

## Preface by the Editors

Parkinson's disease (PD) and Huntington's disease (HD) are the paradigms of opposite movement disorders originating in the basal ganglia. On one hand, poverty and slowness of movement (hypokinesia and bradykinesia) are pathognomic to PD and related conditions. On the other hand, excessive and uncontrolled movements are a hallmark of HD. Indeed, the latter condition is the most common genetic cause of involuntary, fleeting and writhing movements (chorea), which is why the disease used to be called 'Huntington's chorea'. Both PD and HD are not only disorders of movement, however. In both conditions, mental processing and mood are affected, and metabolic or autonomic dysfunction cause a range of non-neurological symptoms.

From both etiological and epidemiological standpoints, PD and HD appear as two widely different conditions. PD is the second most common neurodegenerative disease after Alzheimer's and currently affects about 6.3 million people worldwide. It is an age-related disorder lacking an identifiable cause ('idiopathic') in 90 % of the cases. By contrast, HD is a relatively rare familial disease caused by an autosomal dominant mutation in the *HTT* gene. Symptoms of HD commonly become manifest between the ages of 35 and 50 years, but they can begin at virtually any age depending on the CAG repeat length (see below).

The genetic basis of HD was discovered in 1993 by an international collaborative effort spearheaded by the Hereditary Disease Foundation. Since then, several other neurological diseases were found to depend on a similar genetic defect, consisting in the expansion of a CAG (cytosine-adenine-guanine) triplet repeat stretch within the disease-causing gene.

During the past 17 years, it has become increasingly clear that PD has a strong genetic component, too. Since 1997, several genetic mutations have been positively associated with PD in affected families. Beside these monogenic cases, genetic susceptibility has been suggested to underlie the common idiopathic forms of PD. Indeed, recent genome-wide association studies have established that certain common gene variants occur with an increased frequency in people with idiopathic PD. It is however clear that environmental factors, such as exposure to certain toxins, may underlie many cases of idiopathic PD.

Despite their different etiologies, PD and HD have many things in common. Both diseases heavily affect the network functions of the cortico-basal ganglia-thalamo-cortical circuitry. Disturbances in corticostriatal synaptic transmission and atrophic changes of striatal projection neurons are key players in their pathophysiology. And although different events may trigger the primary neurodegenerative process, there are striking commonalities in the pathogenic pathways involved. The commonalities include, misfolding and aggregation of proteins, deficient protein degradation, neuroinflammation, mitochondrial dysfunction, glial pathology, deficits in axonal transport, loss of synapses, glutamate dyshomeostasis, and altered signaling downstream of both dopamine and glutamate receptors. It is therefore not surprising that PD and HD continue to attract the attention of overlapping communities of basic and clinical investigators. In both disease areas, current basic research aims at either determining the mechanisms of neurodegeneration, or improving animal models that will expedite the mechanistic studies. This basic research has already spurred a number of clinical trials of either symptomatic treatments, or approaches to slow the progression of the disease. However, none of the putative disease-modifying approaches thus far tested have yet translated into successful treatments for the human diseases. It is therefore very important to intensify research efforts that can lead to an improved understanding of the pathobiology of PD and HD, revealing new potential therapeutic targets. This kind of research is heavily dependent on the possibility to reproduce key features of PD and HD in simpler models that are accessible to in-depth biological investigation. Animal models are indispensable to unravel non-cell autonomous mechanisms of disease, and the relationship between neurodegeneration and behavioural impairment, or overt neurological deficits can only be addressed in whole-animal models of disease.

We hope that this volume will aid the research on HD and PD by providing an up-to-date coverage of current animal models that can be used to investigate particular pathways, and to link them to both system-level pathophysiology and behavioural abnormalities. No animal models will ever reproduce all the complexity of a human neurological disease, and it is therefore very important for the research community to rely on an articulate repertoire of models tailored to mimic the specific features to be investigated in each study.

The HD part opens with a comprehensive overview of the clinical features of HD by Ghosh and Tabrizi ("[Clinical Aspects of Huntington's Disease](#)") including available symptomatic treatments and new data from large clinical natural history studies, which have identified potential biomarkers and predictors of disease onset and progression to guide future therapeutic interventions. The next chapter ("[The Neuropathology of Huntington's Disease](#)", by Waldvogel, Kim, Tippet, Vonsattel, Faull) then provides a detailed description of the current knowledge of neuropathological changes in human HD brains and emphasizes the association of the heterogeneous nature of HD symptomatology with the heterogeneous nature of the neurodegeneration that occurs throughout the different regions of the brain in different HD patients. Chapter by De Souza and Leavitt ("[Neurobiology of Huntington's Disease](#)") then outlines our current knowledge on the normal

function of huntingtin and the main pathomechanisms by which mutant huntingtin may mediate neurodegeneration in HD.

With the basis set in the three previous chapters, Brooks and Dunnett review in their chapter (“[Mouse Models of Huntington’s Disease](#)”) the similarities and differences in the neurobiology found in the mouse models of HD and the human disease state. Their review also discusses how abnormalities in functional circuitry and neurotransmitter systems impact on the behavioural readouts across the mouse lines and how these may correspond to the deficits observed in patients. While mouse models have provided invaluable information on the pathogenesis and pathophysiology of HD, they might not be the most adequate species for mimicking the human disease. Rats for example have more developed motor learning and motor capabilities. Assays of cognition are more robust in rats than mice, and test more advanced functional aspects. Carreira, Jahanshahi, Zeef, Kocabicak, Vlamings, von Hörsten and Temel provide a comprehensive review (“[Transgenic Rat Models of Huntington’s Disease](#)”) on the transgenic rat models for HD that have been generated so far. However, both rat and mouse model of HD lack the striking neuronal cell loss observed in HD patients. Chapter “[Large Animal Models of Huntington’s Disease](#)” by Li and Li reviews important findings from these pig, sheep and non-human primate models including a discussion on why neurodegeneration is more readily observed in these models than in rodent models for HD.

Last but not least, Mrzljak and Munoz-Sanjuan provide a thorough and comprehensive review of the current state of therapeutic development for the treatment of HD including ongoing randomized clinical trials in HD as well as the past and present preclinical development of small molecules and molecular therapies at CHDI with an outlook on future directions.

The PD part opens with Chap. “[Clinical and Pathological Features of Parkinson’s Disease](#)”, by Schneider and Obeso, which sets the stage for all the following ones. This chapter reviews the pathological and symptomatic features that need to be considered when creating or validating experimental models of PD. In the next chapter, Johnson and Fox review state-of-the-art symptomatic models of PD having utmost face validity to the human condition (“[Symptomatic Models of Parkinson’s Disease and L-DOPA-Induced Dyskinesia in Non-human Primates](#)”).

Chapter by Cebrian, Loike and Sulzer (“[Neuroinflammation in Parkinson’s Disease Animal Models: A Cell Stress Response or a Step in Neurodegeneration?](#)”) compares and summarizes findings on neuroinflammatory responses in a wide range of toxin-based and genetic models of PD. The following Chap. “[Viral Vector-Based Models of Parkinson’s Disease](#)” (by Van der Perren, Van den Haute, Baekelandt) provides an overview of current viral vector-based PD models in rodents, both those based on overexpression strategies for autosomal dominant genes (such as  $\alpha$ -synuclein and LRRK2) and those based on knockout or knock-down strategies for autosomal recessive genes, such as parkin, DJ-1 and PINK1.

The severe cognitive decline occurring in advanced stages of PD is associated with cortical and limbic alpha-synuclein pathology. Hatami and Chesselet have therefore chosen to summarize the cognitive deficits observed in several transgenic mouse lines overexpressing wild-type or mutated alpha-synuclein. The authors also

discuss how these models relate to the disease process in humans (“[Transgenic Rodent Models to Study Alpha-Synuclein Pathogenesis, with a Focus on Cognitive Deficits](#)”).

In addition to alpha-synuclein, the gene coding for leucine-rich repeat kinase 2 (LRRK-2) is implicated in autosomal dominant forms of PD. A comprehensive summary of the different models employed to understand *LRRK2*-associated PD is provided by Daniel and Moore (“[Modeling LRRK2 Pathobiology in Parkinson’s Disease: From Yeast to Rodents](#)”). This chapter covers a wide variety of experimental models, including yeast, invertebrates, transgenic and viral-based rodents, and patient-derived induced pluripotent stem cells.

The PD section of the volume closes with Chap. “[Models of Multiple System Atrophy](#)” (by Fellner, Wenning, and Stefanova). This chapter gives an overview of the atypical Parkinson’s syndrome, Multiple System Atrophy (MSA) and summarizes the currently available MSA animal models and their relevance for pre-clinical testing of disease-modifying therapies.

As with any book, it is impossible to cover every aspect of the current literature, and some important lines of research may not have been sufficiently covered here due to space restrictions. We are very grateful to all our dedicated colleagues who have made great contributions to this book. We think that all chapters provide an accurate and thorough overview of our current knowledge of the behavioural neurobiology of Huntington’s and Parkinson’s Disease and hope that the readers will enjoy each chapter as we did, and that this book will be helpful to them in their research efforts to understand and find treatments for these devastating diseases.

Hoa Huu Phuc Nguyen  
M. Angela Cenci

Behavioral Neurobiology of Huntington's Disease and  
Parkinson's Disease

Nguyen, H.H.P.; Cenci, M.A. (Eds.)

2015, XIII, 397 p. 95 illus., 25 illus. in color., Hardcover

ISBN: 978-3-662-46343-7