The Neuromodulatory Basis of Emotion

Jean-Marc Fellous

Computational Neurobiology Laboratory,
The Salk Institute for Biological Studies,
La Jolla, California

The Neuroscientist 5(5):283-294,1999. The neural basis of emotion can be found in both the neural computation and the neuromodulation of the neural substrate mediating 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 partly due to 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.

Key Words: Neuromodulation, Emotion, Affect, Hypothalamus, Amygdala, Prefrontal

Introduction

The scientific study of the neural basis of emotion is an active field of experimental and theoretical research (See (1,2) for reviews). Partly because of a lack of a clear definition (should it exists) of what emotion is, 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 not the result of the activity of some specific brain structures ('emotional centers'), nor the diffuse (non-localized) 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[1] that this substrate mediates. 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 five-fold.

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 non-emotional functions, and it does not require an explanation for how and why emotional and non-emotional 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.

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[1] In the following, we will consider 'thinking' or cognition as a behavior.

Address reprint requests to: Jean-Marc Fellous, C.N.L, The Salk Institute for Biological Studies, 10010 N. Torrey Pines road, La Jolla, CA 92037 (E-mail: fellous@salk.edu).

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. They therefore modify the neuromodulatory pattern directly, 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 nor 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 into 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, and is essential in the conduct of behavioral experiments 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 patters 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 details, from synapses (6) to single cells (7) to networks in invertebrate (8) and cortex (9) in vivo or in vitro, and theoretically studied using computer modeling techniques (10). I will not discuss neuromodulation in general, referring the reader to the references mentioned above. I will rather 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', but because they are the locus of the influence of emotion on 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), and that 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 theories considering a few brain centers to be the locus of all emotions, and theories proposing that emotion is a non-localized diffuse neurochemical process.

The Hypothalamus: Endocrine and Autonomic Expressions of Emotion.

Neuromodulatory systems

The hypothalamus, due to its preponderant role in neuroendocrine functions, contains a wide variety of neurochemical substances (see (11,12) for a recent account of the major issues and (13) for a classic review). Together with the pituitary, thyroid, parathyroid, 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 (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 due to hyper-secretion of corticotropin (ACTH) or corticotropin-releasing hormone (CRH). These hyper-secretions in turn have been shown to be due to the decrease of secretion of thyroid-stimulating hormone (TSH) elicited by thyrotropin-releasing hormones (TRH), and the decreased sensitivity of hypothalamic alpha2-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 (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 non-rewarding 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). This study argues 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 according to 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 both sensitive to various neuromodulatory substances, and target 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 project to 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...). 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...). 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

differentially 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 proposed 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 down 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 beta-adrenergic system (40). Post-training injection of the beta-adrenergic 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 together, 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 beta-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). Pre-training 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 other 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 (44). These gradients peak in or near the amygdaloid complex, suggesting that the latter 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 to the rest of the neocortex (45), suggesting again that the amygdala is a locus of potent neuromodulations.

Interestingly, such amygdaloid neuropeptides have been found co-localized with other neurotransmitters such as GABA, suggesting a rather complex pattern of intrinsic activity dependent neuromodulation (46).

Neuronal systems

Fear conditioning depends on an intact and fully operational amygdala (see (47,48) or (49) for a review). 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). Amydaloid 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 (multi-synaptic) 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 suffice) or 'complex' (in which case the hippocampus is involved (58,59)).

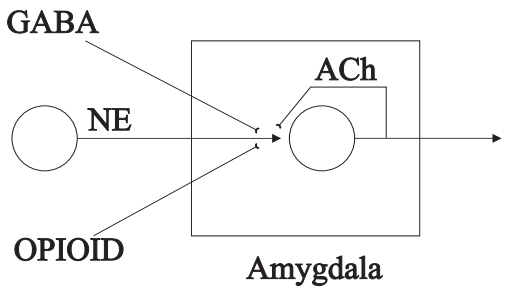

Fig. 1: Neuromodulation of memory storage by the amygdala, adapted from (60,62). Four neurochemical systems are involved: The central and enabling one is mediated by NE (possibly from the nucleus of the solitary tract), the modulating ones are GABAergic, opioid peptidergic, and cholinergic.

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

As seen in the previous section, opioid, beta-adrenergic and other peptidergic neuromodulatory systems coexist in the amygdala. How are they interacting 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 beta-adrenergic (adrenal epinephrine) and is active during stress-related events (64). Both GABAergic and opioid-peptidergic inputs of 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 latter has only the function to 'modulate' memory storage in relation to the internal state of the animal, measured by its endogenous levels of opioids and other hormones. Accordingly, the mediation (by NE) of the amygdaloid modulation of other brain structures (through ACh) is modulated by a neurochemical system (opioid peptidergic) that has been, for a long time, involved in emotional disorders and the excessive and exogenous activation of which, 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 pathways. A first, non-cognitive 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 above mentioned, and probably others. The decoding depends on the complexity of the stimulus, so that a simple stimulus strongly activates mesencephalic systems, while 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, and, if adequate, 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, but 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 which 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 (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 coeruleus on the other hand) are densely found in layers IV and V, while they run tangentially in layer I and VI. The selectivity of these projections is higher in the primate than in the rat, and 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, ACh released from the substantia inominata (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 present 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 co-localization of certain of these peptides in cells containing 'classical cortical' neurotransmitters (71) such as GABA, ACh (72) or dopamine (73). While serotonin receptors (originating from the brain stem) have been found in the prefrontal cortex, thier localization is diffuse and thier density low and uniform, suggesting 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 (75) for a review). Of mesocortical origin (ventral tegmental area), this system appears to be one of the highest points of a general rostro-caudal 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 while it may be relatively unimportant in primary visual areas. It has been further shown that prefrontal dopamine sensitive neurons are mainly located in layer V and VI. Prefrontal tissue exhibits a higher DA 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 CCK (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, suggesting 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 intra-cranial self-stimulation further established the important role of the medial prefrontal dopamine system in positively motivated behavior (77). On the basis of the diversity of the nature of the neurotransmitters involved in cells mediating self-stimulation, this study proposed the existence of many sub-circuits, running to and from the prefrontal cortex and subcortical areas, each involving particular types of neurotransmitters. A dysfunction of these projections lead 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 appears to be evenly distributed in the prefrontal cortex, its metabolite (5-HTP) 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 due to the passage of a metal rod through his lower left cheek up to 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, at least for two decades, prefrontal lobotomy as a clinical treatment for certain human emotional disorders.

In the light of more recent neuro-physiological 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 (67,84) for reviews). Together with electro-physiological data, these results led to the conclusion that the dorsolateral prefrontal cortex mediates cognitive functions related to the cross-temporal 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 human clinical observations.

Due to the existence of numerous cases where 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 been indeed 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). Human clinical observations show further that the frontal lobe damage are 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 orbito-frontal 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 human data suggesting that the frontal lobe is involved in cognitive processing relying on the use of reward contingencies such 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 pre-setting sensory processing mechanisms in accordance to affective landmarks, which, through their temporal arrangement, guide goal-directed behavior in the time domain (99,100).

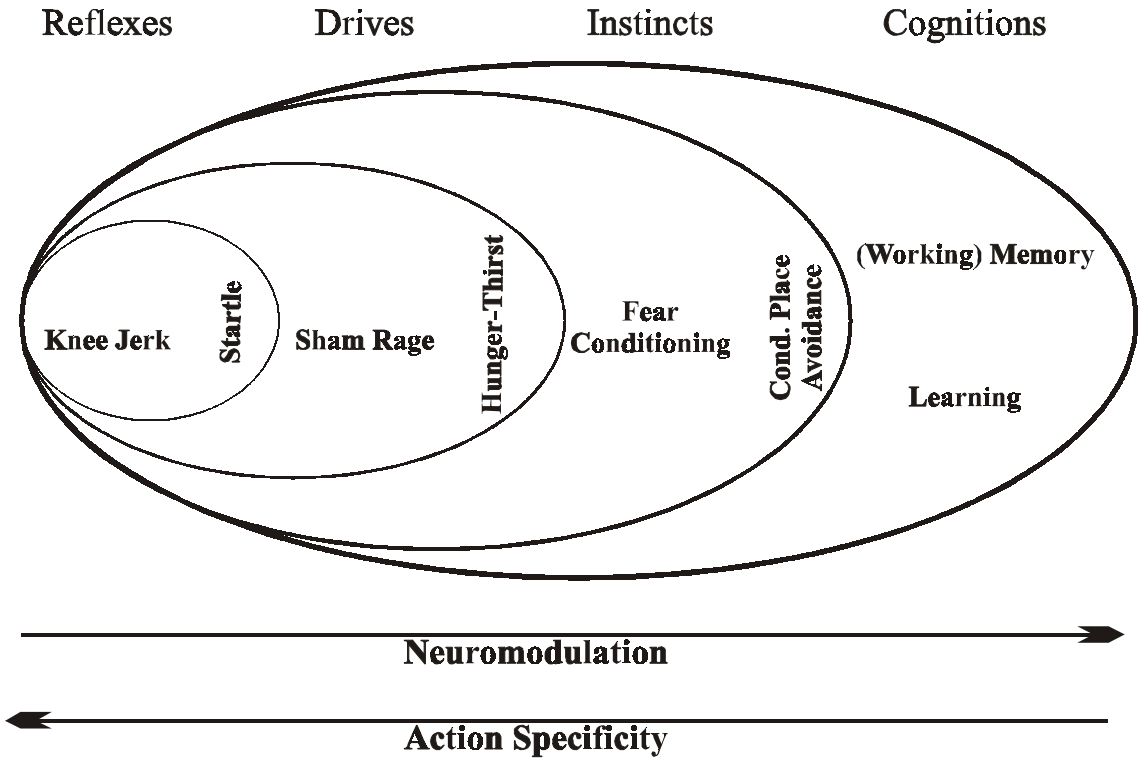

Fig. 2: Organization of behavior with respect to potential neuromodulation and action specificity. Reflexes are fixed motor patterns, the neural substrate of which undergoes few neuromodulations, while 'cognitions' are unspecific (with respect to sensory stimuli) and heavily neuromodulated 'thought processes'.

I propose that the orbito-frontal divisions of the prefrontal cortex, possibly together with the dorsolateral divisions, be 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[2] embedded in prefrontal patterns of neuromodulation (domaninergic and other). This process accounts for environmental (exteroceptive and interoceptive), mnemonic, as well as social factors and is

[2] 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.

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 septo-hippocampal system (102,103) (Fig. 3).

Summary and Conclusions: Emotion, Behavior and Neuromodulation.

The specificity and adaptability of behaviors are partly due to 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 mediating 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 GABAergic 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.

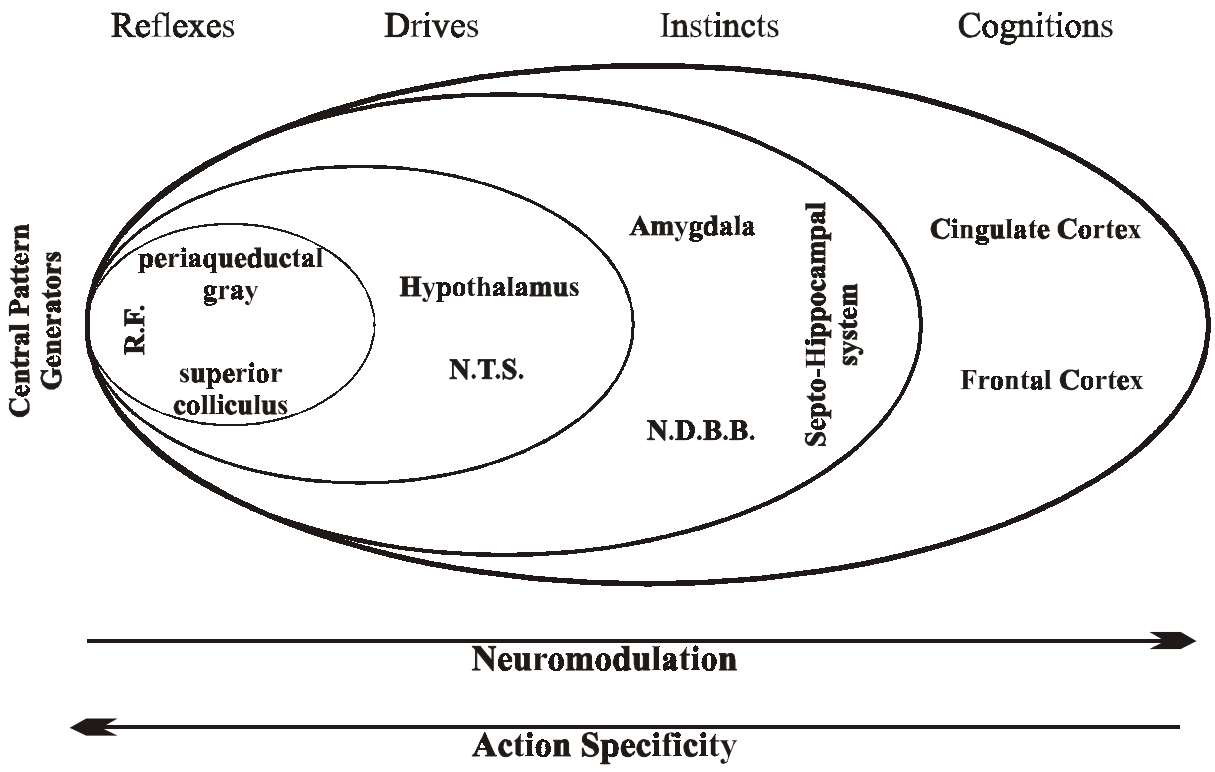

Fig. 3: Mapping of brain structures to Reflexes, Drives, Instincts, and Cognitions. Abbreviations: NDBB (nucleus of the diagonal band of Broca), RF (reticular formation), NTS (nucleus of the solitary tract). Ellipses represent zone of direct influence and possible neural recruitment during emotional expression and experience.

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. 2), and consequently, according to our view, 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...). 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 non-specific 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.

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, hence potentials for emotional influence. For the sake of the example, I define two intermediate behavioral levels below (Fig 2). 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 gastro-intestinal 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)). Drives elicitation and control 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 foot-shocks is an instinct which 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 3). 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 (for example of a more cognitive nature). For example, certain emotional states may depend on both instinctive tendencies characterized by the activity of aversive and appetive neural systems, and the activation of protective-defensive reflexes elicited by a startle-inducing stimulus (104).

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 mediating 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 'non emotional' 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 sub-circuitry, mediating emotional responses.

Because of the versatility of the brain, and given the existing body of research, some of which were 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, 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 sub-threshold activities as well as the neurochemical state of cell populations that have been previously 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.

In spite of the many progresses recently accomplished in elucidating both the functions of neuromodulatory phenomena and the neural circuitry mediating behavior, our understanding of their interaction is still at an early stage. Partly because of the 'distance' between sub-cellular 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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References

1. LeDoux JE. Emotion. In: Plum F, editor. The nervous system V. Bethesda, Maryland: American Physiological Society 1987;419-460.
2. LeDoux JE. The Emotional Brain. New York: Simon & Schuster 1996.
3. Nesse RM, Berridge KC. Psychoactive drug use in evolutionary perspective. Science 1997;278:63-66.
4. Friston KJ, Grasby PM, Bench CJ, Frith CD, Cowen PJ, Liddle PF, Frackowiak RS, Dolan R. Measuring the neuromodulatory effects of drugs in man with positron emission tomography. Neurosci Lett 1992;141:106-10.
5. Andreasen NC. Linking mind and brain in the study of mental illness: A project for a scientific psychopathology. Science 1997;275:1586-1593.
6. Gil Z, Connors BW, Amitai Y. Differential regulation of neocortical synapses by neuromodulators and activity. Neuron 1997;19:679-686.
7. Kaczmarek LK, Levitan IB. Neuromodulation: The biochemical control of neuronal excitability. New York: Oxford University Press 1987.
8. Harris-Warrick RM, Marder E. Modulation of neural networks for behavior. Annual Reviews of Neuroscience 1991;14:39-57.
9. Hasselmo ME. Neuromodulation and cortical function: modeling the physiological basis of behavior. Behavioral Brain Research 1995;67:1-27.
10. Fellous J-M, Linster C. Computational models of neuromodulation. Neural computation 1998;10:771-805.
11. Bernardis LL, Bellinger LL. The dorsomedial hypothalamic nucleus revisited: 1998 update. Proc Soc Exp Biol Med 1998;218:284-306.
12. Lightman SL. Functional anatomy of the neuro-endocrine hypothalamus. Chichester: John Wiley & Sons 1992.
13. Swanson LW. The Hypothalamus. In A. Bjorklund, T. Hokfelt and L.W. Swanson, editors. Handbook of Chemical Neuroanatomy, Integrated Systems of the C.N.S. Amsterdam: Elsevier 1987;1-124.

14. Holsboer F, Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr Rev 1996;17:187-205.
15. Janowsky DS, Rish C, Overstreet DH. Pshychopharmacologic- neurotransmitter-neuroendocrine interactions in the study of the affective disorders. In: Halbreich U, editor. Hormones and Depression. New York: Raven Press 1987;151-160.
16. Prange AJ, Whybrow PC, Loosen PT. Depression and other mental symptoms in endocrine disorders: An overview. In: Uriel H, editor. Hormones and depression. New York: Raven Press 1987;313-324.
17. Malenka RC, Hamblin MW, Barchas JD. Biochemical hypotheses of affective disorders and anxiety. In: Siegel GJ, editor. Basic Neurochemistry: Molecular, Cellular and Medical Aspects. New York: Raven Press 1989;877-891.
18. Cannon WB, Britton SW. Studies on the conditions of activity in endocrine glands. Pseudoaffective medulli-adrenal secretion. American Journal of Physiology 1925;72:283-294.
19. Schildkraut JJ, Kety SS. Biogenic amines and emotion. Science 1967;156:21-30.
20. Olds J. Drives and reinforcements: Behavioral studies of hypothalamic functions. New York: Raven Press 1977.
21. Schultz W, Apicella P, Ljungberg T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. J Neurosci 1993;13:900-13.
22. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science 1997;275:1593-9.
23. Montague PR, Dayan P, Sejnowski TJ. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. Journal of Neuroscience 1996;16:1936-47.
24. Bardo MT. Neuropharmacological mechanisms of drug reward: beyond dopamine in the nucleus accumbens. Crit Rev Neurobiol 1998;12:37-67.
25. Leibowitz SF. Paraventricular nucleus: A primary site mediating adrenergic stimulation of feeding and drinking. Pharmacology Biochemistry and Behavior 1978;8:163-175.
26. Shiraishi T. Noradrenergic neurons modulate lateral hypothalamic chemical and electrical stimulation-induced feeding by sated rats. Brain Research Bulletin 1991;27:347-351.
27. Swanson LW, Lind RW. Neural projections subserving the initiation of a specific motivated behavior in the rat: New projections from the subfornical organ. Brain Research 1986;379:399-403.
28. Bard P. A Diencephalic mechanism for the expression of rage with special reference to the sympathetic nervous system. American Journal of Physiology 1928;84:490-515.
29. Papez JW. A proposed mechanism of emotion. Archive of Neurology and Psychiatry 1937;38:725-744.
30. MacLean PD. Psychosomatic disease and the "visceral brain" (Recent development bearing on the Papez theory of emotion). Psychosomatic Medicine 1949;11:338-353.
31. Devito JL, Smith OA. Afferent projections to the hypothalamic area controlling emotional responses (HACER). Brain Research 1982;252:213-226.
32. Smith OA, DeVito JL, Astley CA. Neurons controlling cardiovascular responses to emotion are located in lateral hypothalamus-perifornical region. American Journal of Physiology 1990;259:R943-R954.
33. Smith OA, DeVito JL. Central neural integration for the control of autonomic responses associated with emotion. Annual Review of Neuroscience 1984;7:43-65.
34. Swanson LW, Sawchenko PE. Paraventricular nucleus: A site for the integration of neuroendocrine and autonomic mechanisms. Neuroendocrinology 1980;31:410-417.
35. Ono T, Nakamura K, Nishijo H, Fukuda M. Hypothalamic neuron involvement in integration of reward, aversion, and cue signals. Journal of Neurophysiology 1986;56:63-79.
36. Kluver H, Bucy PC. "Pshychic Blindness" and other symptoms following bilateral temporal lobectomy in rhesus monkeys. American Journal of Physiology 1937;119:352-353.
37. Weiskrantz L. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. Journal of Comparative Physiology and Psychology 1956;49:381-391.
38. Mishkin M. Memory in monkeys severely impaired by combined but not separate removal of the amygdala and hippocampus. Nature, London 1978;273:297-298.
39. Amaral DG. Memory: Anatomical organization of candidate brain regions. In F. Plum, editor. The Nervous System V. Bethesda, Maryland: American Physiological Society 1987;211-294.
40. Gallagher M, Kapp BS, Musty RE, Driscoll PA. Memory formation: Evidence for a specific neurochemical system in the amygdala. Science 1977;198:423-425.

41. Gallagher M, Kapp BS, McNall CL, Pascoe JP. Opiate effects in the amygdala central nucleus on heart rate conditioning in rabbits. Pharmacology, Biochemistry and Behavior 1981;14:497-505.
42. File SE, Rodgers RJ. Partial anxiolytic action of morphine sulphate following microinjection into the central nucleus of the amygdala in rats. Pharmacology, Biochemistry and Behavior 1979;11:313-318.
43. Gallagher M, Kapp BS. Manipulation of opiate activity in the amygdala alters memory processes. Life Science 1978;23:1973-1978.
44. Lewis ME, Mishkin M, Bragin E, Brown RM, Pert CB, Pert A. Opiate receptor gradients in monkey cerebral cortex: Correspondence with sensory processing hierarchies. Science 1981;211:1166-1169.
45. Hayashi M, Oshima K. Neuropeptides in cerebral cortex of macaque monkey (Macaca fuscata fuscata): Regional distribution and ontogeny. Brain Research 1986;364:360-368.
46. Roberts GW. Neuropeptides: Cellular morphology, major pathways, and functional considerations. In J.P. Aggleton, editor. The Amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction, New York: Wiley-Liss 1992;115-142.
47. LeDoux JE. Systems and synapses of emotional memory. In: Squire LR, Weinberger NM, Lynch G and McGaugh JL, editors. Memory: Organization and locus of change, Oxford: Oxford University Press 1991;205-216.
48. LeDoux JE. Emotion, memory and the brain. , *Scientific American*, 1994, pp. 50-57.
49. Davis M. The Role of the amygdala in fear and anxiety. Annual Review of Neuroscience 1992;15:353-375.
50. Aggleton JP, Mishkin M. The Amygdala: Sensory gateway to the emotions. In: Plutchick R and Kellerman H, editors. Biological foundations of emotion. New York: Academic Press 1986;281-300.
51. LeDoux JE, Cicchetti P, Xagoraris A, Romanski LR. The lateral amygdaloid nucleus: Sensory interface of the amygdala in fear conditioning. The Journal of Neuroscience 1990;10:1062-1069.
52. Swanson LW, Petrovich GD. What is the amygdala? Trends in the Neurosciences 1998;21:323-331.
53. Pitkanen A, Savander V, LeDoux JE. Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. Trends in the Neurosciences 1997;20:517-523.
54. Amaral DG, Price JL, Pitkanen A, Carmichael TS. Anatomical organization of the primate amygdaloid complex. In J.P. Aggleton, editor. The Amygdala, New York: Wiley-Liss 1992;1-66.
55. Quirk GJ, Repa C, LeDoux JE. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. Neuron 1995;15:1029-39.
56. Romanski LM, LeDoux JE. Equipotentiality of thalamo-amygdala and thalamo-cortico-amygdala circuits in auditory fear conditioning. Journal of Neuroscience 1992;12:4501-9.
57. LeDoux JE. Sensory Systems and Emotion: A Model of affective processing. Integrative Psychiatry 1986;4:237-248.
58. LeDoux JE Cognitive-Emotional interactions in the brain. Cognition and Emotion 1989;3:267-289.
59. Phillips RG, LeDoux JE. Differential contribution of the amygdala and hippocampus to cued and contextual fear conditioning. Behavioral Neuroscience 1992;106:274-285.
60. McGaugh JL, Cahill L. Interaction of neuromodulatory systems in modulating memory storage. Behavioral Brain Research 1997;83:31-8.
61. Gasbarri A, Introini-Collison IB, Packard MG, Pacitti C, McGaugh JL. Interaction of cholinergic-dopaminergic systems in the regulation of memory storage in aversively motivated learning tasks. Brain Research 1993;627:72-8.
62. McGaugh JL. Affect, Neuromodulatory Systems, and Memory Storage. In S-A. Christianson, editor. The Handbook of Emotion and Memory: Research and Theory, Hillsdale, New Jersey: Lawrence Erlbaum Associates 1992;245-268.
63. McGaugh JL, Introni-Collison IB, Cahill L, Kim M, Liang KC. Involvement of the Amygdala in Neuromodulatory Influences on Memory Storage. In: Aggleton JP, editor. The Amygdala: Neurobiological sspects of emotion, memory, and mental dysfunction, New York: Wiley-Liss 1991;431-451.
64. Cahill L, Prins B, Weber M, McGaugh JL. Beta-adrenergic activation and memory for emotional events. Nature 1994;371:702-4.
65. Packard MG, Cahill L, McGaugh JL. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. Proc Natl Acad Sci U S A 1994;91:8477-81.
66. Karli P. Cognition, mémoire, affféctivité. Agressologie 1990;31:587-590.

67. Fuster JM. The Prefrontal Cortex: Anatomy, physiology, and neuropsychology of the frontal lobe. Second edn. New York: Raven Press 1989.
68. Mesulam MM, Mufson EJ, Levey AI, Wainer BH. Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in the rhesus monkey. The Journal of Comparative Neurology 1983;214:170-197.
69. Inoue M, Oomura Y, Nishino H, Aou S, Sikdar SK, Hynes M, Mizuno Y, Katabuchi T. Cholinergic role in monkey dorsolateral prefrontal cortex during bar-Press feeding behavior. Brain Research 1983;278:185-194.
70. Inoue M, Oomura Y, Aou S, Nishino H, Sikdar SK. Reward related neuronal activity in monkey dorsolateral prefrontal cortex during feeding behavior. Brain Research 1985;326:307-312.
71. Vincent SR. Neuropeptide coexistence in the mammalian forebrain. In V. Chan-Palay and S.L. Palay, editors. Coexistence of neuroactive substances in neurons. New-York: John Wiley & Sons 1984;127-135.
72. Jones EG, Hendry SHC. Co-Localization of GABA and neuropeptides in neocortical neurons. Trends in Neuroscience 1986;9:71-76.
73. Hokfelt T, Rehfeld JF, Skirboll L, Ivemark B, Goldstein M, Markey K. Evidence for coexistence of dopamine and CCK in meso-limbic neurones. Nature 1980;285:476-8.
74. Brown RM, Crane AM, Goldman PS. Regional distribution of monoamines in the cerebral cortex and subcortical structures of the rhesus monkey: Concentrations and in vivo synthesis rates. Brain Research 1979;168:133-150.
75. Glowinski J, Tassin JP, Thierry AM. The Mesocortico-prefrontal dopaminergic neurons. Trends in Neurosciences 1984;7:415-418.
76. Bannon MJ, Roth RH. Pharmacology of mesocortical dopamine neurons. Pharmacological Reviews 1983;35:53-68.
77. Mora F, Ferrer JMR. Neurotransmitters, pathways and circuits as the neural substrates of self-stimulation of the prefrontal cortex: Facts and speculations. Behavioural Brain Research 1986;22:127-140.
78. Cohen PR, Perrault CR. Elements of a plan-based theory of speech acts. Cognitive Science 1979;3:177-212.
79. Kety SS. The hypothetical relationships between amines and mental illness; A critical synthesis. In H.E. Himwich, S.S. Kety and J.R. Smythies, editors. Amines and schizophrenia. Oxford: Pergamon Press 1967;271-277.
80. Servan-Schreiber D, Printz H, Cohen JD. A network model of catecholamine effects: gain, signal-to-noise ratio, and behavior. Science 1990;249:892-5.
81. MacLean PD. The Triurne Brain in Evolution: Role in paleocerebral functions. New York and London: Plenum Press 1990.
82. Vincent J-D. The Biology of Emotions. Cambridge: Basil Blackwell 1990.
83. Jacobsen CF. Functions of frontal association area in primates. Archives of Neurological Psychiatry 1935;33:558-569.
84. Goldman-Rakic PS. Regional and cellular fractionation of working memory. Proc Natl Acad Sci U S A 1996;93:13473-80.
85. Fuster JM. Behavioral Electrophysiology of the prefrontal cortex of the primate. In: Uylings HBM, Van Eden CG, De Bruin JPC, Corner MA and Feenstra MGP, editors. The prefrontal cortex: Its structure, function and pathology, Vol. 85. Amsterdam: Elsevier 1990;313-324.
86. Brutowski S. Functions of prefrontal cortex in animals. Physiological Reviews 1965;45:721-746.
87. Butter CM, Mc Donald JA. Orality, preference behavior, and reinforcement value of nonfood object in monkey with orbital frontal lesions. Science 1969;164:1306-1307.
88. Van Hoesen GW, Pandya DN, Butters N. Some connections of the enthorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. II. Frontal lobe afferents. Brain Research 1975;95:25-38.
89. Swanson LW, Mogenson GJ. Neural mechanisms for the functional coupling of autonomic, endocrine and somatosensory responses in adaptive behavior. Brain Research Reviews 1981;3:1-34.
90. Chavis DA, Pandya DN. Further observations on corticofrontal connections in the rhesus monkey. Brain Research 1976;117:369-386.
91. Krettek JE, Price JL. The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. Journal of Comparative Neurology 1977;171:157-192.
92. MacLean PD. Some psychiatric implications of physiological studies on frontotemporal portion of the limbic system (visceral brain). Electroencephalography and Clinical Neurophysiology 1952;4:407-418.
93. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain 1995;118:279-306.

94. Thorpe SJ, Rolls ET, Maddison S. The orbitofrontal cortex: Neuronal activity in the behaving monkey. Experimental Brain Research 1983;49:93-115.
95. Rolls E. A theory of Emotion, and its application to understanding the neural basis of emotion. In Y. Oomura, editor. Emotions: neuronal and chemical control. Krager 1986;325-344.
96. Morgan MA, Romanski LM, LeDoux JE. Extinction of emotional learning: contribution of medial prefrontal cortex. Neuroscience Letters 1993;163:109-13.
97. Milner B. Effects of different brain lesions on card sorting: The role of the frontal lobes. Archives of Neurology 1963;9:90-100.
98. Milner B, Petrides M. Behavioural effects of frontal-lobe lesions in man. Trends in Neurosciences 1984;7:403-407.
99. Nauta WJH. The problem of the frontal lobe: A reinterpretation. Journal of Psychiatric Research 1971;8:167-187.
100. Fuster JM. Behavioral Electrophysiology of the prefrontal cortex. Trends in Neurosciences 1984;7:408-414.
101. Damasio AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci 1996;351:1413-20.
102. Gray JA. Neural systems, emotion and personality. In: J. Madden IV, Neurobiology of Learning, Emotion and Affect, New York: Raven Press 1991;273-306.
103. Brady JV, Nauta WJH. Subcortical mechanisms in emotional behavior: Affective changes following septal forebrain lesions in the albino rat. Journal of Comparative Physiological Psychology 1953;46:339-346.
104. Lang PJ, Bradley MM, Cuthbert BN. A motivational analysis of emotion: reflex-cortex connections. Psychological Science 1992;3:44-49.