor responses that are extremely specific to the eliciting stimuli (knee jerk reflex, nictitating membrane response, etc.). Their neural substrate is the seat of few and simple neuromodulations. In experimental settings, such reflexes can therefore be considered emotion-independent. On the other hand, cognitive behaviors (such as certain forms of learning and memory) are characterized by a highly nonspecific set of actions (some mental) and are subjected to rich and functionally important neuromodulations. Hence, experimental procedures ought to carefully control the emotional state of the animal or subjects. The theory proposed here suggests that this control may be scientifically achieved through the control of those neuromodulatory systems that are known to influence the emotional state of the animal.

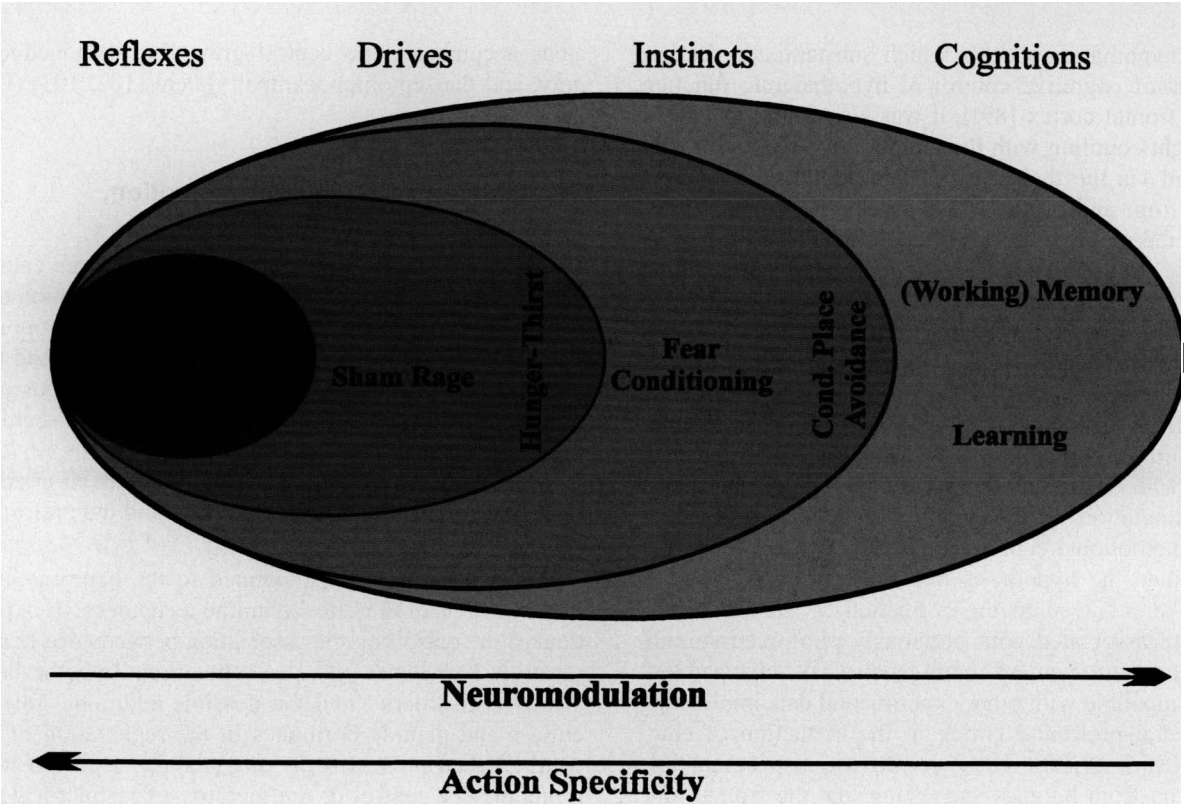

Fig. 2. Organization of behavior with respect to potential neuromodulation and action specificity. Reflexes are fixed motor patterns, the neural substrate of which undergoes few neuromodulations, whereas 'cognitions' are unspecific (with respect to sensory stimuli) and heavily neuromodulated 'thought processes'.

Reflexes and cognition yield a set of end-actions, which in the case of reflexes are purely motor responses and in the case of cognition mainly 'thought processes'. In between these two extreme behavioral levels, one finds various degrees of action specificity and potentials for functionally relevant neuromodulation and, hence, potentials for emotional influence. For the sake of the example, I define two intermediate behavioral levels below (Fig. 3). The following are simply working definitions.

Drives (which I define as need-based, instinctive behaviors) activate motor pattern generators of various degree of complexity, such as running, accelerating the heart rate, and stopping the smooth muscle of the gastrointestinal tract, when experiencing fear. Drive circuits may be modulated in intensity (how much are the muscles mobilized when jumping because of a loud noise). Drive and reflex are, of course, overlapping notions. For example, we would call the response to a sudden loud noise, both a startle reflex (because it involves the same motor end-actions) and a drive (because the end-action of jumping can be modulated to a large extent [49]). Elicitation and control of drives are essentially stimuli driven (internal or external), their neural implementation involving much of the reflex circuitry (motor pattern generators).

Instincts are behaviors that are modulated in intensity, but also involve complex and adaptive sequences of intermediate drive-like actions. Such sequences remain fixed (for a given instinct) and therefore predictable. In a rat, for example, freezing at the sound of loud high frequency pitches or when undergoing electrical footshocks is an instinct that results in various organized intermediate motor actions such as crouching or orienting. Such behaviors are species-specific. Under the same circumstances, humans would probably jump or escape rather than freeze. Instincts can be modulated (as in the case of passive avoidance) in a rather 'smooth' fashion. Again, the notions of drive and instincts overlap insofar as need-based instincts are drives, according to our definition.

The emotional state influences each of these behavioral levels. An animal under stress or in an acute state of fear will react differently to stimuli normally eliciting a reflex, a drive, an instinct, or a set of cognitive processes. I propose that each of these classes of behaviors involve more and more brain structures, as we move from reflexes to cognition (Fig. 2). A priori, cognitive emotions (e.g., love) might involve brain structures implicated in some reflex (visceral, for example) drive or instinct as well as other specific structures (of a more cognitive nature, for example). For example, certain emotional states may depend on both instinctive tendencies characterized by the activity of aversive and appetitive neural systems and the activation of protective-defensive reflexes elicited by a startle-inducing stimulus (104).

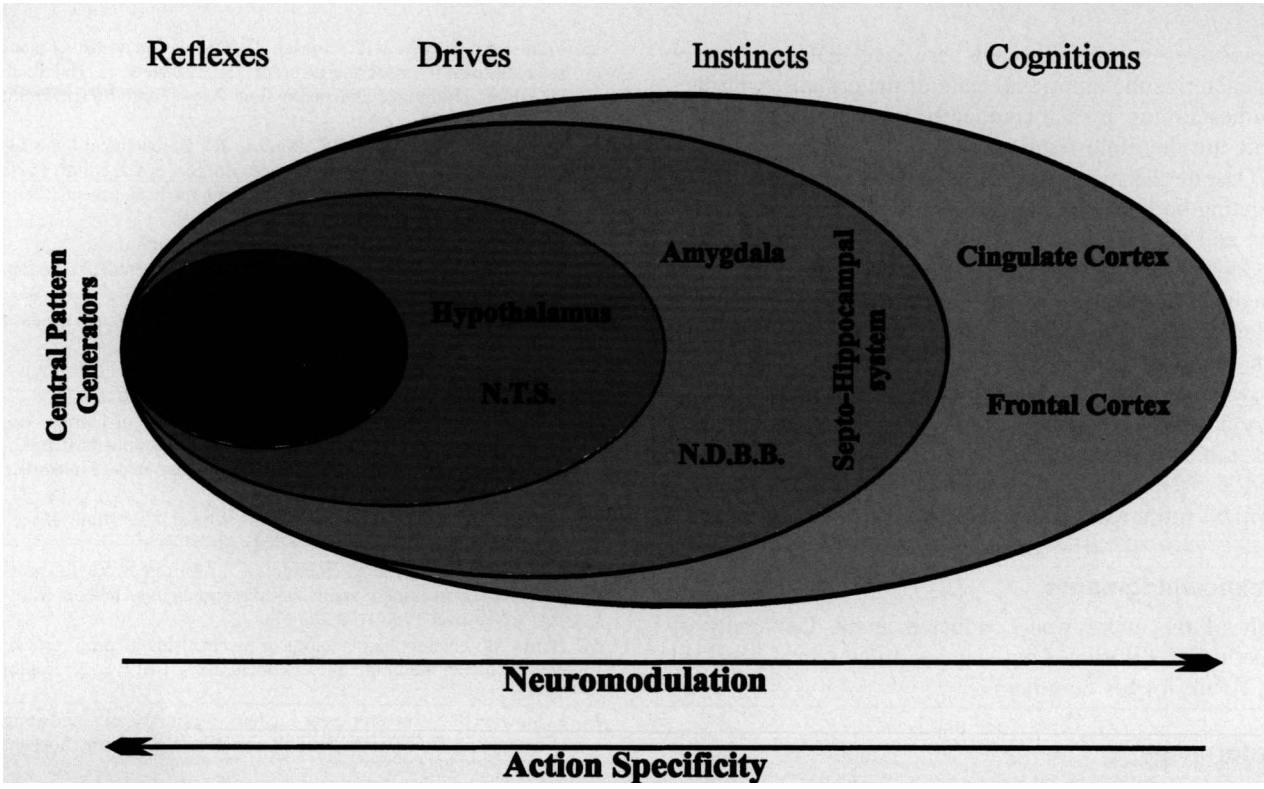

Fig. 3. Mapping of brain structures to reflexes, drives, instincts, and cognitions *N D B B*, nucleus of the diagonal band of Broca, *R F*, reticular formation, *N T S*, nucleus of the solitary tract Ellipses represent zone of direct influence and possible neural recruitment during emotional expression and experience

There are, of course, modulations of brain centers that do not bear any emotional nature. Some can be implemented by specific neural inputs to these centers and account for the interactions of different aspects of sensory-motor behaviors (contribution of different senses, cooperation or competition between different drives and instincts). For example, the sight of a tempting water area can amplify 'primary (hypovolemic) thirst' (89). The emotional state, therefore, constitutes only a part of the internal state of the organism and is in any case intimately linked to the computational state of the substrates that mediate behavior.

The study of the neural substrate of the interaction between emotion and behavior suggests clearly that emotion is not mediated by specialized 'brain centers.' If indeed certain structures, such as the hypothalamus, the amygdala, or the prefrontal cortex, are involved in emotion, none of them do so in a specific manner. Each are involved in 'nonemotional' behaviors as well: the hypothalamus mediates endocrine and autonomic responses, the amygdala detects species-specific, instinct-triggering 'dangerous' stimuli, and the prefrontal cortex is involved in planning and cognitive tasks. Such an observation may lead to two extreme theoretical standpoints The first would consider that emotion is an epiphenomenon, a subjective assessment of the way behavior is mediated. The second would acknowledge our still poor understanding of the brain, and hope that further detailed studied will point to specialized, distributed subcircuitry that mediates emotional responses.

Because of the versatility of the brain, and given the existing body of research, some of which was mentioned before, emotion may not be best understood as the result of the neural computations of some distributed set of structures. Because of the undeniable effects of drugs of abuse and their known neuromodulatory mechanisms, emotion is also not an epiphenomenon or byproduct of some normal or abnormal behavior. I hypothesize that, in the same manner as Hebb first proposed that brain processes were the result of the activation of certain neural assemblies, the emotional state can be best seen as *patterns of neuromodulation of these assemblies*. These neuromodulations can be quantitatively assessed by considering subthreshold activities as well as the neurochemical state of cell populations that have previously been known to be involved in emotional behavior. Neural computation and neuromodulation are reciprocally causally linked, reflecting the interdependence of the emotional state and the ongoing behavior. Hence, such an approach may in principle provide a quantitative characterization of the emotional state.

This characterization is of course theoretical at this point I have not presented evidence that it effectively proves useful It might be the case that the patterns of neuromodulations, even when considered within some limited set of brain structures as proposed here, are

themselves so versatile and pervasive that they do not characterize the emotional state of the organism. Further studies aiming at such characterizations of the emotional state are therefore required.

Despite the many recent examples of progress in elucidating both the functions of neuromodulatory phenomena and the neural circuitry that mediates behavior, our understanding of their interaction is still at an early stage. Partly because of the 'distance' between subcellular neurochemistry and neural assembly-based behavior, such studies are difficult to conduct in general. However, I believe that the study of the neuromodulatory basis of emotional behaviors will prove to be a useful framework in which to investigate such an interaction and, consequently, confirm, refine, or invalidate the theoretical framework presented here.

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