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A review of systems and networks of the limbic forebrain/limbic midbrain

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Abstract

Evolutionarily older brain systems, such as the limbic system, appear to serve fundamental aspects of emotional processing and provide relevant and motivational information for phylogenetically more recent brain systems to regulate complex behaviors. Overall, overt behavior is, in part, determined by the interactions of multiple learning and memory systems, some seemingly complementary and some actually competitive. An understanding of limbic system function in emotion and motivation requires that these subsystems be recognized and characterized as extended components of a distributed limbic network. Behavioral neuroscientists face the challenge of teasing apart the contributions of multiple overlapping neuronal systems in order to begin to elucidate the neural mechanisms of the limbic system and their contributions to behavior. One major consideration is to bring together conceptually the functions of individual components of the limbic forebrain and the related limbic midbrain systems. For example, in the rat the heterogeneous regions of the prefrontal cortex (e.g., prelimbic, anterior cingulate, subgenual cortices and orbito-frontal areas) make distinct contributions to emotional and motivational influences on behavior and each needs consideration in its own right. Major interacting structures of the limbic system include the prefrontal cortex, cingulate cortex, amygdaloid nuclear complex, limbic thalamus, hippocampal formation, nucleus accumbens (limbic striatum), anterior hypothalamus, ventral tegmental area and midbrain raphé nuclei; the latter comprising largely serotonergic components of the limbic midbrain system projecting to the forebrain. The posterior limbic midbrain complex comprising the stria medullaris, central gray and dorsal and ventral nuclei of Gudden are also key elements in the limbic midbrain. Some of these formations will be discussed in terms of the neurochemical connectivity between them. We put forward a systems approach in order to build a network model of the limbic forebrain/limbic midbrain system, and the interactions of its major components. In this regard, it is important to keep in mind that the limbic system is both an anatomical entity as well as a physiological concept. We have considered this issue in detail in the introduction to this review. The components of these systems have usually been considered as functional units or 'centers' rather than being components of a larger, interacting, and distributed functional system. In that context, we are oriented toward considerations of distributed neural systems themselves as functional entities in the brain.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine; CRH, corticotrophin-releasing hormone; GABA, gamma-amino-butyric acid; LF/LM, limbic forebrain/limbic midbrain; LTP, long-term potentiation; PFC, prefrontal cortex

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1. Introduction

The focus of this review centers on the neurochemical networks of the limbic forebrain/limbic midbrain (LF/LM) complex (Nauta, 1958; Nauta and Domesick, 1981, 1976) and summarizes the organization of the major neuronal circuits and networks of the distributed limbic brain. It also attempts to bring back into focus the overall concept of the distributed limbic system which has been the subject of considerable debate in recent years (Poletti, 1986; Isaacson, 1992, 1993; Blessing, 1997; Hebert, 1997; Spyer, 1997; Swanson and Petrovich, 1998). Specific structures, both cortical and subcortical, comprising the LF/LM complex will be related to each other and to the entire limbic system as a whole. Descriptions of the LF/LM complex to date have generally lacked an integrated systems approach and have not been considered in terms of the extended LF/LM complex, which now needs a clearer delineation and definition.

We are not intending to discuss in detail the varied concepts of the limbic system or to argue its precise role in understanding the various functions and mechanisms of emotion. The continued usefulness of the limbic system concept and its empirical foundations have been reviewed by Poletti (1986), Kötter and Meyer (1992), and Kötter and Stephan (1997). Isaacson and others appear to have abandoned the limbic system concept on what we feel are highly insufficient grounds (Isaacson, 1980, 1992; Blessing, 1997; Hebert, 1997; Spyer, 1997; Swanson and Petrovich, 1998). It has long been known that the limbic system primarily expresses its functions in the form of states of affect and motivation. These psychological states are not unitary events and are themselves difficult to define and functionally dissect but such approaches are eventually necessary for a better understanding of the many components of limbic function.

One cannot possibly discuss the organization and function of the distributed limbic system without defining all of its major cortical and subcortical components and its widespread extensions (distributed limbic nuclear formations and systems). Broca's original ''limbic lobe'' was described as a cortical ring surrounding the hilus of the hemispheres (Broca, 1878). For most of the last century, workers thought of the limbic lobe as primarily ''cortical'' until it became obvious that many major nuclei were also limbic (e.g., amygdaloid complex, hippocampal formation). The limbic system was first defined by Pierre Paul Broca (1878) and we have translated his statement as follows: ''the name of gyrus cinguli I have adopted indicates the constant connections of this convolution with the limbus of the hemisphere; it implies no theory whatsoever; because it does not indicate a specific shape; it applies to all mammal brains, to those which have a true corpus callosum as much as to those which have no corpus callosum or a rudimentary one (Owen's lyencephala), to those which have a real olfactory lobe, as much as to those with a vestigial olfactory lobe. Finally, it can be conveniently used to designate without changing the adjective the parts that are contained in the description of this convolution: the great limbic lobe, the limbic fissure, the superior or inferior limbic arch''.

Functional studies by Klüver and Bucy (1937, 1938, 1939) began to elucidate complex emotions and motivational processes associated with the limbic lobe. MacLean (1949, 1954), in particular, termed the cortical and subcortical systems and their fiber hookups as the ''limbic system'' implying a series of major subcortical limbic structures interrelated with limbic nuclei passing to the basal forebrain and comprising a major formation he termed the ''triune brain'' in evolution (MacLean, 1990). The Klüver–Bucy syndrome has been at the forefront of limbic biology since 1937 (Klüver and Bucy, 1937, 1938, 1939). Bilateral temporal lobectomy in monkeys produced visual agnosia,

oral tendencies, hypermetamorphosis, and marked changes in emotional behavior, changes in dietary habits and altered sexual behavior. In psychic blindness or visual agnosia, the animal is unable to recognize the nature and meaning of objects. The oral tendencies indicate a strong desire to examine every object by mouth and to smell it. In hypermetamorphosis there is a compulsion to attend and react to every visual stimulus. The emotional changes involve diminished anger and fear, basically showing tameness in the face of danger. Sexual behavior involves increased amounts and varieties of sexual behavior, including homosexual and heterosexual behavior. Finally, the change in dietary habits involves monkeys eating meat and large quantities of food.

In subsequent years, considerable effort was made to fractionate the Klüver–Bucy syndrome, attempting to produce only one or a few of the components by less extensive or differently situated lesions which, as noted by Klüver (1958), has been fraught with considerable inconclusive results. For example, Schreiner and Kling (1953) found primarily hypersexuality after bilateral amygdalectomy and Morgane and Kosman (1957a, 1957b) found hyperphagia and obesity. Klüver and Bucy found on histological study that temporal association cortex was removed as well as the amygdaloid complex and hippocampus and, importantly, the fornix was severely damaged. Thus, a key part of the circuit of Papez (see further) was involved in these temporal lobectomies. Klüver and Bucy never attempted to localize their behavioral findings to specific neuroanatomical substrates. However, a considerable discussion of damaged structures with histology was described by Klüver (1951) and Bucy and Klüver (1955). The idea that fractionation of the syndrome is possible must rest on a behavioral analysis demonstrating conclusively that a particular sign, when independently produced, is the same as the symptom appearing in a complex or aggregate of other symptoms (Klüver, 1958).

Nauta (1958, 1986) and Nauta and Domesick (1981) studied the limbic system using silver degeneration techniques and found that the limbic forebrain structures projected preferentially to areas of the paramedian midbrain they termed the limbic midbrain area. They also emphasized the hypothalamus to be a component of the limbic system although historically that was not usually typical. However, even with limbic functions as related to emotion and motivation it is impossible not to consider the hypothalamus as a key part of the extended limbic system and, hence, it must be included as a critical component of the limbic system.

At the time of Nauta's classic paper on the LF/LM system (Nauta, 1958), little was known of the chemical pathways comprising major components of the limbic system. A brief summary of these follows. Major discussions of these pathways, particularly as related to prefrontal cortex, have been provided by Bronstein and Cummings (2001). Some emphasis here is on the limbic/prefrontal cortex relations since these are associated with numerous behavioral alterations when damaged (circuit-specific behavior syndromes). The serotonergic, dopaminergic, and noradrenergic pathways in the medial forebrain bundle are well known. There has been some neglect of the cholinergic, GABAergic and glutaminergic pathways, as well as the role of neuropeptides in the limbic system. Descending cholinergic fibers arise from the nucleus basalis and amygdaloid complex while ascending cholinergic fibers project in medial forebrain bundle to the frontal cortices including the medial prefrontal cortex and are thought to modulate the thalamo-cortical input.

Heavy 5-HT input to the medial prefrontal cortex is well known, terminating largely on GABA interneurons. As noted by Bronstein and Cummings (2001), 5-HT appears to be involved in disorders characterized by poor impulse control (e.g., homicidal and suicidal behavior). In fronto-subcortical circuits and basal ganglia several neuropeptide pathways are seen including enkephalin, neurotension, dynorphin and substance P. Their precise functions are yet to be determined. As noted also by Bronstein and Cummings (2001) and Lichter and Cummings (2001), fronto-subcortical circuits are major organizational networks in the brain, which are involved in many brain–behavior relations. They appear to unite specific areas of frontal cortex with the basal ganglia and mediodorsal and other limbic thalamic nuclei.

As noted, the origins of the limbic structural concept go back to Broca (1878) and, more recently, to MacLean (1949, 1954). It has become obvious from the key functional studies of Klüver and Bucy (1938, 1939) and the theoretical anatomical presumptions of Papez (1937) that the limbic system plays a major role in emotional and motivational activity and other basic psychological functions of the brain. The central emotive process of cortical origin was conceived by Papez (1937) on anatomical grounds to be built up in the hippocampal formation and then transferred to the mamillary body and, through the anterior thalamic nuclei (limbic thalamus), to the cingulate gyrus as the receptive region for experiencing of emotion as the result of impulses from the hypothalamus. He noted that the physiologic results of other investigators imply that the emotion process is mediated, in part, by the hypothalamus. Further, he thought of emotion as a physiologic process, which depends on an anatomical mechanism and substrate.

Papez thus proposed that the hypothalamus, anterior thalamic nuclei, cingulate gyrus and hippocampus and their interconnections constitute a harmonious mechanism, which elaborates the functions of central emotion as well as participating in emotional expression. He proposed that this mechanism is a unit within the larger architectural mosaic of the brain. Obviously emotion is such an important function that its mechanism(s) should be placed on a structural basis and Papez was the first to propose such an emotional circuit. Interestingly, Papez did not attempt to disrupt this circuit and study emotional changes. The limbic system comprises both

cortex and subcortical systems including the hippocampal formation, amygdaloid complex of nuclei, hypothalamus, nucleus accumbens, cingulate cortex, ventral tegmental area, major areas of the prefrontal cortex and limbic midbrain areas. The term ‘‘limbic brain’’ encompasses these formations and their distributions to forebrain, midbrain and hypothalamus. In particular, it also encompasses significant medial components of the midbrain including the nucleus raphé dorsalis, nucleus raphé medianus, central gray, and dorsal and ventral nuclei of Gudden. These formations are strongly interconnected, usually by reciprocal pathways, e.g., reciprocal limbic forebrain/limbic midbrain loops (Fig. 1). Nauta (1958) showed that large areas of the midbrain and posterior midline brainstem receive especially strong limbic forebrain projections, hence the term ‘‘limbic midbrain area’’. In MacLean’s (1949) and Nauta’s (1958) important concepts, the limbic system was defined as a heterogeneous group of medial and basal telencephalic structures, together comprising that part of the cerebral hemisphere which is most directly related to the hypothalamus (Nauta and Domesick, 1981). We present here an overview of these systems including ideas on how far into the brainstem the descending limbic ramifications actually go. In Fig. 1, we have concentrated only on a part of this system extending to the midbrain raphé (anterior limbic midbrain area). It is clear that the midbrain part of this continuum comprises the ventral tegmental area, the ventral half of the central gray substance, the median and dorsal raphé and the ventral and dorsal tegmental nuclei of Gudden, all of these comprising the limbic midbrain area of Nauta (1958). Since this represents reciprocal relation to the limbic forebrain area it forms the limbic forebrain/limbic midbrain circuit. Morgane et al. (1982) provided a quantitative cytoarchitectonic analysis of the limbic lobe indicating a wide diversity of limbic fields and presumably functional domains. Heimer (2003) recently provided an extensive summary of many of the primary pathways of the limbic brain and added new insights into the limbic system and its

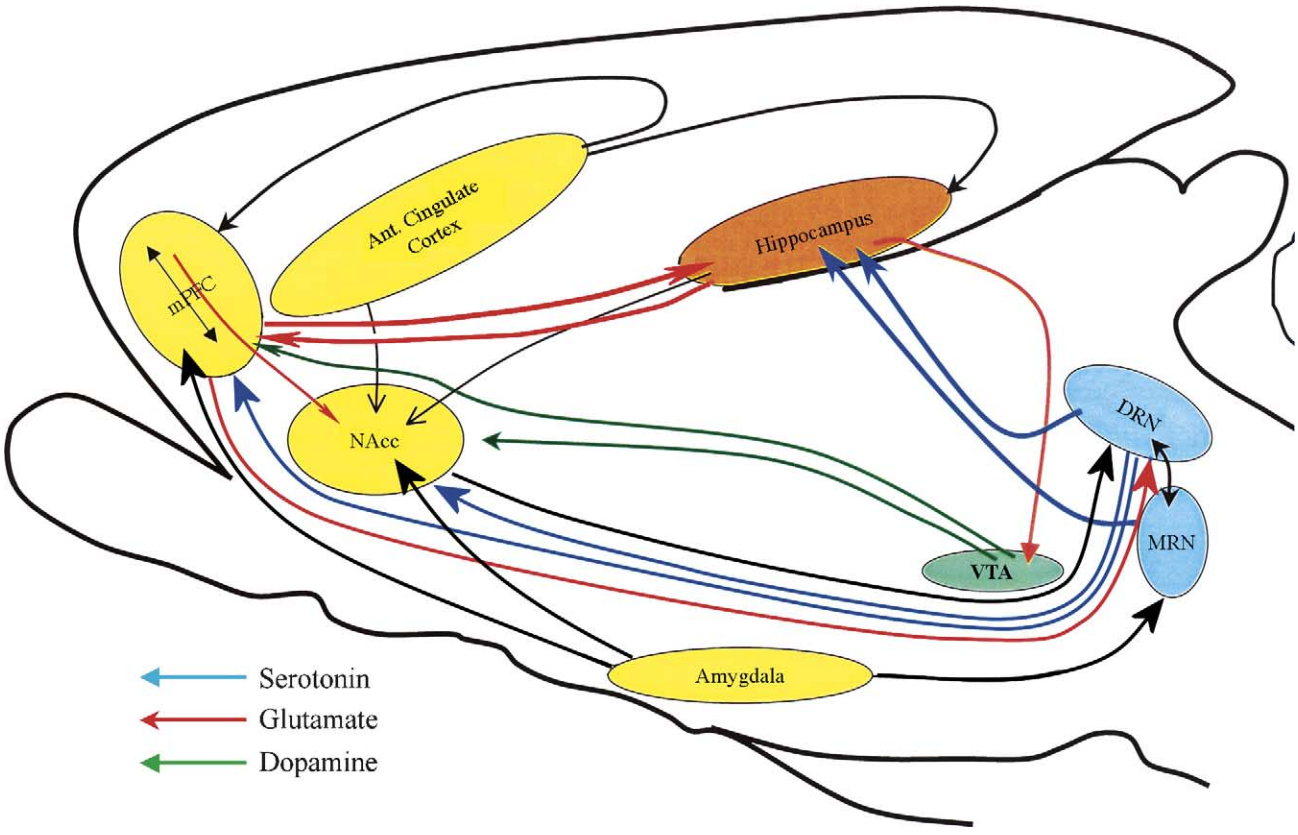

Fig. 1. Schema of the principal neuron systems in the limbic forebrain and anterior part of the limbic midbrain (midbrain raphé and ventral tegmental area). There is considerable interaction of these systems forming networks involved in numerous limbic functions. So-called psychological functions form, as a group, a behavioral substrate of these limbic forebrain/limbic midbrain systems. Note inputs to midbrain raphé related to control of serotonergic activity in the forebrain. There is functional coherence of these components in learning and memory (e.g., multiple learning and memory systems). Note frontal model part of these systems involving the medial prefrontal cortex. This cortex is generally divisible into a dorsal and ventral component with each showing multiple cytoarchitectonic areas. Not shown are the septal area and inputs from the mediodorsal thalamic nucleus (limbic thalamus). Similarly, the posterior components of the limbic midbrain areas (central gray, ventral and dorsal nuclei of Gudden and insula) are not shown. The reciprocity indicated between the nuclei raphé dorsalis and medianus are tentative although Dugal et al. (2003) have begun to examine these relations. Select chemical pathways relating to this review are emphasized. mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; VTA, ventral tegmental nucleus; DRN, dorsal raphé nucleus; MRN, median raphé nucleus.

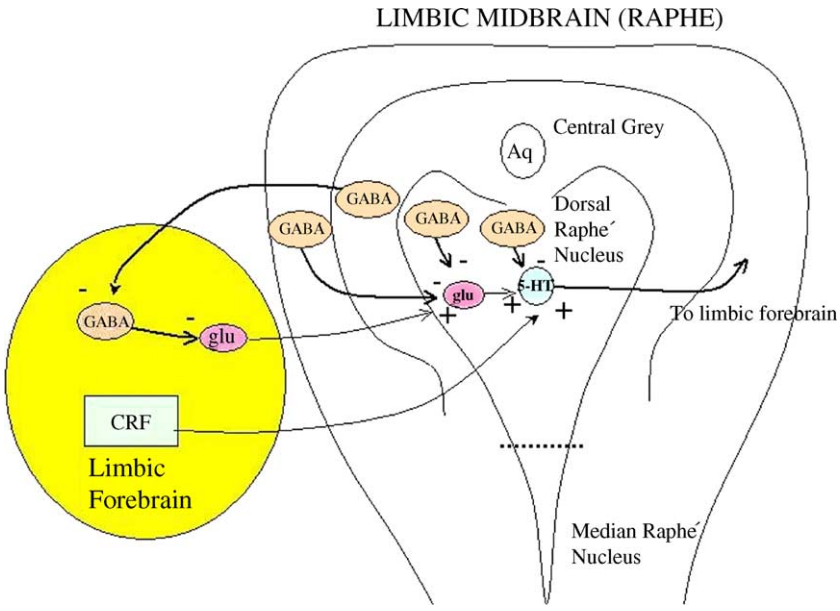

Fig. 2. Schema of organization of dorsal raphé nucleus and interactions of GABA, glutamate and serotonergic neurons. GABA in raphé nuclei directly inhibits serotonin activity and/or 5-HT functions by inhibiting glutamate activity. Excitatory neurons from limbic forebrain may also directly activate serotonergic neurons or GABA interneurons in the raphé.

extended subsystems. More recently, various questions have been raised (Poletti, 1986; Isaacson, 1992, 1993; Blessing, 1997; Hebert, 1997; Spyer, 1997; Swanson and Petrovich, 1998) as to how morphologically dissimilar basal telencephalic structures and their projection areas came to be grouped into a unitary concept termed the limbic system. Some of the basis of this is discussed further.

MacLean (1949, 1954) re-emphasized that the cortical formations of the limbic system surround the limbus (or border) of the hemisphere. He provided a unifying evolutionary concept and termed these cortical and subcortical nuclei in toto as the ''limbic system''. In his 1958 paper, Nauta stressed its powerful interconnectivity with the hypothalamus (Nauta, 1958). This review seeks to assess the limbic complex as a whole, summarizing aspects of its organization and certain functions in a broad overview approach.

MacLean's earlier works (MacLean, 1949, 1954) pointed out the evolutionary history of the limbic system leading to new views of the organization of this remarkable part of the

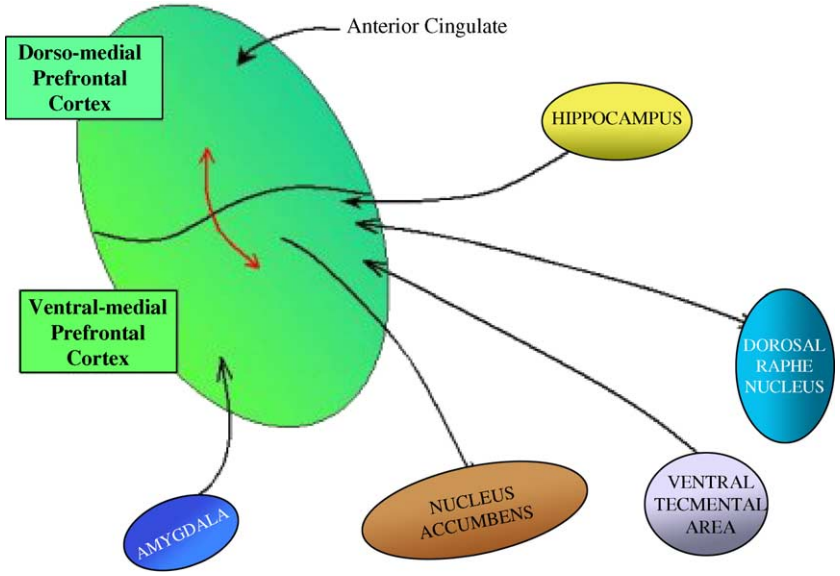

Fig. 3. Schema illustrating select pathways of the dorsal and ventral medial prefrontal cortex. This model cortex is a key region for limbic system functions (see text).

brain. Panksepp (1998), in particular, has provided excellent reviews of the limbic complex and has discussed how MacLean's theories have enlightened modern aspects of the limbic brain. His forward in the book dedicated to MacLean (Panksepp, 2004) argues strongly in favor of MacLean's triune brain concepts with which we largely agree. Accordingly, we argue that studies confined to single complexes in the limbic system (e.g., the amygdaloid complex of nuclei) cannot alone provide sufficient data needed to understand the fundamental workings of the limbic system (LeDoux, 2000).

Most of our studies to date have focused on the hippocampal formation and some select distributed neural systems innervating (usually reciprocally) other formations of the limbic forebrain and raphé nuclei of the midbrain (Mokler et al., 1998, 1999, 2003). The hippocampus, in turn, has extensive, strong connections with prefrontal cortex, anterior cingulate cortex, nucleus accumbens and amygdaloid nuclei forming a larger network that also encompasses the raphé nuclei in the midbrain (Fig. 1). Specific functions of many of these substructures are not unitary and are difficult to precisely identify, but in this overview we attempt to bring some cohesion to these distributed systems and illustrate their potential interactions as a larger and distributed functional complex (Figs. 1–3). Clinically, it is of interest that some of the major forms of psychosis (e.g., schizophrenia) are associated with malfunction of these sub-networks of the limbic system (Dolan, 2002).

2. General aspects of some neuronal formations of the limbic brain

It now seems probable that attempts to assign specific "functions" having any physiological significance to limbic system structures such as the hippocampal formation, amygdaloid complex, prefrontal cortex and nucleus accumbens, among others, are likely to fail since psychological functions are performed in the limbic brain not by single formations but by complexes of interacting systems. Activity of limbic structures can be understood largely in the context of the action of the entire interacting system to which they belong. Before we can arrive at an understanding of the psychological correlates of the assorted physiological data, it is necessary to form a general concept of how the limbic system is organized. We show a working outline of several major limbic subsystems in Fig. 1. We particularly need to know what its several component parts are and, especially, how they may be functionally interconnected. Overall, the limbic brain appears in general to be organized less in terms of precise physiological functions than in terms of elaboration and coordination of varied complexes of behavior.

In general, physiological methods of studying interconnectivity are based on both observation, i.e., simultaneously observing the responses of neuronal assemblies in different parts of a network, and direct intervention, i.e., observing the effect of disrupting neuronal activity in sites remote from the disruption. In this regard, mammalian brain organization is largely based on two complementary principles: the first of these is modularity which is the specialization of function in different loci of the brain, with local assemblies of neurons in each area performing their own unique operations on their inputs (Ramnani et al., 2002). The second of these is that complex functions, such as learning and memory, are emergent properties of interacting brain areas within networks. Complex traits such as intelligence, memory, learning and personality surely cannot be specifically localized or "represented" as a "locus" but rather are emergent properties of activity in coherent and distributed functional systems. In other words, these traits are thought to reflect cellular and integrative functions, ensembles, or functional networks. Accordingly, these general principles lend themselves to two corresponding approaches to explaining function. One of these is functional segregation, which aims to localize functions to specific cellular aggregations, particularly nuclear assemblies. Until recently, this has been the most common approach. The other is functional integration in which function is interpreted in terms of the flow of information between different brain areas. Recently, there has been more focus on the distributed nature of information processing in the limbic brain (Roberts, 1966; Kötter and Meyer, 1992). The challenge here has been to understand brain function in terms of the dynamic flow of information in well-defined neuronal networks. Accordingly, in this latter approach we have begun assessing this flow in specific neuronal networks that interact in terms of memory, addiction, stress and plasticity, as well as involving the 5-HT, dopamine, norepinephrine, GABA, glutamate and acetylcholine neurotransmitter systems, which have all been shown to play major roles in vigilance states, reward and in regulation of hippocampal–septal activity. It has proven impossible to predict the rich behavior of the entire limbic forebrain and midbrain by merely extrapolating from the behavior of its individual components. Clearly, it seems more fruitful to develop concepts of how selected limbic forebrain and midbrain systems can be brought together anatomically, physiologically and conceptually. In this way, dysregulation following neuronal insults can be better interpreted in terms of dysfunction in specific systems.

In systems analysis, we proceed from individual functional "centers" to larger dynamic neural networks (functional wholes or ensembles). Thus, attempts are made to develop a functional scaffold within which to better interpret limbic functions of plasticity, stress, vigilance states, memory and affective behavior in terms of neurotransmitter function in selected networks (which, for example, can be examined by dual probe microdialysis as in our recent studies (Hoffman et al., 2003; Dugal et al., 2003). M ultiple neurotransmitter systems are involved, and by

examining the integrity of these systems we can better understand overall disruptions of excitatory/inhibitory balances, which may be the essential common denominators for perturbations seen following systemic insults to the brain. For example, various studies show that memory involves multiple brain systems representing multiple types of intelligence (Squire and Zola-Morgan, 1991; Thompson and Kim, 1996), and components of these systems need to be identified and examined in order to assess how manipulating one component affects neuronal activity in interrelated areas.

We now summarize some key issues as to limbic systems functions within the components noted earlier. A model of such an extended functional system is proposed as a cornerstone for examining the limbic system complex (Fig. 1). Overall, this approach should help in developing new theories about the functions of the limbic system and to define its components, connectivity and borders. Hopefully, this should help resolve some of the ''mysteries'' about the greater limbic brain (distributed limbic systems).

2.1. Hippocampal formation

Important to discussions of this LF/LM model system is the role of the hippocampal formation and its theta oscillations in overall function of this extended limbic network. One major question is to determine how theta oscillations group and segregate neuronal assemblies and ''assign'' various computational tasks to them (Buzsaki, 2002). Theta oscillations certainly appear to represent the ''on-line'' or ''ready'' state of the hippocampus (Vertes and Kocsis, 1997). These oscillations are the result of coordination of neuronal networks and result in the modification of synaptic connections (synaptic plasticity) within the hippocampal formation. It has been found that tetanus stimulation patterned after endogenous theta rhythms is the most effective stimulus for inducing long-term potentiation (LTP), a model of neuroplasticity (Larson et al., 1986). Thus, endogenous theta rhythms appear to contribute to the induction of LTP. It has also been reported that exposure to inescapable shock (stress), but not escapable shock, results in a significant decrease in endogenous theta rhythms (Balleine and Curthoys, 1991). Further, a variety of studies show that theta rhythm appears to be critically involved in memory processing functions of the hippocampus (Buzsaki, 2002). Disruption of theta suppresses LTP and memory in part, which may be related to enhanced inhibition which we have previously reported in paired-pulse studies of the hippocampal formation (Bronzino et al., 1996a, 1996b, 1997, 1999).

Based on a systems analysis of various limbic pathways and circuits, we have become aware of the remarkable overlap and interdigitation of common limbic pathways related to learning and memory, stress, addiction, vigilance states and their powerful links with the hippocampal formation. The fact that vigilance states, plasticity, degree of inhibition and theta activity are all impacted by neonatal insults such as prenatal malnutrition (Morgane et al., 1992, 1993, 2002) indicates that these select pathways need to be studied as an interacting group using systems approaches, such as dual-probe in vivo and reverse microdialysis. Although our group has recently concentrated on the hippocampal formation, we are now beginning to assess pathology in these other limbic forebrain areas such as the prefrontal cortex. Also, their trajectories to the raphé nuclei and other select lower brainstem limbic projection areas such as the ventral tegmental area and nuclei of Gudden (a probable termination of the LF/LM system (Nauta, 1958)) need to be examined in the context of the distributed limbic system.

2.2. Medial prefrontal cortex

The prefrontal cortex (PFC) is a heterogeneous region of the brain of the rat that includes the prelimbic cortex, infralimbic cortex, anterior cingulate cortex and agranular insular cortices as well as orbito-frontal areas, among other subfields (Zilles and Wree, 1995; Cardinal et al., 2002; Heidbreder and Groenewegen, 2003) (Fig. 3). Each of these subregions of the PFC appears to make individual contributions to emotional and motivational influences on behavior (Zilles and Wree, 1995; LeDoux, 2000). The prefrontal cortex has complex functions such as working memory as well as attention, cognition, emotion and executive control (Damasio et al., 1994; Roberts et al., 1998; Goldman-Rakic, 1999; Varga et al., 2001; Yamasaki et al., 2002). The prefrontal cortex also regulates behavioral inhibition (Mishkin, 1964; Roberts et al., 1998) with different specific aspects of inhibition being mediated by different regions within the prefrontal cortex (Dias et al., 1996, 1997).

The anterior cingulate cortex projects to the nucleus accumbens core via glutaminergic projections (Cardinal et al., 2002) and is part of the midline prefrontal cortex that has been implicated in emotional processing (Neafsey et al., 1993; Öngür and Price, 2003) (Fig. 1). Additional descending projections from prefrontal cortex to nucleus accumbens, amygdala and other limbic brain regions appear to exert regulatory control over reward-seeking behavior. Importantly, the prefrontal cortex has now been shown to be divisible into dorsal and ventral divisions (Heidbreder and Groenewegen, 2003). Thus, the ventral part of the medial prefrontal cortex is a key source of raphé afferents (Peyron et al., 1998; Hajos et al., 1998) (Fig. 1). Overall, the medial prefrontal cortex has reciprocal relations with both raphé dorsalis and medianus serotonergic systems (Fig. 1). Evidence is strong that the inhibition of raphé 5-HT neurons elicited by stimulation of the ventral-medial prefrontal cortex is mediated by intra-raphé inhibitory GABA neurons (Fig. 2), (Varga et al., 2001). The findings of Hajos et al. (1998) and Varga et al. (2001) showed that a high proportion

of 5-HT neurons in the raphé nuclei are directly inhibited by medial prefrontal activation. This is one key to limbic 5-HT functional organization (Figs. 2 and 3).

Recent studies suggest that parts of the medial PFC (mPFC) of the rat brain are analogous to the dorsolateral prefrontal cortex of the primate brain. On the basis of both behavioral and anatomical evidence, Kolb (1984) suggested that the medial wall of the prefrontal cortex of the rat brain is generally undifferentiated and that this area may subserve cognitive functions that in the primate are localized more to the dorso-lateral prefrontal cortex. In any event, the mPFC is a key component of the limbic forebrain system with many inputs and outputs, and its heterogeneous cytoarchitectonic structure suggests a complex functional organization.

The prefrontal cortex has also been implicated in a variety of attention, executive and memory operations. For example, attentional and emotional mechanisms appear to be segregated into dissociable prefrontal networks in the brain (Damasio et al., 1994; Goldman-Rakic, 1999; Varga et al., 2001). The reciprocal relationship between dorsal and ventral prefrontal cortex (Fig. 1) may provide a neural substrate for cognitive–emotional interactions, and dysregulation in these systems is clearly related to various mental diseases in this sphere. For this reason alone, unraveling the functional organization of the various limbic subsystems is of particular interest.

Heidbreder and Groenewegen (2003) reported in detail on subdivisions of the prefrontal cortex. The entire wall of the prefrontal cortex shows primary thalamic connections with the mediodorsal thalamic nucleus with distinctions between the dorsal and ventral prefrontal cortices. The subfields of the dorsal prefrontal cortex (dorsal prelimbic and anterior cingulate) and ventral prefrontal cortex (ventral prelimbic and infralimbic prelimbic area) show differential afferent terminations. The dorsomedial prefrontal areas have connections with sensorimotor and association neocortex, while the ventral prefrontal areas do not show these projections, but rather show strong connections with the amygdaloid complex and limbic association cortices. The ventral prefrontal cortices project heavily to the subcortical limbic structures including the hypothalamic areas and septum. Of particular interest, the ventral medial prefrontal cortex shows more powerful influences on brainstem monoaminergic cell assemblies than does the dorsal prefrontal areas. In considering the prefrontal limbic cortex, it is thus crucial to note the many cytoarchitectonic differences in the ventral and dorsal components and respective subfields illustrated partially in Fig. 3.

2.2.1. Thalamo-cortical relations

Reciprocal and topographically organized connections between the medial prefrontal cortex and various thalamic nuclei are well known (Krettek and Price, 1977; Ferron et al., 1984; Sesack et al., 1989; Hurley et al., 1991; Vertes, 2002). A ventral to dorsal gradient in medial prefrontal cortex appears to map onto a medial to lateral gradient in the dorsal thalamus where the medial prefrontal projections primarily involve the midline, mediodorsal and intralaminar thalamus. In general, the cortico-thalamic projections are largely reciprocated by thalamo-cortical fibers. The midline thalamic nuclei appear to be largely involved in arousal and visceral functions while the intralaminar nuclei subserve orienting and attentional aspects of behavior (Van der Werf et al., 2002; Heidbreder and Groenewegen, 2003). The limbic thalamus includes both the anterior thalamus (part of circuit of Papez) and the mediodorsal thalamic nucleus. Both fit the category of limbic forebrain formations. The mediodorsal nucleus is a major element within the thalamus of all mammals and undergoes a progressive expansion of cytoarchitectonic differentiation in higher animals, reaching its greatest development in man (Clark, 1932a, 1932b; Leonard, 1969). Importantly, this development parallels the development of the prefrontal cortex (Krettek and Price, 1977).

Krettek and Price (1977) showed the mediodorsal thalamic nucleus projects to a large area of the frontal cortex in the rat, including the medial precentral area, the anterior cingulate area, the prelimbic area, the ventral and lateral orbital areas, and the dorsal and ventral agranular insular areas. In fact, the orbital frontal cortex is anatomically defined as the projection field of the mediodorsal thalamic nucleus. Projections to insular cortex also help define the insula as part of the extended limbic system. Within a limbic framework, it is important to note that the mediodorsal thalamus is reciprocally related to both the amygdaloidal complex and insula. We previously showed an anatomical continuity between the limbic formations medially and the insula and orbital lobe basolaterally (Jacobs et al., 1984). Yakovlev (1972), in studies of human brain, showed that the insula represents an extension of the limbic lobe into the lateral wall of the hemisphere.

2.2.2. Hypothalamo-cortical relations

Medial prefrontal projections to the hypothalamus originate from ventrally located cortical areas (Sesack et al., 1989; Sesack and Bunney, 1989). Via the hypothalamic projections, the prefrontal cortex has powerful influences on behavioral and various autonomic functions. Floyd et al. (2001) have shown a clear topography in projections of medial prefrontal cortex to highly specific regions of the hypothalamus. Also, reciprocal hypothalamic projections to prefrontal cortex have been described (Saper, 1985). These interconnections appear to play key roles in the functional organization of the limbic forebrain.

2.3. Nucleus accumbens (limbic striatum)

The nucleus accumbens (ventral striatum) plays a key role in limbic neural circuits that are responsible for motivated, goal-directed behaviors (such as those that underlie compulsive drug seeking in cocaine addicts)

(Kelley, 1999; Groenewegen and Uylings, 2000). Various studies have revealed that dopamine innervation of the nucleus accumbens is related to reinforcement and reward as well as actions of addictive drugs and aspects of schizophrenia (Joseph et al., 2003). Many goal-directed behaviors are thought to be regulated by glutamate projections that originate in limbic frontal cortical regions (collectively anterior ''limbic forebrain''), including the basolateral amygdala, the hippocampal formation and the medial prefrontal cortex, which converge on spiny neurons of the nucleus accumbens (Heidbreder and Groenewegen, 2003) (Fig. 1). The output of nucleus accumbens is conveyed through projections to the ventral pallidum, which is likely responsible for motor execution of these goal-directed behaviors. Thus, the nucleus accumbens has been hypothesized as an interface between limbic and motor systems (Nauta and Domesick, 1976; Mogenson et al., 1980; Kelley, 1999; Groenewegen and Uylings, 2000; Heimer, 2003). Ultimately, drug-seeking behavior would appear to depend upon glutamate transmission in the nucleus accumbens (Sesack and Pickel, 1992; DiCiano et al., 2001). Normally, descending projections from prefrontal cortex to nucleus accumbens, as well as other limbic regions, exert inhibitory control over reward-seeking behaviors. As discussed in the review of Vanyukov et al. (2003), the reward systems for different drugs of abuse appear to share similar structures in the limbic brain, such as the mesocorticolimbic dopamine system.

Various features of addiction suggest that it may involve an exceptionally powerful form of limbic neuronal plasticity that can be broadly defined as the ability of the nervous system to modify its response to a stimulus based on prior experience (Wolf, 2002). Plasticity may also underlie addiction, because signaling in the mesolimbic dopamine system, through glutamate, the key neurotransmitter for producing and maintaining synaptic plasticity, is important for the formation of behavioral sensitisation—a notable animal model of addiction (Karler et al., 1989; Wolf and Khansa, 1991). Therefore, behavioral sensitization in addiction appears to be a synonymous process to LTP in learning and memory. At a cellular level, considerable evidence indicates that addiction, and memory and learning are encoded by changes in usage of interneuronal connections (Wolf, 2002; McGaugh, 2002).

2.4. Amygdaloid complex

Although it is now clear that the amygdaloid nuclear complex is involved in many aspects of behavior, stimulation of the amygdaloid complex has revealed no single high-level function (Roberts, 1966), suggesting that its exact function in the overall organization of the limbic system is not unitary. The amygdala has been implicated in numerous aspects of emotional processing including the possible impairment of memory for emotional events (Cardinal et al., 2002). It appears to be critically involved in mediating the effects of stress on hippocampal LTP and hippocampal-dependent memory processes. It is of special interest to characterize the neuroanatomical–neurochemical projections from the amygdaloid complex to the hippocampal formation to further elucidate the modulating mechanisms of stress on neural plasticity and memory. In this regard, there is now evidence of amygdalo-hippocampal interactions in memory formation with the amygdala modulating consolidation of memory by influencing the hippocampus (McGaugh, 2002).

The amygdala as a whole is extraordinarily complex in terms of its internuclear and input–output wiring. Many authors have attempted to divide this complex into clear functional units, largely without clear success. The basolateral amygdala shows extensive reciprocal relations with polysensory neocortex and the frontal lobes and projects strongly to the ventral striatum and prefrontal cortex, where it influences complex behavior (Everitt and Robbins, 1992; Everitt et al., 2000). The central nucleus of the amygdala has widespread projections to the hypothalamus, midbrain reticular formation and other areas of the brainstem to regulate behavioral, autonomic, arousal and neuroendocrine responses (Cardinal et al., 2002). The central nucleus of the amygdala has projections to the nuclei of the reticular formation that, in turn, provide chemically-defined, diffuse projections to the forebrain, e.g., the dopaminergic ventral tegmental area and substantia nigra, the noradrenergic locus coeruleus, the 5-HT raphé nuclei and the basal forebrain cholinergic system. Thus, attentional enhancement and motivational arousal may be conceptualized within the framework of these relations. It seems likely that understanding of the multifold functions of the amygdaloid complex will largely come down to our future understanding of the workings of the internal circuits of the amygdaloid complex (Pitkänen, 2000).

A particular functional relationship of the amygdaloid complex relates to its links with the hypothalamus by the stria terminalis and ventral direct amygdalofugal system. Gloor (1955) stressed that the amygdala acts as a modulator for most behavioral, endocrine and autonomic functions of the hypothalamus. Little wonder, then, that the hypothalamus is a key part of the limbic system.

The complexities of the amygdaloid complex, along with its multiple distributed connections, make assigning single specific functions almost impossible. Its links to the Klüver–Bucy syndrome (Klüver and Bucy, 1938) still attract considerable attention though what its primary role is in overall limbic function remains in doubt. As for substrates of emotion, so usually attached to the limbic system, they are widely distributed and clearly not unitary. As Swanson and Petrovich (1998) noted, the amygdala is neither a structural nor a functional unit: the same can be said of other major limbic structures as well (hippocampal formation, nucleus accumbens, prefrontal cortex). The complexities of the amygdaloid complex is one of the many reasons why some workers have been frustrated by

the components of the functional and anatomical organization of the greater limbic system, but Swanson and Petrovich (1998) and Heimer (2003) have brought the amygdaloid complex into the best anatomical and functional order to date.

2.5. Gudden's nuclei

A relatively neglected area of the limbic midbrain and limbic pons has been what Nauta (1958) first indicated as the probable termini of the limbic forebrain system, i.e., Gudden's ventral and dorsal tegmental nuclei. Anatomy and connections of these nuclei have been extensively studied but not usually in the framework of the limbic systems (Petrovický, 1971, 1972, 1973, 1985a, 1985b; Hayakawa and Zyo, 1983; Irle et al., 1984).

Early on, it was postulated that the two Gudden's nuclei are probably not a functional unit and the types of connections with the limbic systems appear to bear this out. Further, interconnections between the two are minimal (Petrovický, 1972). They both have strong reciprocal interconnections with the medial or lateral mamillary nuclei and thus come in contact with the Papez circuit and other components of the limbic circuitries. Their close relation to the limbic midbrain and forebrain is clear (Irle et al., 1984). Their intimate relations with the ventral half of the central gray and insula have also been demonstrated (Irle et al., 1984). Substantial prefrontal innervations are also of note. Projections from the habenular complex are also prominent.

From a functional point of view, Bassant and Poindessous-Jazat (2001) proposed these nuclei (especially the ventral Gudden's nucleus) may be a pontine generator of hippocampal theta activity. Kocsis et al. (2001) found that neuronal activity in Gudden's nuclei exhibits strong vigilance-state dependant synchrony with the rhythmic hippocampal EEG (theta state). Torterolo et al. (2002) likewise related these nuclei to states of sleep and waking. In the Hernández-Peón et al. (1963) cholinergic mapping studies, one of the best areas for inducing REM sleep was the dorsal nucleus of Gudden.

3. Neurotransmitters and the limbic system

3.1. Serotonin

As is well known, the 5-HT innervation of the cerebral cortex including limbic forebrain takes origin from the midbrain raphé (dorsalis and medianus). These nuclei provide two distinct classes of fibers (fine axons with small varicosities from the dorsal raphé and beaded axons with large varicosities from the median raphé nucleus) (Mamounas et al., 1991). The fine axon serotonin terminals abound in different cortical areas. Beaded 5-HT axon terminals reach primarily the outer cortical layers. The functional significance of this terminal topography is still to be determined. In turn, the infralimbic cortices project powerfully to the dorsal raphé (Peyron et al., 1998; Hajos et al., 1998). This clearly demonstrates that pathways between medial prefrontal cortex and raphé nuclei involve primarily the ventral prefrontal cortex (infralimbic and ventral prelimbic cortices) and the dorsal raphé nucleus.

The ascending serotonergic system plays a crucial role in the control of complex brain functions including learning, memory and brain regulation across different vigilance states of the sleep–waking cycle (Fig. 1) (McCarley and Hobson, 1975; Jacobs and Azmitia, 1992). 5-HT projections to the medial septum and hippocampus participate in shifting their activity between patterns of irregular activity (during quiet-waking) and rapid-eye-movement sleep (Vertes and Kocsis, 1997). Hippocampal theta rhythm which is thought to provide synchrony in the hippocampal network required for the generation of LTP is suppressed by activation of serotonin median raphé neurons (Huerta and Lisman, 1993; Holscher et al., 1997). 5-HT neurons show a characteristic slow pacemaker activity, which, according to the vigilance state of the animal, is modulated by a large number of intra- and extra-raphé transmitter systems (Fig. 2). The inhibitory transmitter GABA (Fig. 2) has a central role in this regulation (Jacobs and Azmitia, 1992). GABAergic control is mediated by a large population of cells within the raphé nuclei and by strong GABAergic projections from other brain areas (Wang and Aghajanian, 1977; Maloney et al., 1999). Overall, it is clear that GABAergic mechanisms participate in the control of the ascending 5-HT system involved in vigilance state regulation and in the hippocampal formation it regulates switching between theta and non-theta states (Fig. 2).

Considerable evidence indicates that the median raphé is also directly involved in the modulation of hippocampal EEG, particularly states of hippocampal desynchronization. Various studies have shown that stimulation of median raphé desynchronizes the hippocampal EEG (Vertes and Kocsis, 1997). Accordingly, median raphé lesions result in continuous theta activity (Sundararaman et al., 2004). Vinogradova (1995) concluded that the median raphé could be regarded as a functional antagonist of the reticular formation by powerfully suppressing theta bursts of medial septal area neurons and the hippocampal theta rhythm. Thus, the serotonergic system regulates the activity of the hippocampus across vigilance states. Additional studies have shown that serotonin is involved in the regulation of function in other limbic forebrain subsystems, i.e., the reward system (Koob, 2000).

Recent work on the pathogenesis of depression has focused on cellular neurogenesis in the dentate gyrus of the hippocampal formation. Stress and the resulting depression decrease dentate granule cell neurogenesis, which might then lead to the cognitive problems associated with depression (Santarelli et al., 2003). Administration of drugs which increase serotonin lead to a reversal of this effect. Such drugs are the mainstay of the therapy for depression

and include the selective serotonin reuptake inhibitors such as fluoxetine.

Serotonin has also been implicated in the regulation of other subsystems of the limbic brain. Antagonists at the 5-HT_3 receptor reduce drug-induced increases in dopamine in the prefrontal cortex and the nucleus accumbens (Costall et al., 1990). This work has suggested that serotonin modulates dopamine release in the limbic forebrain by inducing release in the ventral tegmental area. As pointed out earlier, dopamine release in the forebrain, and especially the nucleus accumbens, has been associated with the rewarding effects of drugs of abuse (Salamone et al., 2003). Current theories of drug abuse have targeted the nucleus accumbens and the prefrontal cortex as key areas in craving following dependence on drugs. Thus, 5-HT_3 antagonists have been proposed as therapeutic agents to reduce the craving associated with drug dependence (Costall and Naylor, 2004).

A similar role of 5-HT has been seen in another disorder of the limbic forebrain, i.e., schizophrenia. A key receptor action of atypical antipsychotic drugs such as quetiapine is the blockade of 5-HT_2 receptors presumably in the frontal cortex (Meltzer, 1999). Addition of this receptor activity to the mode of action of antipsychotics has improved their efficacy. Additional research is needed to determine how this antagonism is related to the therapeutic effects of these drugs.

3.2. Norepinephrine (NE)

The medial prefrontal cortex is strongly innervated by the locus coeruleus, and the locus coeruleus receives reciprocal innervation from the medial prefrontal cortex (Heidbreder and Groenewegen, 2003). Stimulation of the locus coeruleus produces a decrease in basal neuronal activity (Mantz et al., 1988) and a marked increase in extracellular levels of dopamine in the prelimbic and infralimbic cortices (Kawahara et al., 2001). The NE links have been recently summarized by Heidbreder and Groenewegen (2003). Overall, as with the serotonin system, the norepinephrine pathways from locus coeruleus innervate wide areas of the limbic forebrain including the hypothalamus. They are involved in arousal and activation in these widespread areas.

3.3. Dopamine

The medial prefrontal cortex is supplied with dopaminergic fibers with the ventral prefrontal cortex receiving the heaviest innervation (Heidbreder and Groenewegen, 2003). This mesocortical dopamine innervation originates mainly from the ventral tegmental area (Steketee, 2003). The more dorsally located dopamine neurons in the ventral tegmental area innervate the more ventral areas of the medial prefrontal cortex, whereas ventrally located neurons in the ventral tegmental areas project to the dorsal part of the medial prefrontal cortex (Deutch, 1993). Dopamine is also differentially available in both the dorsal and ventral parts of the medial prefrontal cortex. Medial prefrontal cortical fibers project back to the ventral tegmental area and substantia nigra pars compacta and have strong influence on dopamine neurons in the ventral mesencephalon (Sesack et al., 1989). Ventral areas in the medial prefrontal cortical areas project heavily to these dopamine cell groups (Sesack et al., 1989) (Fig. 1).

3.4. Acetylcholine

The limbic cholinergic systems originate from two primary sources: the mesopontine laterodorsal tegmental nucleus and the nucleus basalis magnocellularis of the forebrain (Satoh and Fibiger, 1986). The release of acetylcholine in the prefrontal cortical area is associated with widespread EEG desynchronization (activation) (Kainai and Szerb, 2004). Cholinergic activation of the cerebral cortex is also a function of the nucleus basalis magnocellularis of the forebrain. Thus, activation of basal forebrain cholinergic neurons projecting to prefrontal cortex also results in arousal required for processing of sensorimotor and cognitive information (Durkin, 1994; Sarter and Bruno, 1997; Heidbreder and Groenewegen, 2003). The types of cognitive processes that acetylcholine enhances seems to depend largely on specific cytoarchitectonic and functional subareas within the medial prefrontal cortex. Hernández-Peón et al. (1963) mapped a REM sleep system in the limbic system by cholinergic stimulation extending from prefrontal cortex to the dorsal nucleus of Gudden, thus implicating the limbic forebrain/limbic midbrain system to REM sleep.

4. Functional subsystems of the limbic system

4.1. Stress

Key neuronal circuitry inter-relating various limbic brain regions that are important in mediation of behavioral responses to stress and other so-called limbic behaviors is shown in Fig. 1. This circuitry in its various components involves limbic forebrain areas, including the hippocampal formation, prefrontal cortex and amygdaloid complex of nuclei, among others, as well as the limbic midbrain, including the ventral tegmental area, the midbrain raphé nuclei, central gray and Gudden's nuclei.

A principal neuropeptide of the hypothalamus that is integrally involved with the stress system is corticotrophin-releasing factor (CRF). Corticotrophin-releasing factor is abundant in the amygdaloid complex, hippocampal formation and limbic cortical areas (prefrontal and cingulate cortices) where it most likely enhances arousal and cognitive function (Behan et al., 1997). CRF has a diverse range of physiological and behavioral effects, acting both as a neurohormone at the level of the anterior pituitary and as a neurotransmitter in various areas of the brain. The likely site

of action of CRF on 5-HT release is at the level of the cell bodies in the dorsal raphé nucleus (Fig. 2) (Kirby et al., 2000). There are multiple CRF receptor subtypes within the raphé nuclei where CRF primarily shows an inhibitory effect on raphé cell discharge (Kirby et al., 2000). Functionally, various studies indicate a strong role for CRF in mediating the effects of stress on the 5-HT system. Thus, this single neurotransmitter system has an opportunity to influence a wide variety of neural elements, rather than selected neuronal circuits. A critical question still outstanding is what regulates this complex system. Immunohistochemical findings (Kirby et al., 2000) indicate a dense innervation of the dorsal raphé nucleus by CRF and reveal a strong topographic organization. Hence, CRF's actions on dorsal raphé activity may have a major effect on 5-HT release in select target areas (Price et al., 1998).

The stress system (stress axis) in the brain interrelates closely with the limbic neuronal systems passing from the midbrain raphé and other limbic midbrain areas to the hippocampal formation and neuronal pathways from the limbic forebrain into the limbic midbrain (including the midbrain raphé nuclei). Serotonergic cell firing in the raphé is primarily under 5-HT_{1A} receptor control. In the raphé nuclei, this 5-HT_{1A} receptor is a somato-dendritic inhibitory autoreceptor on 5-HT neurons (Middlemiss and Fozard, 1983; Verge et al., 1985). In the 5-HT regulatory system, 5-HT acts locally on the somato-dendritic autoreceptors to inhibit further release of 5-HT (Wang and Aghajanian, 1977). Overall, it appears that the raphé–hippocampal 5-HT system attenuates stress by facilitation of hippocampal 5-HT_{1A}-mediated neurotransmission.

From studies of the limbic serotonin system(s) of the brain it is clear that there are close relations with the CRF system (stress axis), reward seeking and memory. An understanding of many of the interrelationships of these systems has not previously been put into broader context for interpreting how stress and addictive behavior may affect memory function and the raphé–hippocampal system in terms of serotonin release in several areas of the limbic forebrain. These serotonin systems form an interconnected system (involving the prefrontal cortex, hippocampal formation, midbrain raphé and the limbic midbrain terminating posteriorly in the dorsal nucleus of Gudden). Orchinik et al. (2001) have shown that corticosterone alters GABA-mediated inhibitory transmission. Hence, the $GABA_A$ receptor system likely contributes to dendritic remodeling and other stress-related change in hippocampal function. Orchinik et al. (2001) concluded that prolonged exposure to stress levels of corticosteroids might alter hippocampal inhibitory tone by regulating the pharmacological properties of $GABA_A$ receptors in discrete dendritic subfields. Thus, it appears that corticosterone induces shifts in balance between excitatory and inhibitory neurotransmission. This again expands thinking beyond single systems, provides a better handle on how insults impact larger functional systems (networks) rather than more limited nodes or "centers", and begins to provide a basis for physiological and pharmacological dissection of limbic functional subsystems.

Various studies suggest that stress acts in many ways to affect the processes that underlie learning and memory. Thus, stress has been shown to affect plasticity, particularly hippocampal plasticity, dendrite morphology, neurotoxicity and neurogenesis within the dentate gyrus of the hippocampal formation (McEwen, 2002). All of these can impact learning and memory with changes in hippocampal plasticity probably being the most disruptive.

Stress is a naturalistic factor that contributes to memory impairment. The hippocampal formation is involved in memory processing, the regulation of the hypothalamic–pituitary axis and appears to be especially susceptible to exposure to stress (McEwen, 1999). Stress diminishes synaptic plasticity within the hippocampal formation, produces morphological changes in dendritic development, and decreases neurogenesis in the dentate granule cells. Stress effects on the hippocampal formation and on memory are more complex than simple neuroendocrine models suggest and involve other neural structures (e.g., hypothalamus) and neuromodulators (norepinephrine and GABA). Despite its apparent simplicity, this tentative model helps to illustrate the importance of studying interacting components of neural systems in order to gain understanding of how stress affects the brain, cognition, and synaptic plasticity, all of which are differentially impacted by neuronal insults. In this regard, the hippocampal formation is a direct target of stress hormones, having one of the highest concentrations of receptors for corticosteroids in the mammalian brain (McEwen, 1999).

4.1.1. Stress and hippocampal plasticity

For several decades, the primary physiological model of memory has been long-term potentiation, which is a sustained enhancement of synaptic efficacy. This has been most often studied in the hippocampal formation, and it is probable that changes in synaptic efficacy underlie information storage (Hebb, 1949). The finding that stress impairs hippocampus-dependent memory predicts that stress interferes with induction of hippocampal LTP and that stress and stress hormones impair induction and impairment of LTP (Shors and Dryver, 1994). Of special interest is the observation that stress decreases LTP in the dentate gyrus of the hippocampal formation (Shors and Dryver, 1994). During most forms of stress, high levels of corticosterone produce a greater activation of the corticosterone receptors, which results in a marked inhibitory effect on hippocampal plasticity, e.g., LTP. Production of new dentate granule cells is inhibited by stress or elevation of corticosterone (Gould and Tanapat, 1999). Additionally, the 5-HT system is clearly involved in mediating stress effects on the hippocampus (Graeff et al., 1996; Xu et al., 1997; McEwen, 1999; Fujino et al., 2002; Kim and Diamond,

2002; Sewards and Sewards, 2002). Stress elevates 5-HT levels in the hippocampus and, given that 5-HT exerts a suppressant effect on synaptic plasticity, this may be an additional mechanism for the suppression of memory formation following stress.

Kim et al. (2001) have shown that an intact amygdala is also necessary for the expression of the modulatory effects of stress on hippocampal LTP and memory. As noted, the raphé nuclei also project strongly to the amygdaloid nuclei (Fig. 1). Thus, the connection between stress and the serotonin system suggests that a raphé–amygdala–hippocampal formation pathway may also regulate memory formation and plasticity in the hippocampus.

CRF in the raphé nucleus is mainly excitatory on serotonin release. These effects are limited to a subpopulation of 5-HT neurons adding to the complexity of the organization of the raphé nuclei (Fig. 2). Thus, considerable evidence indicates that CRF affects physiological actions via effects on the 5-HT system, which, in turn, affect the modulation of memory in the hippocampal formation, by interactions with an extended network including the amygdala and the medial septum, as well as other forebrain structures.

4.1.2. Stress and the GABA connection

Chronic stress alters the balance between excitation and inhibition leading to dendritic remodeling and changes in hippocampal function. Corticosterone modifies the actions of GABA, and GABA is known to be a primary regulator of hippocampal excitability (Freund and Buzsaki, 1996). Corticosterone also alters the pharmacological properties of $GABA_A$ receptors (Orchinik et al., 2001). Chronic corticosterone alters information flow through the hippocampal formation such that the massive excitatory input to CA_3 from mossy fibers originating in the dentate gyrus is inhibited (Sapolsky et al., 1985, 1990).

The cortical and hippocampal systems consist of many different subclasses of GABA interneurons, each having unique phenotypes defined by their morphology, neuropeptide content, electrophysiological properties and synaptic connectivity (Freund and Buzsaki, 1996; Morgane et al., 2002). GABAergic cells engage in complex interactions not only with projection neurons, but also with one another (Freund and Buzsaki, 1996). The intricate networks derived from these interactions are associated with the generation of both oscillatory rhythms and detailed aspects of discriminative information processing. A defect in only one component of such a system would have profound implications for the functioning of limbic local circuits, as well as larger scale macrocircuits within the corticolimbic system. Basically, GABA interneurons are critical for the formulation of complex behaviors, and defects in their functioning can give rise to a broad array of neural dysfunctions (Freund and Buzsaki, 1996).

GABA-to-GABA interactions in the limbic cortex and other brain areas are an especially intriguing type of connection and they have been shown to form neuronal networks (Freund and Buzsaki, 1996). From a functional point of view, these networks of GABAergic neurons are thought to form one of the most basic functional units in the cortex (Gupta et al., 2000). It has been shown that 5-HT containing neurons of the median raphé selectively contact (and presumably excite via $5\text{-}HT_3$ receptors) GABAergic cells of both the septum and hippocampus (Freund and Buzsaki, 1996; Tao and Auerbach, 2000). These findings together with the demonstration that GABAergic cells of the medial septum and hippocampal formation inhibit projection cells of respective structures suggest that 5-HT median raphé neurons exert a net suppressive effect on the output of the septal/hippocampal formation.

4.2. Addiction and reward

The reinforcing effects of all drugs of abuse are likely due to actions in the limbic forebrain, a circuit of multiple brain pathways and nuclei that play key roles for the influence of emotional, affective and motivational information on behavior. Within the same limbic forebrain, reward-related behaviors emerge from the dynamic activity of neural networks. The functions of the nucleus accumbens, amygdala, prefrontal cortex, ventral tegmental area and the raphé nuclei in natural reward or addiction can be understood best in terms of the extended neural system within which they reside (Fig. 1). Understanding the roles of key brain areas in reward requires analysis of network interactions between subareas of the amygdala, nucleus accumbens, prefrontal cortex, ventral tegmental area and other structures involved in reward and motivation (Everitt et al., 2000; Schultz, 2000; Jackson and Moghaddam, 2001).

One critical component of a broader conceptualization of drug-reward circuitry is the glutamate neuronal system innervating and directly influencing the mesocortical dopamine system (Fig. 1). Glutaminergic inputs to ventral tegmental area and nucleus accumbens, arising from the prefrontal cortex, hippocampal formation and basolateral amygdala have all been implicated in addiction (Wolf, 2002). A systems review of the interplay between cellular/molecular and behavioral/systems neuroscience with respect to the processes of addiction is needed. Thus, there seems little question that identifying the systems involved in specific behaviors will direct cellular/molecular studies of both acute and chronic drug action. Efforts relating to tying specific brain circuits to aspects of behavioral changes have broadened considerably the number of affected brain regions and emphasize the continued need to expand cellular/molecular studies to these limbic areas. This has been made more possible by refinements in behavioral approaches coupled with systems neuroscience. Studies of network interaction are proving to be the best approach for defining

pathological effects on the brain. Though we now have a working knowledge of key brain structures of reward, further understanding will require neurochemical (e.g., dual probe in vivo microdialysis) studies of network interactions between sub-regions of the amygdaloid complex, hippocampal formation, prefrontal cortex, nucleus accumbens and other structures implicated in reward and motivation.

In particular, the glutamate circuits have been strongly implicated in learning and memory. By tapping into mechanisms similar to LTP and long-term depression (LTD), drugs of abuse can influence fundamental processes accounting for long-lasting changes in limbic structure and function that underlie addiction, including changes in dendritic spines in the amygdaloid complex, nucleus accumbens and prefrontal cortex (Wolf, 2002). Of course, drugs may produce neuroplasticity by regulating GABA-mediated inhibition in addition to glutamate excitation. Examining plasticity in limbic neuronal circuits regulated by GABA appears to be an especially important approach in further untangling the function of this systems complex.

Of particular interest regarding the limbic subsystems involved in stress and addictive behaviors that we have summarized is the extensive overlapping nature of the neuronal systems. In each system, we have seen the distributed network involving structures of the LF/LM including the medial prefrontal cortex and the nucleus accumbens, as well as the raphé nuclei. Each system involves considerable modulation by GABAergic, glutaminergic, noradrenergic, serotonergic and dopaminergic systems (Lavielle et al., 1978; Roth et al., 1982; Rosecrans et al., 1986; Kalivas and Duffy, 1989; McEwen et al., 1997; Van de Kar and Blair, 1999; Chaouloff, 2000). Functionally there is considerable overlap within all of these transmitter systems. Acute stressors and many drugs of abuse (e.g., cocaine) increase dopamine, serotonin and glutamate release in these basal forebrain regions. Furthermore, with repeated exposure to either stress or cocaine, sensitization occurs as the result of increased glutamate activation of *N*-methyl-D-aspartate (NMDA) receptors leading to increased release of dopamine in the frontal cortex and the nucleus accumbens (Sorg and Kalivas, 1990; Kalivas and Stewart, 1991). Importantly, previous exposure to stress sensitizes the brain to the behavioral and biochemical effects of psychostimulants (Antelman et al., 1980; Sorg and Kalivas, 1990).

The role of glutamate and specifically NMDA receptor activation in the development of sensitization to stress and drugs of abuse also has distinct similarities to the development of LTP in the formation of memory and learning (Vanderschuren and Kalivas, 2000; Myhrer, 2003). Certain differences do exist here, however. In contrast to cross-sensitization between stress and psychostimulants (Robinson et al., 1985), both learning and LTP are inhibited by stress (Kim and Diamond, 2002). Further studies on the limbic networks involved with learning and memory and those involved with reward will be necessary to delineate these differences.

5. Long-term prospects and summary

In summary, a complex of neurochemical pathways within the limbic forebrain/limbic midbrain systems mediates a variety of emotional and motivational processes. Embedded in these assemblies are systems that mediate stress, addiction responses, reinforcement/reward and learning and memory. A variety of neurotransmitter control systems precisely modulate these pathways. Though investigations of components of the limbic system reveal many partial aspects of limbic organization, extensions and distributed components, there is still no overarching theory of the functions of the limbic system. As noted, the inner landscape of this system is exceedingly complex, not lending most components to simple functional reduction. A grand unified theory of the limbic system is not yet possible leaving us to ponder partial psychological functions that do not yet fit together conceptually. No wonder the continued difficulty of assigning "function" to the interrelated components, much less the whole. The other aspect of interest is that emotion, motivation and reinforcement/reward are not unitary phenomena but have multiple "representations" in the brain. Learning and memory occur across a distributed set of systems that may be studied best as an integrated set of systems. Thus, anatomy and "partial" functions need to be better pieced together than they have in the past. As in the case of the amygdaloid complex, the whole distributed limbic brain is neither a structural nor functional unit. The Klüver–Bucy syndrome at least indicated that some 68 years ago! This overview hopefully will help to clarify some of the functional interactions of the limbic brain and its distributed systems. For eventual therapeutic developments related to motivation and emotion, it is essential that the several neuronal systems described here are understood in the context of the basic limbic network and its distributed systems. This review also outlines the advantages of using the extended limbic forebrain/limbic midbrain as a model system to examine key questions in neuroscience and to argue against degrading or minimizing the limbic brain. The limbic system is indeed alive and well, though often misunderstood.

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