Neurobiology of Cingulate Cortex and Limbic Thalamus

A Comprehensive Handbook

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Editors

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Preface

Model systems have played an important role in the development of the neurosciences. Neurobiology has reached a point, however, where attention to a limited number of sensorimotor, hippocampal, and culture systems exclude a large body of research and issues critical to CNS function and understanding of neurological diseases. One of the vacuums created by the model systems approach has been in the understanding of cingulate cortex and limbic thalamus, a region that occupies much of the dorsomedial surface of the brain. The study of cingulate cortex enlightens our understanding of complex and distributed functions such as spatial memory and pain perception and provides new insights into neurological diseases. Over the past two decades understanding of the connections of cingulate cortex and other components of the limbic system, including the anterior and midline thalamic nuclei, hippocampal formation, amygdala, and mamillary bodies, has progressed far beyond the views embodied in the circuitry proposed by early investigators such as Papez. Much current research points to this region as critical in responses to noxious stimuli, vocalization, sensorimotor integration, discriminative avoidance and spatial learning and memory, autonomic function, and reinforcement phenomena. Furthermore, this system is critically involved in diseases like schizophrenia and Alzheimer's disease.

It is almost a doctrine among students of the cerebral cortex that the function of a particular cortical area is determined to a large extent by its thalamic afferents. Our understanding of thalamic function is dominated by studies of the sensory divisions of thalamus, and so the function of the thalamus is usually couched in terms of its role in the central transmission of sensory inputs and modulation of receptive field properties as well as plasticities following peripheral deafferentation lesions. However, a surprisingly large part of the thalamus has its principal connections with limbic cortex and so may be referred to as the limbic thalamus. These nuclei include the anterior, midline, intralaminar, lateral, and mediodorsal divisions. It behooves the neuroscience community, therefore, to characterize both the organization and functions of this prominent component of the diencephalon. As will be discussed throughout this volume, the limbic thalamus is involved in complex learning and memory functions, interactions between the cingulate and hippocampal systems, and disruption of these nuclei or

their afferents may account for cognitive dysfunction in Wernicke-Korsakoff's syndrome and in Alzheimer's disease.

This book originated in a collaboration between the editors starting in 1981. The project of providing a comprehensive assessment of cingulate cortex and limbic thalamus, current research findings, and unifying theories proved to be a moving target that could not be achieved by two investigators. Therefore, 42 neuroscientists were approached in 1990 with the suggestion that they write the first definitive volume on this part of the brain. In order to assure that a mature and integrated text was produced, each chapter was written in preliminary form and the highlights presented at a Satellite Symposium at the 1991 Society for Neuroscience meeting in New Orleans. This historical meeting brought the world's authorities on this part of the limbic system together for the first time. It resulted in a careful rethinking of the content of each chapter and provided the foundation for the present volume. These efforts resulted in an unusual degree of continuity among the chapters when viewed from the perspective of an edited volume.

There are a number of goals for the present volume. Foremost among these is to provide a comprehensive source for information on the structure, connections, and functions of cingulate cortex and the limbic thalamic nuclei with which it is connected as well as the theoretical constructs necessary for the elucidation of their role in particular behaviors. This includes the cytoarchitecture of cingulate cortex in the most frequently used experimental animals and in the human brain. All neurotransmitter systems are analyzed with an emphasis on those features that are unique to cingulate cortex. A thorough analysis of each of the principal functions of cingulate cortex including its role in the behavior of experimental animals and humans is presented as individual chapters. There are many functions which cingulate cortex may share with other areas such as prefrontal or parietal cortices and there are diseases of the nervous system that have a significant impact on cingulate cortex, but which are not limited to it. In these instances, the authors have attempted to winkle out the particular contribution of cingulate cortex to these functions or complex clinical presentations without making pretentious arguments that cingulate cortex is solely responsible for them.

Another goal of this volume is to directly apply findings of basic neuroscientific investigations to an understanding of the human brain. The maturation of neuroscience as a discipline and its validation as an intellectual pursuit rest on accomplishing this goal. In many of the chapters there are direct analyses of human cingulate cortex or limbic thalamus or there are pertinent interpretations of its role in human behavior. This includes cytoarchitectural, receptor binding, and peptide immunohistochemistry. Neurological disorders including the cingulate epilepsy syndrome are discussed as is the role of cingulate cortex in attention functions as revealed by positron emission tomography studies. Neuropathological entities that involve cingulate cortex and parts of the limbic thalamus are considered in chapters on schizophrenia and Alzheimer's disease. Another subject of importance to neuroscientists as well as society as a whole is the role of particular neural systems in drug self-stimulation and abuse. Cingulate cortex and limbic thalamus have been directly implicated in reinforcement processes, and an understanding of their contributions to human behavior may lead to treatment regimens for dealing with drugs of abuse. Thus, the information contained in this volume will be of value to individuals involved in fundamental neuroscience and the practice of clinical medicine.

The authors of these chapters are leading anatomists, physiologists, pharmacologists, psychologists, psychiatrists, neurologists, and neuropathologists who are currently engaged in studies of cingulate cortex and limbic thalamus. Therefore, another goal of this volume is to present the most recent findings of their research and in so doing to explore the excitement that underlies their work. A sampling of some of the more interesting findings that are reported in this volume include the role of neuropeptides in the development of cingulate cortex; morphological characterization of individual anterior thalamocortical axons; immunohistochemical localization of antibodies for neurotransmitters and calcium-binding proteins; dendritic and axonal localization of numerous neurotransmitter receptors including multiple heteroreceptors on anterior thalamic axons; the unique involvement of cingulate neurons in *N*-methyl-D-aspartic acid-antagonist neurotoxicity; characterization of long-term potentiation in cingulate cortex and its modulation by afferents from the hippocampal formation; the structure and connections of the cingulate motor regions and their role in motor activity; the role of limbic cortex and thalamus in mnemonic retrieval processes; the involvement of cingulate cortex and limbic thalamus in self-stimulation and drug self-administration; the role of cingulate cortex in spatial and other sensorimotor functions; the mechanisms by which cingulothalamic connections modulate learned autonomic functions; the cingulate epilepsy syndrome and the consequence of unilateral and bilateral removal of cingulate cortex in human brain; alterations in cingulate cortex in schizophrenia and how they might contribute to brain dysfunction; alterations in the architecture of cingulate cortex and limbic thalamus in Alzheimer's disease.

There are a number of evolving themes that resulted from attempts to produce a coherent volume. One of the most consistent messages is that cingulate cortex is critically involved in motor function. Thus, cingulate cortex has more extensive projections to the caudate and putamen than does any other limbic cortical area; it has motor areas that are topographically connected with motor cortex and the spinal cord, and it is involved in modulating autonomic functions associated with skeletomotor processes. In addition, many observations indicate an important involvement of cingulate cortex and limbic thalamus in such processes as working memory, encoding of spatiotemporal contexts that define particular learning situations, and mnemonic retrieval. These results make it clear that cingulate neurons are not directly involved in the details of motor execution but, rather, represent a class of neurons that associate limbic sensory, motivation, and mnemonic information processing. Cingulate cortical output to the motor system, under the control of neocortical and hippocampal memory-based environmental inputs, provides a signal that may coordinate motor outputs with important environmental events that are learned and remembered as significant. Therefore, cingulate cortex is likely one of the most important structures in the limbic system that directs motor function.

This volume is organized into four broad areas. The introduction by Dr. Paul D. MacLean serves the important function of setting the general theoretical context for studies of cingulate cortex and limbic thalamus and provides a historical context for such work. The first section of this book presents the structure, connections, development, and neurochemistry of transmitter systems in the cingulate cortex and limbic thalamus in Chapters 1–9, 12, and 19. The transmitter systems are assessed with immunohistochemical and receptor binding

techniques and include the glutamatergic, cholinergic, peptidergic, GABAergic, and monoaminergic systems. There is also a consideration of calcium-binding proteins that mark subsets of inhibitory neurons. In addition to providing a unifying and comprehensive analysis of these features, principles of organization across species are developed where appropriate. The species considered include the rat, rabbit, cat, monkey, and human. The second section details the information-processing functions of cingulate cortex and limbic thalamus in experimental animals and is composed of Chapters 6 and 10–14. The integrative functions of cingulate neurons are demonstrated from intracellular recordings. The responses of cingulate neurons to noxious stimuli are presented as is their relevance to understanding pain perception in the human. Autonomic/visceral responses produced by electrical stimulation of cingulate cortex and parts of the limbic thalamus are characterized as is their modulation in learning paradigms. The responses of cingulate neurons in the cat and monkey cingulate cortex that are modulated by visual stimuli as well as those generated after eye movements are assessed. Finally, the distribution of the cingulate motor areas is specified and their role in regulating movement is evaluated. The third section is composed of Chapters 15–17 and considers the role of cingulate cortex in behavioral processes. These include its role in reinforcement and drug self-administration and spatial processing. There is also a comprehensive assessment of neuronal plasticities that occur in cingulate cortex and limbic thalamus during acquisition and retrieval processes associated with discriminative avoidance learning. The fourth section focuses on the role of cingulate cortex in human behavior and the neuropathological disruption of limbic thalamus and cortex as presented in Chapters 18, 20, and 21. Although this part of the limbic system is not presently used for the diagnosis of psychiatric diseases or Alzheimer's disease, it may contribute significantly to the clinical presentations of these diseases particularly in terms of memory, affect, and motor dysfunctions. In addition, a cingulate epilepsy syndrome is documented that lends new insights into the role of cingulate cortex in human behavior. Chapter 19 is a transitional chapter between experimental and clinical/neuropathological assessments of cingulate cortex. This chapter includes an analysis of the glutamatergic and cholinergic systems and specifies the selective neurotoxicity of glutamate receptor antagonists in cingulate cortex. The protective role of cholinomimetics is then discussed and the authors suggest mechanisms for neuron degeneration in diseases of the limbic system that involve cingulate cortex.

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