# Preface

## Cingulate Neurobiology in the Context of a Human Brain Imaging Revolution

Over the past 15 years parts of cingulate cortex have been activated in thousands of neuroimaging studies and it has become a primary site of interest in structural and functional analyses of many neurological and psychiatric diseases. As the first few hundred reports were made, investigators often generalized its function to attention because it was activated in many different imaging paradigms and attention-to-"X" often activated some part thereof. Now, however, the specific functions (i.e., the term "X") of individual regions, subregions, and even some areas of the human cingulate cortex are being clarified and we understand specific cingulate information processing functions beyond its possible involvement in attention shifting and general memory functions. The number of Medline citations in 5 year periods starting in 1976 with "cingulate" as a keyword generates a parabolic function: 117, 293, 441, 787, 1529, 2543. Thus, the number of publications has grown by almost 22 times in 30 years. These new insights have led to applying very precise task paradigms and new localization information to understanding impairments of specific functions in human neuron diseases.

The scientific process engages primarily in the reduction of complex events to its simplified components and this is certainly true of brain function. Surprisingly little time, however, is spent putting the system back together in the form of models such that an understanding of the brain itself can be achieved. The primary mission of this book is to codify the recent burst of new information on human cingulate cortex and its diseases and to *synthesize* these with other approaches including neurophysiology and neuroanatomy in experimental animals; mainly in monkeys. The book considers cingulate infrastructure in terms of its cytology, receptor binding and circuitry, functions such as emotion and autonomic and skeletomotor regulation, pain processing and chronic stress syndromes, cognition, and visuospatial orientation. Many diseases that have a direct impact on cingulate cortex including a primary cingulate-mediated etiology include chronic pain and stress syndromes, depression, alterations in movement and cognition such as obsessive-compulsive and attention-deficit/hyperactivity disorders, and neurodegenerative diseases such as schizophrenia, mild cognitive impairment, dementia with Lewy bodies, and Alzheimer's disease. Thus, this volume represents a major synthesis of basic and clinical science research in the cingulate cortex. In terms of the specific circuit models of functions and disease, this volume will serve as a resource of specific hypotheses that will influence human imaging and animal research over the coming decades.

### Cingulate Neurobiology

In the purest sense, neuroscience is an integrative process that finds common endpoints by building on the principles of brain organization and function derived in many areas of academic research. No single methodology, model system, or clinical population can resolve important problems in neuroscience nor can the exploits of investigators in any one discipline. Although cingulate cortex has always had a prominent place in grand theories of limbic functions (Gerdy, 1838; MacLean, 1990), the mechanisms of its contributions to brain function have been elusive, early limbic theories have failed, and cingulate research now emphasizes facts rather than grand speculation. According to the structure of scientific revolutions proposed by Kuhn (1962), we may conclude that the limbic paradigm was failing throughout the 1990s, including theories tied

to cingulate cortex, and the paradigm shift was underway that was driven to a large extent by the revolution in human imaging and the ability to explore internal feelings in human subjects and changes associated with many neuronal diseases. Failure of early limbic paradigms and dispersion of core cingulate research within the neuroscience literature led to the need to codify observations and to develop and centralize experimentally compelling theories and hypotheses. This is the niche of the present volume.

A tradition of integrative cingulate research was initiated by a pioneering group of investigators in the early 1990s who sought to bring together the important principles of cingulate organization and its dysfunction in neuronal diseases. *Neurobiology of Cingulate Cortex & Limbic Thalamus* was the first volume to bring together the specific circuits and neuron impairments observed in neurological and psychiatric diseases of the cingulate gyrus. The 44 investigators responsible for this volume produced a substantial work and began a tradition of integrative cingulate neurobiology that becomes more important with each passing decade and it is driving the paradigm shift to new limbic theories of cingulate functions and diseases today.

The problems of limbic theory in general and concepts of cingulate function in particular became pronounced during the preparation of *Neurobiology of Cingulate Cortex & Limbic Thalamus*. Many authors questioned the nature of "limbic" functions in cingulate cortex as new findings about the cingulate motor areas and their role in skeletomotor control came to the forefront of research. As the editor, I too had doubts about the role of the entire cingulate gyrus in "limbic" functions. For example, at what point is a visual response "limbic?" Carl Olson and his colleagues evaluated neuron responses in posterior cingulate cortex in behaving monkeys and could not find activity associated with the reward properties of particular movements. Conversations with Paul MacLean over the nature of visual responses that he recorded in posterior cingulate cortex have been summarized in his treatise on the triune brain (1990), yet the emotion-coded features of visual activity were not understood.

In spite of these doubts, there were the observations of EJ Neafsey and his colleagues that subgenual anterior cingulate cortex is a visceromotor control region and directly regulates autonomic functions. Thus, some parts of cingulate cortex are definitely involved in what are generally considered limbic functions. At the request of EJ, we began the effort to localize particular functions in the primate cingulate cortex and, over the next decade, this activity resulted in a four-region map or what is now termed the four-region neurobiological model. This localization perspective provides a new context for understanding the specific role of cingulate cortex in emotion and emotional expression and requires a substantial reconsideration of the concept of limbic functions in terms of "submodalities" of emotion. It is from this perspective that the present volume was launched and these issues are considered in detail. Indeed, the concept of submodalities of emotional processing provides a basis for understanding how cingulate cortex processes small packets of information and employs them to direct the outputs of the limbic motor systems including the cingulate motor areas as discussed in Chapters 13 and 26.

With the explosion of functional imaging in healthy human and patient populations over the past 15 years, the need for continued integrative efforts has increased. The need for a substantially new vision of the 1993 volume is often apparent in discussions at professional meetings where interesting and important but isolated facts are often discussed outside a broad organizational framework. The neuropathology of depression, for example, involves the subgenual anterior cingulate cortex, however, the many findings in this literature have never been integrated such that changes in particular classes of neurons can be related changes in glia, cingulate circuitry, and information processing functions. The need to integrate cingulate neurobiology has never been greater and how to integrate this aspect of neurobiology and disease is a major problem that can only be resolved by a large cadre of committed investigators.

## Cingulate Neurobiology and Disease

The present volume is not a second edition of the first one. Instead, the 63 authors seek a fundamentally new and qualitatively unique strategy based on extensive new findings. This volume emphasizes primate brain organization, primate disease models, monkey neuroanatomy and neurophysiology, and human patient populations, although rodent studies are pivotal to some chapters. Many investigators in the latter part of the past century sought to understand the structure and functions of human brain with the most recent imaging modalities and to integrate this information with histological and neurophysiological observations. We now seek the Holy Grail of the next century; objective diagnosis of human brain diseases and documentation of the efficacy of cingulate-mediated therapeutics using hypnotic, cognitive-behavioral, drug, and other, yet to be discovered, cingulate-mediated strategies.

A critical consideration in producing this volume is defining functional units of cortex along non-traditional perspectives. Indeed, one wonders, what is the fundamental functional unit of cingulate cortex? The answer

to such a question has profound implications because it will serve as the basis for assessing functional impairments in chronic disease. Consider posterior cingulate cortex for an example. It has been activated with emotional and non-emotional facial expressions and words, during attention tasks such as the Stroop-interference task, in topokinetic tasks as taxi drivers imagine routes through London, more readily by faces and words related to self rather than in relation to others, and single neurons are optimally driven by the position of the eye in the orbit and large visual receptive fields. Is there more than one functional substrate in this region, are there many functions processed in each area, or does each cytologically unique area provide for functional heterogeneity? Although there are at least three divisions of the posterior cingulate gyrus, including the dorsal and ventral posterior cingulate and retrosplenial cortices, there may be as many as 14 individual areas in this region including parts of the retrosplenial areas and there appear to be many overlapping vertical modules with different functions as well. We do not yet understand the overarching functional substrates that characterize each major region including those of the posterior cingulate gyrus. This issue of defining functional units is being replayed for each part of the cingulate gyrus and likely will for decades to come as methods resolve to functional analyses of individual areas.

This volume crosses disciplinary, departmental, and clinical research boundaries as required for the critical analysis of cingulate cortex organization and disease. For example, many sections have a consideration of depression as when reviewing pain processing, chronic pain and stress syndromes, neurodegeneration, and the section on depression itself. Mayberg's (2003) evaluation of the general features of depression in many diseases concludes there are "critical common pathways for the expression of depression in distinct neurological populations with potential relevance to primary mood disorders" and **Chapter 11** provides a general overview of neuropsychiatric diseases in the context of altered cingulate functions. The neurobiology of disease defines patterns of circuit disruption that are common to many clinical populations and this is not limited to depression. Indeed, pathologies of cingulate cortex do not evolve according to the DSM-IV criteria and the mechanisms of psychiatric disease and the etiological impact of each on cingulate cortex is not yet understood.

## Cingulocentric Circuit Models "versus" Network Models

There are two approaches to the connectivity and functions of any cortical area. One approach seeks to identify specific connections that drive/mediate particular functions, while the other emphasizes a broader network of connected areas and general functions such as in the attention networks and pain neuromatrix. The present volume emphasizes the former types of models and seeks to explain individual functions of cingulate cortical subregions and areas. These models can be extended to accommodate changes associated with neuron diseases and remodeling following drug and other therapeutic interventions. At no point does the focus on cingulate cortex preclude the larger network of other cortical and subcortical structures nor does it imply that cingulate cortex is the only player in a function or disease process; the issue is the contribution of cingulate cortex itself. For example, there are many cortical premotor areas yet two additional ones are in the cingulate sulcus. Without detracting from the many others, it remains an important question as to what unique role the two cingulate premotor areas play in behavior.

Cingulate circuitry models are pivotal to most chapters in this book and circuitry is used in its broadest definition to refer to a directional flow of information. Although circuit models include those derived from monosynaptic transport studies in monkey, these studies have become so detailed it is often difficult to discern the exact direction and flow of information through these systems. Furthermore, some areas in the human brain do not exist in the monkey and cannot be studied with these methods; an example of such an area is area 32'. In the human, correlation studies in resting glucose and functional and behavioral activation states provide important functional interactions, some of which have support in monkey studies as monosynaptic connections. The circuit concept is broadly used to include specific transmitter systems and their receptor binding as well as extrinsic projection patterns. In the longer term, of course, circuit models will be broadened to include neurochemical transduction pathways on single neurons and in functional brain circuits.

## Strategic Issues and Chapter Organization

In designing this volume, it was determined that a thorough grounding in neurocytology was necessary because current human neuroimaging methods still rely on neuron-free structural images. To assist in providing the cytological meat for the imaging bones, we included not only very detailed cytological information on the cingulate areas and regions, but also on subcortical structures. Line drawings of coronal sections through the thalamus, hypothalamus, and midbrain could have been used; however, this leaves too much to the imagination in instances where particular nuclei,

such as the parabrachial and subnucleus retricularis dorsalis, may be poorly understood by the broader research community and direct cingulate links could be very important. Instead, immunohistochemical preparations form the basis for discussing imaging, connections, and models of cingulate functions throughout the brain; not just in cingulate cortex. Consider figures in Chapters 10, 14, 15, and 22 in this regard. This mode of presentation provides exact details of cell structure and nuclear location and such information can be used to interpret activation sites in human imaging studies.

Another anatomical resolution issue in human imaging is the lack of information about specific monosynaptic connections. Although diffusion tensor imaging studies often claim to provide connection information, this is not the case. At best, it resolves the structure of white matter and does not have the resolution to establish point-to-point corticocortical connections nor projections to specific subcortical nuclei in the amygdala, hypothalamus, and midbrain. To close this information gap in human imaging, we incorporate a large body of non-human primate connection information. This circuitry provides concrete information not available in the human literature and is part of many circuitry assessments in the following chapters.

This volume is arranged in sections such that each builds sequentially on previous sections. Cingulate cortex structure, comparative anatomy, neurotransmitter receptor binding and immunohistochemistry, and large classes of connections with the thalamus and various cortical regions sets the framework for subsequent sections of functions including reward, cognitive, and pain processing. Final sections evaluate diseases that have early and cingulate-mediated symptoms. The critical cingulate focus is shown with imaging, neuropathology, and animal models. Although in decades past there were substantial sampling problems, the question now can be objectively considered as to whether or not cingulate cortex has a major and early role in the etiology of many diseases. Its role was often overlooked previously because surface recording electrophysiology is difficult on the medial surface and drug actions were often attributed to other regions due to a lack of understanding of the functions of cingulate cortex. Another theme in this volume is resolving the structure and function correlations and selective disease vulnerabilities throughout the cingulate gyrus. There has been a proliferation of subregions and areas due to cytological analyses and the fact that high resolution functional imaging strengthens such correlations and enhances the foundation upon which human studies are based.

Although the chapters are written from the unique perspectives of particular disciplines of scientific research, they also consider general issues common to all studies of cingulate cortex and links from the work in one chapter are often made to others. Some of these issues may have been overlooked in the general research literature and will be treated in detail here for the first time, while others will consider important logical issues that are raised in cingulate research but are not addressed in other brain regions. Individual chapters often consider some or all of the following issues: a) temporal relations of cingulate damage to disease progression and how early cingulate cortex is damaged, b) other relevant and interacting structures that are part of the pathology and correlation of seven cingulate subregions to primary sites of damage, c) correlations of cingulate damage with the expression of specific symptoms/evidence for functional determination, d) measures of cingulate damage with imaging, glucose, transmitter/receptor, neuron damage/loss, and markers, e) interpretive issues relating to each chapter, section, and the book as a whole.

## New Information in This Volume

Although books often summarize a literature with overviews, this volume is a substantial divergence from this approach. In addition to new perspectives and summaries, recent imaging findings and neuropathological observations are available in this volume for the first time. For example, ***Chapter 2*** is the first comprehensive autoradiographic assessment of the entire cingulate cortex for 15 transmitter systems in human brain. Ligand binding fingerprint analysis and multivariate models for each region and area provide the first viewing of the transmitter organization of the cingulate gyrus. In another example, ***Chapter 3*** presents exactly comparable photographs at many levels of magnification in rat, monkey, and human cingulate areas with the same histological preparations such that exact comparisons can be made among regions, subregions, and areas in each species for the first time. This results in the first determinations of which areas the human has that monkey does not have and these findings were reserved for the present volume. Examples of other firsts are provided in the next paragraph.

***Chapters 4 and 6:*** These are broad overviews of thalamic and temporocingulate interactions. Of particular importance is the dichotomy drawn within posterior cingulate cortex and how this underpins the unique functions of each subregion. ***Chapter 5:*** For the first time, frontocingulate circuitry has been reviewed in the context of the two cingulate motor areas in addition to the gyral parts of cingulate cortex. ***Chapter 7:*** This is the first report of dopamine-innervation selective to the rostral cingulate motor area and demonstration of the impact of prenatal ethanol exposure on

the development of dopamine systems in the monkey cingulate gyrus. ***Chapter 12:*** This is the first comprehensive review of the role of anterior midcingulate cortex in cognition and its involvement in attention deficit/hyperactivity disorder and pharmaceutical treatment impact in this region. ***Chapter 13:*** This is the first time resting glucose studies of parietal and midcingulate areas are used to understand differential information flow through the dorsal and ventral posterior cingulate cortices. Comparative observations are made in the context of unique inferior parietal areas in the human and monkey and information flow evaluated in terms of a six-stage model whereby ventral posterior cingulate cortex extracts information that is valence coded, context dependent, and self relevant. ***Chapter 14:*** This is the first presentation of the Cingulate Premotor Pain Model that codifies four specific roles of the cingulate gyrus in pain processing. This model extends the role of the gyral surface in sensory processing to motor output from the sulcal motor areas. ***Chapter 17:*** This is the first time a specific circuit model of cingulate-mediated hypnosedation has been proposed based on the hypnotic method of pleasant personal reflection. ***Chapter 19:*** The role of cingulate cortex in maintaining neuropathic pain is explored and psychological mechanisms are used to develop a new cortical model of allodynia. ***Chapter 22:*** The links between anterior cingulate and midcingulate efferents and those of the locus coeruleus have never been explored. New immunohistochemical preparations are shown of dopamine-β hydroxylase, cingulate-mediated mechanisms of allostasis and chronic stress are reviewed and two circuit models are defined to explain functional pain and stress syndromes with primarily nocigenic and psychogenic origins. ***Chapter 23:*** This chapter provides the first complete circuit viewpoint on cortical stress mechanisms and the impact of depression on cingulate cortex during chronic functional pain and stress syndromes. ***Chapter 25:*** A postmortem assessment of 10 depression cases is performed for the first time in terms of neuron and glial densities and laminar patterns of neurodegeneration in the framework of cytoarchitectural disorganization. The deposition of amyloid-β 42 in both bipolar disorder and major depression is reported for the first time as is a model of the temporal course of neurodegeneration and toxic peptide deposition. ***Chapter 26:*** This chapter presents the first circuit model showing how the altered flow of valenced information and uncoupling of autonomic arousal with such information likely accounts for the cingulate-mediated aspects of psychopathic behavior. Deficits in significance coding of sensory information, decision making, empathy, and the recognition of pain in others and language impairments are reviewed in detail in terms of cingulate subregional functions. ***Chapter 27:*** This is the most comprehensive review available with extensive tables on the role of cingulate cortex in obsessive-compulsive behavior. ***Chapter 28:*** This chapter provides a new open-loop circuitry for anterior cingulate cortex through the basal ganglia that updates a famous closed loop circuit that modeled interactions mainly through midcingulate cortex. Disruptions in the open-loop system are evaluated in terms of symptoms in major psychiatric illnesses. ***Chapter 29:*** Human imaging has provided a major new impetus to understanding cingulate seizure activity; whereas in previous decades cingulate studies of seizure activity were limited to subdural recordings and they were quite rare. This is the first major review of how functional imaging is radically changing our understanding of the cingulate epilepsies. ***Chapters 30 and 31:*** This is a rare pairing of chapters that evaluates both human structural and functional imaging of human cingulate cortex as well as the specific cellular mechanisms of schizophrenia based on elegant immunohistochemical analyses. ***Chapter 32:*** Although dementia with Lewy bodies is diagnosed with postmortem samples of anterior midcingulate cortex, there are no systematic studies of the cingulate gyrus in terms of the overall expression of α-synuclein or laminar patterns of neurodegeneration and this chapter presents the first such analysis. ***Chapter 33:*** Some forms of mild cognitive impairment transition to Alzheimer's disease and the posterior midcingulate and dorsal posterior cingulate cortices are pivotal to this process. This chapter presents new immunohistochemical findings and a detailed assessment of the early and most vulnerable "hot spot" in a case that expresses proteins confirming this is a case of early Alzheimer's disease. ***Chapters 34 and 35:*** This pair of chapters considers symptom and cingulate cortex imaging in the context of multivariate statistics and variability of cingulate neuropathology. The authors consider the extent to which variations in cingulate involvement represent uniform variability on a continuum of disease progression, subgroups, or neuropathological subtypes of the disease. ***Imaging Appendix Chapter 36:*** Since there are few consistent landmarks by which to identify particular regions and subregions of interest in the cingulate cortex, this chapter provides protocols for localizing subregions of interest in Talairach and ICBM152 coordinate systems guided by the cytoarchitecture of postmortem studies with a relatively high degree of security. Within subject variability is resolved in each subregion so that sulcal variability contributes less than usual to the volumetric outcomes.

Finally, I would like to thank the National Institute of Neurological Diseases and Stroke for their support of our studies of cingulate structure, connections, functions, pain processing, and neurodegenerative diseases

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Brent Alan Vogt
*Cingulum NeuroSciences Institute*
Manlius, NY, USA April 2008

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# List of Contributors


**Gary Aston-Jones** Department of Physiology and Neuroscience, Medical University of South Carolina, Georgia, SC, USA

**Francine M. Benes** Program in Structural and Molecular Neuroscience, McLean Hospital, Belmont, MA, and Program in Neuroscience and Department of Psychiatry, Harvard Medical School, Boston, MA, USA

**Sabina Berretta** Program in Structural and Molecular Neuroscience, McLean Hospital, Belmont, MA, USA and Program in Neuroscience and Department of Psychiatry, Harvard Medical School, Boston, MA, USA

**J. Douglas Bremner** Emory University School of Medicine, Department of Psychiatry, Atlanta, GA, USA

**George Bush** Psychiatric Neuroscience Division, Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

**Ronald B. Chin** Department of Psychiatry, University of Texas Southeastern Medical School, Dallas, TX, USA

**Robert C. Coghill** Department of Neurobiology and Anatomy, Wake Forest University School of Medicine, Winston-Salem, NC, USA

**Miles G. Cunningham** Program in Structural and Molecular Neuroscience, McLean Hospital, Belmont, MA, and Program in Neuroscience and Department of Psychiatry, Harvard Medical School, Boston, MA, USA

**Stuart W.G. Derbyshire** School of Psychology, University of Birmingham, Edgbaston, Birmingham B12 2TT UK, USA

**Orrin Devinsky** Department of Neurology and Comprehensive Epilepsy Center, New York University School of Medicine, New York, NY, USA

**Marie-Elisabeth Faymonville** Department of Anesthesiology and Reanimation, University of Liège, Liège, Belgium

**K. Nikos Fountoulakis** Department of Psychiatry, Division of Neuropsychiatry, HUG Belle-Idée University of Geneva School of Medicine, Geneva, Switzerland

**Luis Garcia-Larrea** Central Integration of Pain – Inserm U879, France Neurological Hospital, University Lyon, France

**Barbara Gisabella** Program in Structural and Molecular Neuroscience, McLean Hospital, Belmont, MA, and Program in Neuroscience and Department of Psychiatry, Harvard Medical School, Boston, MA, USA

**Joel D. Greenspan** Department of Biomedical Sciences, School of Dentistry, and Program in Neuroscience, University of Maryland, Baltimore, MD, USA

**Elizabeth Head** Institute for Brain Aging and Dementia, University of California, Irvine, CA, USA

**Patrick R. Hof** Departments of Neuropathology and Neuroscience, Mount Sinai School of Medicine, New York, NY, USA

**Paul E. Holtzheimer** Department of Psychiatry and Behavioral Sciences, Emory University, 1841 Clifton Road NE, Atlanta GA, USA

**Anthony K.P. Jones** Human Pain Research Group, Institute of Neuroscience, University of Manchester Rheumatic Diseases Centre, Hope Hospital, Salford, UK

**Julene K. Johnson** Department of Neurology, Memory and Aging Center, UCSF, 350 Parnassus, San Francisco, CA, USA

**Enikö Kövari** Department of Psychiatry, Division of Neuropsychiatry, HUG Belle-Idée University of Geneva School of Medicine, Geneva, Switzerland

**Bhavna Kulkarni** Human Pain Research Group, Institute of Neuroscience, University of Manchester Rheumatic Diseases Centre, Hope Hospital, Salford, UK

**Richard D. Lane** Department of Psychiatry, University of Arizona, Tucson, AZ, USA

**Steven Laureys** Cyclotron Research Centre and Department of Neurology, CHU Sart Tilman, University of Liège, Liège, Belgium

**H. Chris Lawson** Neurosurgery Department, Johns Hopkins Hospital, Baltimore, MD, USA

**Frederick A. Lenz** Neurosurgery Department, Johns Hopkins Hospital, Baltimore, MD, USA

**Fausta Lui** Department of Biomedical Sciences, University of Modena and Reggio Emilia, Italy

**Joseph Maarrawi** Central Integration of Pain – Inserm U879, France, Neurological Hospital, University Lyon, France

**Pierre Maquet** Cyclotron Research Centre and Department of Neurology, CHU Sart Tilman, University of Liège, Liège, Belgium

**Athinoula A. Martinos** Center for Functional and Structural Biomedical Imaging, Massachusetts General Hospital, Massachusetts Institute of Technology & Harvard Medical School, Boston & Cambridge, MA, USA

**Helen Mayberg** Department of Psychiatry and Behavioral Sciences, Emory University, 1841 Clifton Road NE, Atlanta GA, USA

**Frank A. Middleton** Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA

**Michael W. Miller** Department of Neuroscience and Physiology, State University of New York-Upstate Medical University, Syracuse NY, USA
Research Service, Veterans Affairs Medical Center, Syracuse NY, USA

**Robert J. Morecraft** Division of Basic Biomedical Sciences, Laboratory of Neurological Sciences, Sanford School of Medicine, University of South Dakota, Vermillion, South Dakota, USA

**Siddhartha Nadkarni** Department of Neurology and Comprehensive Epilepsy Center, New York University School of Medicine, New York, NY, USA

**S. Ohara** Neurosurgery Department, Johns Hopkins Hospital, Baltimore, MD, USA

**Jonathan A. Oler** Department of Psychiatry, HealthEmotions Research Institute, University of Wisconsin, Madison, WI, USA

**Joseph O'Neill** Division of Child and Adolescent Psychiatry, Semel Institute for Neurosciences, UCLA, Los Angeles, CA, USA

**Nicola Palomero-Gallagher** Institute of Medicine, JARA, Research Centre Jülich, 52425 Jülich, Germany.

**Roland Peyron** Central Integration of Pain – Inserm EMI-342, France University Hospitals of St Etienne, France

**Roger K. Pitman** Department of Psychiatry , Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA

**Carlo Adolfo Porro** Department of Biomedical Sciences, University of Modena and Reggio Emilia, Italy

**Teresa A. Powrozek** Department of Neuroscience and Physiology, State University of New York-Upstate Medical University, Syracuse NY, USA

**Adrian Preda** Department of Psychiatry, University of Texas Southeastern Medical School, Dallas, TX, USA
Present address: Department of Psychiatry and Human Behavior, UC Irvine School of Medicine, Orange, CA, USA

**Dushyant P. Purohit** Departments of Neuropathology and Neuroscience, Mount Sinai School of Medicine, New York, NY, USA

**Gregory J. Quirk** Department of Physiology, Ponce School of Medicine, Ponce, Puerto Rico

**Scott L. Rauch** Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

**Laurie M. Rilling** Department of Psychiatry, University of Texas Southeastern Medical School, Dallas, TX, USA

**Edmund T. Rolls** Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford, OX1 3UD, England

**Eric Salmon** Cyclotron Research Centre, University of Liège, Liège, Belgium

**Dimitrios Samaras** Department of Psychiatry, Division of Neuropsychiatry, HUG Belle-Idée University of Geneva School of Medicine, Geneva, Switzerland

**Sanjaya Saxena** Division of Child and Adolescent Psychiatry, Semel Institute for Neurosciences, UCLA, Los Angeles, CA, USA

**Hideshi Shibata** Department of Behavioral Physiology, Tokyo Metropolitan Institute for Neuroscience, Tokyo Metropolitan Organization for Medical Research, Fuchu, Tokyo 183-8526, Japan, Laboratory of Veterinary Anatomy, Field of Basic Veterinary Science, Division of Animal Life Science, Institute of Symbiotic Science and Technology, Tokyo University of Agriculture and Technology, Fuchu, Tokyo 183-8509, Japan

**Lisa M. Shin** Department of Psychology, Tufts University, Medford, MA, and Department of Psychiatry, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA

**Robert W. Sikes** Northeastern University, Department of Physical Therapy, Boston, MA, USA

**Thomas L. Sobel** Ahmanson-Lovelace Brain Mapping Institute, Department of Neurology, UCLA, Los Angeles, CA, USA

**Carol A. Tamminga** Department of Psychiatry, University of Texas Southeastern Medical School, Dallas, TX, USA

**Jun Tanji** Professor, Brain Science Research Institute, Tamagawa University, Tamagawa-Gakuen, Machida, Tokyo, 194-8610, Japan

**Brent A. Vogt** Department of Neuroscience and Physiology, State University of New York-Upstate Medical University, Syracuse NY, USA Cingulum NeuroSciences Institute, Manlius, NY, USA

**Leslie J. Vogt** Department of Neuroscience and Physiology, State University of New York-Upstate Medical University, Syracuse NY, USA Cingulum NeuroSciences Institute, Manlius, NY, USA

**Paul J. Whalen** Department of Psychological and Brain Sciences, Dartmouth College, Hanover, NH, USA

**Masao Yukie** Department of Child Psychology, Tokyo Future University, 34-12, Akebono-cho, Senju, Adachi-ward Tokyo, Japan, 120-0023

**Karl Zilles** Institute of Medicine, Brain Imaging Centre West, Research Centre Jülich, 52425 Jülich, JARA, C. & O. Vogt-Institute of Brain Research, Heinrich Heine University Düsseldorf, 40001 Düsseldorf, Germany