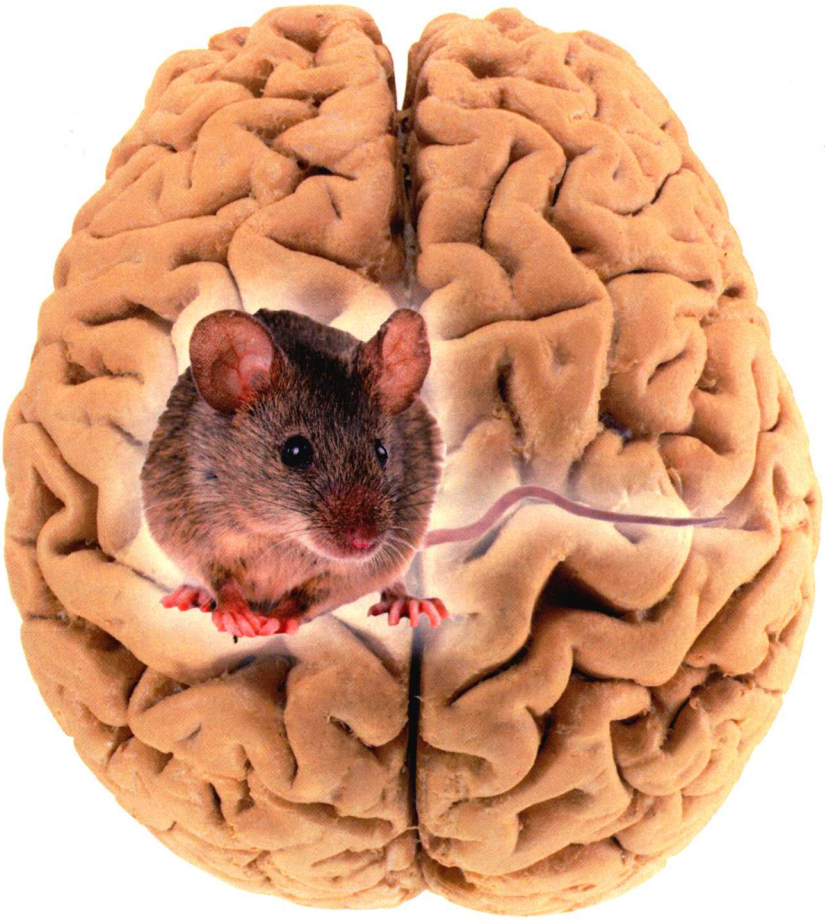

The Cerebral Cortex in Neurodegenerative and Neuropsychiatric Disorders

Experimental Approaches to Clinical Issues

Edited by
David Cechetto
and Nina Weishaupt

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Foreword

Knowledge accrues in pieces, but it is understood in patterns. As subspecialties grow, so do the gaps between them. The greatest gap of all occurs between experimental research and clinical application, within and among fields. This book goes a long way in bridging these gaps. It begins with an introductory chapter on the cerebral cortex, stressing the similarities and differences among species, particularly between humans and rodents, the favorite experimental species. Next comes a chapter on cortical plasticity and response to injury, setting out the dynamics of injury and repair that underpin most brain conditions. The chapter on imaging outlines how it is increasingly possible to study pathological and repair mechanisms in vivo both in humans and in animals. This is followed by a section on seven common neurodegenerative disorders, ending with a section on neuropsychiatric disorders, the other set of manifestations of a disordered brain.

A remarkable feature of this book lies in the joint coauthorship of basic scientists and clinicians accustomed to working with each other. This provides a coherent and unique understanding of how integrated, experimental, and clinical work can move forward together.

This volume should have a broad appeal to clinicians trying to understand experimental methodologies, techniques, and approaches; to basic scientists in seeing the clinical relevance of their work; and to all those interested in the brain who want to know how a myriad of little pieces coalesce to make up increasingly understandable patterns.

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Introduction

The cerebral cortex has approximately 10 billion neurons that provide an inordinate amount of high-level processing. It is the neurons in the cerebral cortex in humans that is responsible for the cognitive processing or the conscious mind. The final site of termination for sensory signals is the cerebral cortex, leading to an awareness of the external and internal milieu. Complex processing using several different cortical networks leads to the generation of simple movements or even very complex executive functions, such as decision making and setting goals.

The cerebral cortex plays an important part in some of the most prevalent neurological diseases and neuropsychiatric disorders in our society. For some conditions, involvement of the cerebral cortex has only recently been emerging. Experimental research into the role of the cortex in disease has contributed greatly to our current knowledge, and further advances are needed. This book focuses on how preclinical investigations are addressing the clinical issues surrounding the involvement of the cerebral cortex in selected conditions of the nervous system. Each chapter has been written by an expert in his/her field in an effort to provide a comprehensive review of the clinical manifestations of cortical involvement, and a resource on leading animal models and experimental techniques currently available to tackle cortical issues in disease. Thus this book provides a link between cortical clinical problems and investigational approaches that we hope will help foster future research with high translational value.

Textbook resources on the cerebral cortex are abundant. The intent of this volume is to contribute cutting-edge insights into how the cerebral cortex functions in disease states, and how it is affected by individual neurological and neuropsychiatric disorders. What makes this book unique is the link it provides between clinical issues and preclinical research related to the cerebral cortex. The focus on animal models and experimental techniques is aimed at providing a practical resource on modeling clinical issues to be useful for researchers from students to principal investigators. A resource of this kind, covering major neurological and neuropsychiatric diseases and the role of the cerebral cortex, has not been previously available.

In this book, we have provided three general topics of particular importance to understanding and undertaking experimental investigations of diseases of the cerebral cortex. The remaining chapters are devoted to particular neurological

or neuropsychiatric conditions and the role of the cerebral cortex. These chapters have some common themes related to pathology, as well as to the associated imaging technologies and the type of models used to investigate each condition.

The first chapter provides an excellent overview of the anatomy of the cerebral cortex. In particular, this chapter eloquently describes the similarities in the cerebral cortex between species, as well as the areas in which species have developed specialized components for specific behaviors. It is clear that there are many organizational similarities in the cerebral cortex of humans and animal models, even rodents. This chapter specifically states, "the primary cortical areas are recognizable across species, as are the basic cortical layers and cell types, and the main neurochemical transmitter and neuromodulatory systems." However, the description of the differences emphasizes one of the major limitations in using animal models to examine important neurological and neuropsychiatric conditions. Unlike many subcortical sites, in animal models there is some degree of diversion from the patterns and cytoarchitecture seen in the human that may complicate the interpretation of results.

Chapter 2 deals with one of the unique features of the cerebral cortex that has major implications for the cerebral cortex in response to disease. This chapter emphasizes the importance of plasticity in CNS injury and disease, particularly in the cerebral cortex, in spite of the inability of cortical neurons to undergo adult neurogenesis. Of particular importance for some neurodegenerative and neuropsychiatric diseases is the impact of experience in plasticity in the cerebral cortex, especially as it relates to sensory input, using key examples from visual and auditory deprivation. Thus experience may begin to restore the loss of function caused by altered connections or chemistry of the cerebral cortex. On the other hand, after brain trauma or cerebral infarcts caused by stroke, part of the brain recovery process for function may be relocated in adjacent cortical areas, compensating for the loss of tissue. There are several means by which innate cortical plasticity may be manipulated to play a therapeutic role in neurodegenerative and neuropsychiatric diseases, many of which are described in other chapters. Some of the possible means may include maximizing cognitive reserve and cognitive training, transcranial magnetic stimulation to induce plasticity, and use of growth factors such as insulinlike growth factor (IGF), ciliary neurotrophic factor (CNTF), glial cell–derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF) that are proving to be important in cortical plasticity.

As many of the chapters on specific cortical conditions indicate, neuroimaging experts continue to develop essential tools for early identification, experimental investigations, and assistance in therapeutic approaches. Chapter 3 does an excellent job of summarizing all of the recent imaging approaches available for neurodegenerative diseases and provides an excellent overview directly related to some of the discussion found in individual chapters on specific conditions of neurodegenerative diseases. The information provided listing the latest approaches, methods, and agents that are available for imaging the cerebral

cortex can be very helpful to scientists intending to undertake new investigations. Furthermore, of particular interest is the discussion on the increased role that imaging is playing in the management of patients with neurodegenerative disease. For example, in Alzheimer disease (AD), neuroimaging can be used as a biomarker in the presymptomatic phase, to identify the etiology, establish pathophysiological changes, and predict progression.

This discussion on the role of imaging for cerebral cortex conditions is supported by many of the chapters on specific neurological and neuropsychiatric conditions affecting the cerebral cortex, indicating that imaging is becoming increasingly important. Many of these chapters indicate that new approaches are being used to monitor the progress of the disease or even may be critical biomarkers in early, treatable stages of cortical diseases.

For example, in Chapter 3 on brain imaging, the resting brain networks are described and it is stated that the default mode network (DMN) is the most relevant in AD because it is involved in episodic memory formation and attention. The DMN is composed of cortical regions such as the cingulate, precuneus, inferior parietal cortex, medial prefrontal cortices, and the hippocampus. Chapter 4 indicates how the DMN regions are involved in AD using the Pittsburgh-B (PiB) compound and positron emission tomography (PET) for imaging amyloid. PET has also been effective in neuropsychiatric conditions. Chapter 12 indicates that PET has demonstrated addiction-related effects in multiple cortical regions.

Functional magnetic resonance imaging (fMRI) is becoming particularly useful in several conditions because it is capable of demonstrating changes in the neural networks associated with cortical activity. Chapters 4 and 6 describe how fMRI is used to demonstrate a lower connectivity in the DMN in AD and frontotemporal dementia (FTD). Chapter 9 describes how a number of fMRI studies have been effective in showing that amyotrophic lateral sclerosis (ALS) produces changes in neural networks. In particular, this chapter describes how resting state fMRI has shown the impact of ALS on three different neural networks, including the salience network, the DMN, and the central executive network. Chapters 11 and 12 also indicate how the neural networks are affected in neuropsychiatric conditions using fMRI. Schizophrenic patients are unable to deactivate the DMN network during cognitive tasks, and regions such as the anterior cingulate cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex have altered functional activity as a result of addiction.

In addition, Chapter 4 on AD suggests how fMRI techniques might be a very useful approach as an early biomarker of cortical changes. The role of fMRI as a biomarker is particularly emphasized in Chapter 6 on FTD, in which reduced connectivity of the DMN is seen 10–15 years before the neurological symptoms. This potential biomarker role is also described in Huntington disease, Chapter 8, in which impairments in the functional connections between the anterior cingulate and lateral prefrontal cortices are observed before the onset of symptoms. Furthermore, fMRI has demonstrated possible plasticity

in Huntington disease because it has shown compensatory brain responses and reorganization of circuits.

In addition to imaging, there are some common themes that appear in the chapters on specific neurodegenerative and neuropsychiatric conditions. For example, several chapters refer to the role that tau and amyloid play in the pathology of the disease. The role of tau and amyloid is relatively well known in dementia, as described in Chapters 4, 5, and 6. For example, Chapter 4 describes how neurofibrillary tangles (NFTs) and insoluble aggregates of amyloid present different patterns of progression of AD pathology in the cerebral cortex, even though both of these were previously thought to be integral pathological components of the disease. Chapter 4 indicates that this discrepancy in disease progression may be resolved by an examination of the pattern of soluble oligomeric forms of amyloid. However, Chapter 9 has a very interesting discussion on the controversy surrounding alterations in tau metabolism in the frontotemporal dysfunction associated with ALS.

Another defining condition that appears to be important in many of the cerebral cortex disorders is neuroinflammation. This is emphasized in Chapters 4, 5, and 6 on AD, vascular dementia, and FTD. In Chapter 10 on multiple sclerosis (MS) the deleterious effects of inflammatory cytokines are described with effects that can include direct damage by the disruption of synaptic transmission leading to excitotoxicity and even demyelination or inhibition of remyelination. In Chapter 6 there is a discussion on antiinflammatory therapies for FTD. In Chapter 9 it is also indicated that immunoreactive glia are a significant feature of ALS. The discussion surrounding the role of neuroinflammation in multiple conditions suggests that the cerebral cortex may be particularly vulnerable to degeneration resulting from neuroinflammation. It also suggests that an antiinflammatory regimen developed for one condition may in fact be relevant for other degenerative conditions of the cerebral cortex. Of particular interest in this regard is the new methodologies provided by neuroimaging. As described in Chapter 3, it is now possible to use PET with benzodiazepine receptor ligands to visualize activated microglia in the cerebral cortex. This is permitting clinical investigations to be run in parallel with experimental studies to confirm some basic mechanisms related to neuroinflammatory changes in neurodegenerative diseases. Thus although the cerebral cortex is a very complex and differentiated structure anatomically and damage to specific cortical structures results in very different clinical expression of neurodegenerative disease, some common pathological mechanisms remain, including tau, amyloid, and neuroinflammation, that may be exploited for the purpose of understanding the diseases and designing therapeutic strategies.

Because of the large area of the cerebral cortex and the diverse regions all with different functions, it is difficult to create animal models that are based on making lesions, occluding blood vessels, stimulation of cortical sites, or other surgical techniques. As can be seen from multiple chapters, many experimental models for AD, FTD, ALS, and MS have focused on genetic changes associated

with the condition. Often, because of the molecular heterogeneity of the cerebral cortex, transgenic or gene knockout models permit relatively specific molecular cortical disruptions that closely align with the neurodegenerative or neuropsychiatric condition. The exception to this approach, almost by definition, is that of the role of the prefrontal cortex in addictive disorders. In this case, as described in Chapter 12, animal models are based on the administration of drugs to induce animal concomitants of clinical addictive syndromes.

The last 2 chapters focus on conditions that can be considered neuropsychiatric. Chapter 12 on addiction examines in detail the role of the prefrontal cortex, similar to the focus of Chapter 11 on schizophrenia. Given that the overwhelming bulk of our understanding of how the prefrontal cortex controls reward and addiction-related behaviors comes from rodent-based basic neuroscience research approaches, a critical question concerns whether the rodent prefrontal cortex can actually serve as an effective analog for the complexity of the primate prefrontal cortex, an issue that was addressed to some extent in Chapter 1 in the examination of comparative cortical anatomy. It seems that both of these chapters indicate that current experimental models are very useful in our understanding of cortical mechanisms in neuropsychiatric conditions, as was also seen in the use of rodent models in neurodegenerative diseases.

Thus this volume provides the necessary information to understand the role of the cerebral cortex in a number of neurodegenerative and neuropsychiatric diseases, as well as a reference to important information on cortical anatomy, plasticity, and neuroimaging for context to these conditions. It is hoped that these chapters form the basis to assist those working in clinical settings, and early or advanced experimental investigators. In particular, the common themes, as well as the peculiar differences seen in the various diseases, suggest excellent opportunities for novel experimental and therapeutic approaches.

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