

Gerald F. Gebhart  
Robert F. Schmidt  
*Editors*

# Encyclopedia of Pain

*Second Edition*

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Editors

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Second Edition

With 795 Figures and 217 Tables

 Springer Reference

*Editors*

Gerald F. Gebhart  
Department of Anesthesiology  
Center for Pain Research  
University of Pittsburgh  
Pittsburgh, PA, USA

Robert F. Schmidt  
Physiologisches Institut der  
Universität Würzburg  
Würzburg, Germany

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## Preface to the Second Edition

As was pointed out in the Preface to the first edition, pain is the principal reason individuals seek medical and dental attention. Fortunately, acute tissue insults associated with pain – and typically inflammation – readily resolve with appropriate treatment and care. Chronic pain states, in contrast, are notoriously difficult to manage and are commonly associated with comorbidities (e.g., depression, cross-organ sensitization) and reduced quality of life. Indeed, chronic pain has come to be considered by some as a disease in its own right. This edition of the *Encyclopedia of Pain* updates the content of the 1st edition and introduces new topics consistent with advances in our knowledge of underlying mechanisms of pain. Thus, new content on channelopathies, expanded and updated material on the role of glia and immune-competent cell interactions with nociceptive neurons, and advances in imaging and changes in brain structure in chronic pain states are included in this edition.

The cardinal objective of research on pain is the translation of knowledge between the laboratory and the clinic. The present prevailing refrain is “bench to bedside,” but in fact many ideas for research in pain derive from clinical observations and the absence of knowledge to explain clinical pain states. In the recent past, basic and clinical science research has seen the application of imaging techniques to visualize areas of the brain that are involved in both the sensory and affective aspects of pain, cloning of pain-related channels and receptors, and the application of elegant genetic manipulations that selectively “label” functionally distinct dorsal root ganglion sensory and spinal neurons, two-photon imaging, and optogenetic approaches.

Accordingly, much is new in this second edition of the *Encyclopedia of Pain*. The number of authors who have contributed to this edition is close to 800. In addition to a print edition, the publisher, Springer-Verlag, will produce an electronic version that will make comprehensive searches easy to manage. The electronic version, to be made available on the online publishing platform SpringerReference, can be updated regularly to ensure that the content remains current.

October 2013  
Gerald F. Gebhart  
Pittsburgh, PA, USA

Robert F. Schmidt  
Würzburg, Germany



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## Preface to the First Edition

As all medical students know, pain is the most common reason for a person to consult a physician. Under ordinary circumstances, acute pain has a useful, protective function. It discourages the individual from activities that aggravate the pain, allowing faster recovery from tissue damage. The physician can often tell from the nature of the pain what its source is. In most cases, treatment of the underlying condition resolves the pain. By contrast, children born with congenital insensitivity to pain suffer repeated physical damage and die young (see Sweet WH (1981) *Pain* 10:275).

Pain resulting from difficult to treat or untreatable conditions can become persistent. Chronic pain “never has a biologic function but is a malefic force that often imposes severe emotional, physical, economic, and social stresses on the patient and on the family. . .” (Bonica JJ (1990) *The Management of Pain*, vol 1, 2nd edn. Lea & Febiger, Philadelphia, p 19). Chronic pain can be considered a disease in its own right.

Pain is a complex phenomenon. It has been defined by the Taxonomy Committee of the International Association for the Study of Pain as “An unpleasant emotional and sensory experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey H and Bogduk N (1994) *Classification of Chronic Pain*, 2nd edn. IASP Press, Seattle). It is often ongoing, but in some cases it may be evoked by stimuli. Hyperalgesia occurs when there is an increase in pain intensity in response to stimuli that are normally painful. Allodynia is pain that is evoked by stimuli that are normally non-painful.

Acute pain is generally attributable to the activation of primary efferent neurons called nociceptors (Sherrington CS (1906) *The Integrative Action of the Nervous System*. Yale University Press, New Haven; 2nd edn, 1947). These sensory nerve fibers have high thresholds and respond to strong stimuli that threaten or cause injury to tissues of the body. Chronic pain may result from continuous or repeated activation of nociceptors, as in some forms of cancer or in chronic inflammatory states, such as arthritis.

However, chronic pain can also be produced by damage to nervous tissue. If peripheral nerves are injured, peripheral neuropathic pain may develop. Damage to certain parts of the central nervous system may result in central neuropathic pain. Examples of conditions that can cause central neuropathic pain include spinal cord injury, cerebrovascular accidents, and multiple sclerosis.



Research on pain in humans has been an important clinical topic for many years. Basic science studies were relatively few in number until experimental work on pain accelerated following detailed descriptions of peripheral nociceptors and central nociceptive neurons that were made in the 1960s and 1970s, by the discovery of the endogenous opioid compounds and the descending pain control systems in the 1970s and the application of modern imaging techniques to visualize areas of the brain that are affected by pain in the 1990s. Accompanying these advances has been the development of a number of animal models of human pain states, with the goal of using these to examine pain mechanisms and also to test analgesic drugs or non-pharmacologic interventions that might prove useful for the treatment of pain in humans. Basic research on pain now emphasizes multidisciplinary approaches, including behavioral testing, electrophysiology, and the application of many of the techniques of modern cell and molecular biology, including the use of transgenic animals.

The *Encyclopedia of Pain* is meant to provide a source of information that spans contemporary basic and clinical research on pain and pain therapy. It should be useful not only to researchers in these fields but also to practicing physicians and other health care professionals and to health care educators and administrators. The work is subdivided into 35 fields, and the Field Editor of each of these describes the areas covered in each in a brief review entry. The topics included in a field are the subject of a series of short essays, accompanied by key words, definitions, illustrations, and a list of significant references. The number of authors who have contributed to the encyclopedia exceeds 550. The plan of the publisher, Springer-Verlag, is to produce both print and electronic versions of this encyclopedia. Numerous links within the electronic version should make comprehensive searches easy to manage. The electronic version will be updated at sufficiently short intervals to ensure that the content remains current.

The editors thank the staff at Springer-Verlag who have provided oversight for this project, including Rolf Lange, Thomas Mager, Claudia Lange, Natasja Sheriff, and Michaela Bilic. Working with these outstanding individuals has been a pleasure.

July 2006

ROBERT F. SCHMIDT  
Würzburg, Germany

WILLIAM D. WILLIS  
Galveston, Texas, USA

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## About the Editors



**Gerald F. Gebhart** received his PhD from The University of Iowa at Iowa City, Iowa, USA, after which he completed a 2-year fellowship at the Université de Montréal, Montréal, Canada, under the direction of Herbert H. Jasper. He began his academic career in the Department of Pharmacology at The University of Iowa in 1973, where he developed a productive research program and led a Pain Interest Group. His career includes a sabbatical year in Heidelberg, Germany (1981–1982), and leadership as head of the Department of Pharmacology from 1996 to 2006. In 2006, Dr. Gebhart was named director of the Center for Pain Research, Department of Anesthesiology, the University of Pittsburgh at Pittsburgh, Pennsylvania, USA. Dr. Gebhart has served the pain community throughout his career. He was elected to the Board of Directors of the American Pain Society (1991–1994) and subsequently elected president of the APS (1997). In 2000, he became the founding editor of *The Journal of Pain*, the official journal of the APS, serving as editor-in-chief until 2010. Dr. Gebhart also served on the Council and later as president-elect, president, and past president of the International Association for the Study of Pain (2005–2012).

Dr. Gebhart is best known for his research contributions in descending modulation of pain and mechanisms of visceral pain, and was designated in 2004 by Thomson ISI as a Highly Cited Researcher (Neuroscience). His scientific contributions have been recognized with several awards, including a 5-year Bristol Myers-Squibb Award for Excellence in Pain Research (1989–1994), a 10-year MERIT Award from the National Institutes of Health (1993–2003),

the Frederick W.L. Kerr Award from the American Pain Society (1994), the Purdue Pharma Prize for Pain Research (2004), the Janssen Award in Gastroenterology (2005), the Founders Award from the American Academy of Pain Medicine (2006), and the Patrick D. Wall Award from the British Pain Society (2012).



**Robert F. Schmidt** studied medicine at Heidelberg University (Germany). He graduated in 1959 and was promoted to Dr.med. in the same year. After residencies in clinical disciplines, Dr. Schmidt went to the John Curtin School of Medical Research of the Australian National University in Canberra, ACT, where he worked under the head of the Department of Neurophysiology, Sir John C. Eccles. He received his Ph.D. in 1963, the same year Sir John was awarded the Nobel Prize for Physiology and Medicine.

Returning to Heidelberg Medical School, Dr. Schmidt continued his academic career. He completed his habilitation in 1964, becoming a tenured lecturer (Wissenschaftlicher Rat) in 1966 and an associate professor in 1970. After an 8-month sabbatical with Sir John at the State University of New York, Dr. Schmidt became professor and director of the Department of Physiology at the University of Kiel, Germany. In 1982, he moved to the University of Würzburg to take the same position in the Department of Physiology. In 2000, Dr. Schmidt became professor emeritus at this department.

The research work of Dr. Schmidt and his associates in both Kiel and Würzburg focused on the neurophysiology of fine sensory afferents and their connections and functions in the spinal cord. In Würzburg, he concentrated on the processes leading to the changes in response characteristics of nociceptive afferents (i.e., peripheral sensitization) during inflammation of joints, discovering in the process silent nociceptors, which have subsequently been described in all vertebrates studied, including humans. In addition, Dr. Schmidt has edited, coedited, authored, and coauthored numerous textbooks and monographs, most of them having several editions and translations.

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In recognition of his research contributions, Dr. Schmidt received many prizes, awards, and honors, including a D.Sc. honoris causa from the University of New South Wales, Sydney, Australia, and an Honorary Professorship from the University of Tübingen, Germany. He was elected to membership in the Akademie der Wissenschaften und der Literatur, Mainz, Germany. Dr. Schmidt is an Honorary Member of the Colombian Association for the Study of Pain, the Japan Physiological Society, the German Society for the Study of Pain, the German Pain Association, the International Association for the Study of Pain (IASP), and the German Physiological Society (in which he served as president in 1979). In 2000, he was awarded the Bundesverdienstkreuz 1st Class (Order of Merit of the German Federal Republic).



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## Section Editors



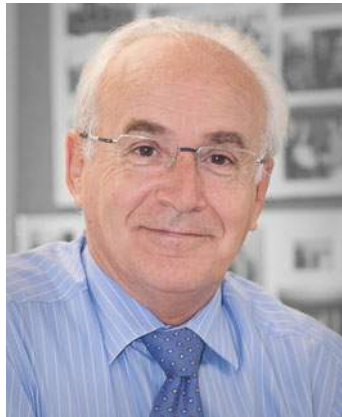
**Ebtesam Ahmed** College of Pharmacy and Health Sciences, St. John's University, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY, USA



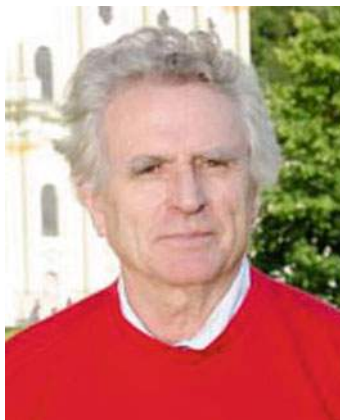
**A. Vania Apkarian** Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA



**Lars Arendt-Nielsen** Center for Sensory-Motor Interaction, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark



**Carlos Belmonte** Instituto de Neurociencias, Universidad Miguel Hernandez-CSIC, San Juan de Alicante, Spain



**Niels Birbaumer** Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany



**Nikolai Bogduk** University of Newcastle, Newcastle Bone & Joint Institute, Royal Newcastle Centre, Newcastle, NSW, Australia





**Jin Mo Chung** Department of Neuroscience and Cell Biology, University Chair in Neuroscience, University of Texas Medical Branch, Galveston, TX, USA



**Joyce DeLeo** Dartmouth Hitchcock Medical Center, Dartmouth Medical School, Hanover, NH, USA



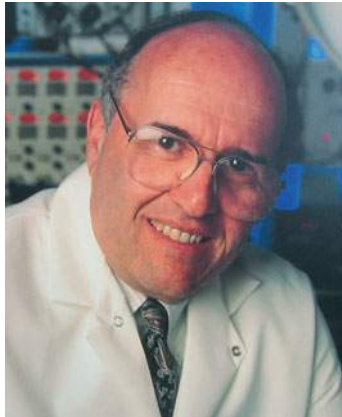
**Marshall Devor** Department of Cell & Developmental Biology, Institute of Life Sciences and Center for Research on Pain, The Hebrew University of Jerusalem, Jerusalem, Givat Ram, Israel



**Hans-Christoph Diener** Department of Neurology, University Hospital Essen, University Duisburg-Essen, Essen, Germany



**Jonathan O. Dostrovsky** Department of Physiology, University of Toronto, Toronto, ON, Canada



**Ronald Dubner** Department of Neural and Pain Sciences, University of Maryland Dental School, Baltimore, MD, USA



**Michel Y. Dubois** NYU Medical School, NYU Langone Medical Centers, Center for Research & Treatment of Pain, NYU Ambulatory Care Center, New York, NY, USA



**Nanna Brix Finnerup** Aarhus University Hospital, Danish Pain Research Center, Aarhus, Denmark



**Herta Flor** Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany



**Gerald F. Gebhart** Department of Anesthesiology, Center for Pain Research, University of Pittsburgh, Pittsburgh, PA, USA



**Maria Adele Giamberardino** Pathophysiology of Pain Laboratory and Centre for Fibromyalgia and Musculoskeletal Pain, Department of Medicine and Science of Aging, University of Chieti, Chieti, Italy



**Glenn J. Giesler** Department of Neuroscience, University of Minnesota, Minneapolis, MN, USA



**Peter Goadsby** Headache Center, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA



**Michael S. Gold** Department of Anesthesiology, Center for Pain Research, University of Pittsburgh, Pittsburgh, PA, USA



**Hermann O. Handwerker** Department of Physiology and Pathophysiology, University of Erlangen/Nürnberg, Erlangen, Germany



**Burkhard Hinz** Institute of Toxicology and Pharmacology, University of Rostock, Rostock, Germany





**Wilfrid Jaenig** Physiologisches Institut, Christian-Albrechts-Universität zu Kiel, Kiel, Germany



**Michaela Kress** Department für Physiologie und Medizinische Physik, Medizinische Universität Innsbruck, Innsbruck, Austria



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



**Tonya M. Palermo** Seattle Children's Hospital Research Institute, CW8-6 - Child Health, Behavior and Development, University of Washington, Seattle, WA, USA



**Frank Porreca** Department of Pharmacology, University of Arizona Health Sciences Center, Tucson, AZ, USA



**Russell K. Portenoy** Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY, USA



**James P. Robinson** Department of Anesthesiology & Pain Medicine,  
University of Washington, Seattle, WA, USA



**Hans-Georg Schaible** Department of Physiology - Neurophysiology,  
Friedrich-Schiller-University of Jena, Jena, Germany



**Robert F. Schmidt** Physiologisches Institut der Universität Würzburg, Würzburg, Germany



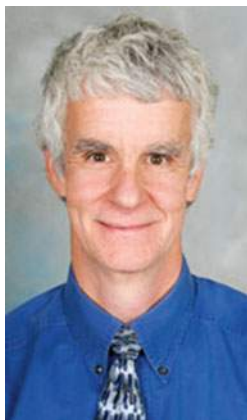
**Stephan A. Schug** School of Medicine and Pharmacology, Royal Perth Hospital, Faculty of Medicine, Dentistry & Health Sciences, The University of Western Australia, UWA Anaesthesiology, Perth, Australia



**Barry J. Sessle** Faculty of Dentistry, University of Toronto, Toronto, ON, Canada



**Bengt H. Sjölund** Department of Community Medicine and Rehabilitation Medicine, Umea University, Umea, Sweden



**Mark D. Sullivan** Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA



**Irene Tracey** Pain Imaging Neuroscience (PaIN) Group, Department of Physiology, Anatomy and Genetics, Oxford University, Oxford, UK



**Dennis C. Turk** Department of Anesthesiology & Pain Research, University of Washington, Seattle, WA, USA



**Félix Viana** Instituto de Neurociencias, Universidad Miguel Hernandez-CSIC, San Juan de Alicante, Alicante, Spain





**Katy Vincent** Nuffield Department of Obstetrics and Gynaecology, The Women's Centre, John Radcliffe Hospital, University of Oxford, Oxford, UK



**Gary A. Walco** Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle Children's Hospital, Seattle, WA, USA



**George L. Wilcox** Department of Neuroscience, Pharmacology and Dermatology, University of Minnesota Medical School, Minneapolis, MN, USA



**Katja Wiech** Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK



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## Contributors

**Tipu Aamir** The Auckland Regional Pain Service, Auckland Hospital, Auckland, New Zealand

**Catherine Abbadie** Department of Pharmacology, Merck Research Laboratories, Rahway, NJ, USA

**Frances V. Abbott** Departments of Psychiatry and Psychology, McGill University, Montreal, QC, Canada

**Heather Adams** Department of Surgery, McGill University Health Centre, Montreal, QC, Canada

**Mary O. Adedoyin** Department of Anatomy, University of California San Francisco, San Francisco, CA, USA

**Rolf H. Adler** University of Berne Medical School, Kehrsatz, Switzerland

**Claire D. Advokat** Department of Psychology, Louisiana State University, Baton Rouge, LA, USA

**Reto M. Agosti** Headache Center Hirslanden, Zurich, Switzerland

**Ebtesam Ahmed** College of Pharmacy and Health Sciences, St. John's University, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY, USA

**Marie-Claire Albanese** Department of Psychology, McGill University, Montreal, QC, Canada

**Kathryn M. Albers** Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

**Phillip J. Albrecht** Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY, USA

**Elie D. Al-Chaer** Center for Pain Research, University of Arkansas for Medical Sciences, Little Rock, AR, USA

**Terry Altilio** Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, USA

**Rainer Amann** Medical University Graz, Graz, Austria

**Ron Amir** Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel

**Praveen Anand** Peripheral Neuropathy Unit, Imperial College London, London, UK

**Karen O. Anderson** The University of Texas MD Anderson Cancer Center, Houston, TX, USA

**Ole K. Andersen** Department of Health Science & Technology, Aalborg University, Aalborg, Denmark

**Stanley W. Anderson** Department of Neurosurgery, Johns Hopkins Hospital, Johns Hopkins Medical Institutions, Johns Hopkins University, Baltimore, MD, USA

**Trevor Anderson** Fairview Pain & Palliative Care, University of Minnesota Medical Center, Minneapolis, MN, USA

**Karl-Erik Andersson** Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston Salem, USA

**Frank Andrasik** Department of Psychology, Applied Psychophysiology and Biofeedback, The University of Memphis, Memphis, TN, USA

**A. Vania Apkarian** Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

**Lars Arendt-Nielsen** Center for Sensory-Motor Interaction, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark

**Kirsten Arndt** CNS Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

**Charles-Daniel Arreto** Université Paris Descartes, INSERM UMR 894, France

**Erik Askenasy** Neurobiology and Anatomy, Health Science Center, University of Texas, Houston, TX, USA

**J. H. Atkinson** Psychiatry Service, VA San Diego Healthcare System and Department of Psychiatry, University of California, San Diego, CA, USA

**Nadine Attal** Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré, INSERM U 987 APHP, Boulogne-Billancourt, France

**Christoph Aufenberg** Functional Neurosurgery, Neurosurgical Clinic University Hospital, Zürich, Switzerland

**Beate Averbeck** Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany

**Qasim Aziz** Section of GI Sciences, Hope Hospital University of Manchester, Salford, UK

**Cathrine Bastrup** Danish Pain Research Center, Aarhus University  
Aarhus University Hospital, Aarhus, Denmark

**F. W. Bach** Danish Pain Research Center, Department of Neurology,  
Aarhus University Hospital, Aarhus, Denmark

**S. K. Back** Neuroscience Research Institute and Department of Physiology,  
Korea University, College of Medicine, Seoul, Republic of Korea

**Misha-Miroslav Backonja** Department of Neurology, University of  
Wisconsin-Madison, Madison, WI, USA

**Banani Banerjee** Division of Gastroenterology and Hepatology and  
Pediatric Gastroenterology, Medical College of Wisconsin, Milwaukee,  
WI, USA

**John D. Banja** Department of Rehabilitation Medicine, Center for Ethics  
Emory University, Atlanta, GA, USA

**Carsten Bantel** Department of Surgery & Cancer? Anaesthetics Section,  
Imperial College of Science and Medicine Chelsea and Westminster Campus,  
London, UK

**Andrew Paul Baranowski** The Pain Management Centre, National Hospi-  
tal for Neurology and Neurosurgery, UCL Hospitals NHS Foundation Trust,  
London, UK

**Alex Barling** Department of Neurology, Birmingham Muscle and Nerve  
Centre Queen Elizabeth Hospital, Birmingham, UK

**Ralf Baron** Department of Neurological Pain Research and Therapy,  
Christian Albrechts University Kiel, Kiel, Germany

**Gordon A. Barr** Department of Anesthesiology and Critical Care Medicine,  
Children's Hospital of Philadelphia University of Pennsylvania, Philadelphia,  
PA, USA

**Emily J. Bartley** Department of Psychology, The University of Tulsa,  
Tulsa, OK, USA

**Jeffrey R. Basford** Department of Physical Medicine and Rehabilitation,  
Mayo Clinic and Mayo Foundation, Rochester, NY, USA

**Michele C. Battie** Department of Physical Therapy, University of Alberta,  
Edmonton, AB, Canada

**Ulf Baumgartner** Chair of Neurophysiology, Center for Biomedicine and  
Medical Technology Mannheim, Heidelberg University, Mannheim,  
Germany

**Nicola Beale** Nuffield Department of Anaesthetics, Oxford University  
Hospitals NHS Trust, UK

**Alain Beaudet** Montreal Neurological Institute, McGill University,  
Montreal, QC, Canada

**Lino Becerra** P.A.I.N. Group, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital Department of Radiology Massachusetts General Hospital Center for Pain and the Brain, Harvard Medicals, Boston, MA, USA

**Yaakov Beilin** Department of Anesthesiology, and Obstetrics, Mount Sinai School of Medicine, New York, NY, USA

**Alvin J. Beitz** Department of Veterinary and Biomedical Sciences, University of Minnesota, St. Paul, MN, USA

**Miles Belgrade** Fairview Pain Management Center, University of Minnesota Medical Center, Minneapolis, MN, USA

**Carlo Valerio Bellieni** Neonatal Intensive Care Unit, University Hospital, Siena, Italy

**Carlos Belmonte** Instituto de Neurociencias, Universidad Miguel Hernandez-CSIC, San Juan de Alicante, Spain

**Allan J. Belzberg** Department of Neurosurgery, Johns Hopkins School of Medicine, Baltimore, MD, USA

**Matt Bender** Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, MA, USA

**Fabrizio Benedetti** Department of Neuroscience, Clinical and Applied Physiology Program, University of Turin Medical School, Turin, Italy

**David L. H. Bennett** Wolfson CARD, Kings College London, London, UK  
Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, The University of Oxford, Oxford, UK

**Robert Bennett** Department of Medicine, Oregon Health and Science University, Portland, USA

**Edward C. Benzel** Department of Neurosurgery, Center for Spine Health Neurological Institute Cleveland Clinic, Cleveland, OH, USA

**David A. Bereiter** Department of Diagnostic and Biological Sciences, University of Minnesota School of Dentistry, Minneapolis, MN, USA

**Elmar Berendes** Klinik für Anästhesiologie, Operative Intensivmedizin und Schmerztherapie, Klinikum Krefeld, Krefeld, Germany

**Karen J. Berkley** Program in Neuroscience, Florida State University, Tallahassee, FL, USA

**Peter Berlit** Department of Neurology, Alfried Krupp Hospital, Essen, Germany

**Jean-François Bernard** INSERM UMR-894, UPMC Site Pitié-Salpêtrière, Paris, France

**Anne K. Bertelsen** Neurology, Aleris Hospital, Bergen, Norway

**Jennifer Bickel** Integrative Pain Management, Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA

**Marcelo E. Bigal** Department of Neurology and Montefiore Headache Unit, Albert Einstein College of Medicine, Bronx, NY, USA

**Yitzchak M. Binik** McGill University, Montreal, QC, Canada

**Niels Birbaumer** Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany

**Frank Birklein** Department of Neurology, University of Mainz, Mainz, Germany

**Kathryn A. Birnie** Department of Psychology, Dalhousie University, Halifax, NS, Canada

**Thomas Bishop** Centre for Neuroscience, King's College London, London, UK

**Henning Bliddal** The Parker Institute, Frederiksberg Hospital, Copenhagen, Denmark

**Nikolai Bogduk** University of Newcastle, Newcastle Bone & Joint Institute, Royal Newcastle Centre, Newcastle, NSW, Australia

**Jorgen Boivie** Department of Neurology, University Hospital, Linköping, Sweden

**Michael R. Bond** University of Glasgow, Glasgow, UK

**Richard L. Boortz-Marx** Division of Pain Medicine, Department of Anesthesiology, University of North Carolina, Chapel Hill, North Carolina, USA

**James M. Borowczyk** Department of Orthopaedics and Musculoskeletal Medicine, University of Otago, Christchurch, Christchurch, New Zealand

**David Borsook** P.A.I.N. Group, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital Department of Radiology Massachusetts General Hospital Center for Pain and the Brain, Harvard Medicals, Boston, MA, USA

**George S. Borszcz** Department of Psychology, Wayne State University, Detroit, USA

**Jasenska Borzan** Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, USA

**Regina M. Botting** London, UK

**Didier Bouhassira** Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré, INSERM U 987 AHPH, Boulogne-Billancourt, France



**Laurence Bourgeois** INSERM UMR 894, Centre de Psychiatrie et Neurosciences, Paris, France

**David Bowsher** Pain Research Institute, University Hospital Aintree, Liverpool, UK

**Emma L. Brandon** Anaesthesiology and Pain Medicine, University of Western Australia Royal Perth Hospital, Perth, WA, Australia

**Jennifer Brawn** P.A.I.N. Group, Center for Pain and the Brain, Boston Children's Hospital, Harvard Medical School, Waltham, MA, USA

**Harald Breivik** Department of Pain Management and Research, Oslo University Hospital, Rikshospitalet and University of Oslo, Oslo, Norway

**Kori L. Brewer** Department of Emergency Medicine, Brody School of Medicine East Carolina University, Greenville, NC, USA

**Christopher R. Brigham** Brigham and Associates, Inc., Portland, USA

**Abigail Broderick** Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, UK

**Jeffrey A. Brown** Department of Neurological Surgery, Wayne State University School of Medicine, Detroit, MI, USA

**Stephen C. Brown** Department of Anesthesia, The Hospital for Sick Children, Toronto, ON, Canada

**Eduardo Bruera** Department of Palliative Care and Rehabilitation Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

**Pablo Brumovsky** Faculty of Biomedical Sciences, Austral University, Buenos Aires, Argentina

Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina

**Kay Brune** Department of Experimental and Clinical Pharmacology and Toxicology, Friedrich Alexander University Erlangen-Nürnberg, Erlangen, Germany

**Maria Burian** Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

**Dan Buskila** Rheumatic Disease Unit, Soroka Medical Center, Beer Sheva, Israel

**Catherine M. Cahill** Anesthesiology & Perioperative Care, University of California, Irvine, Irvine, CA, USA

**Brian E. Cairns** Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

**Nigel A. Calcutt** Department of Pathology, University of California San Diego, La Jolla, CA, USA

- Margarita Calvo** Wolfson CARD, Kings College London, London, UK
- James N. Campbell** Johns Hopkins University School of Medicine, Baltimore, MD, USA
- Lauren Campbell** Department of Psychology, York University, Toronto, ON, Canada
- Ling Cao** Department of Biomedical Sciences, College of Osteopathic Medicine, University of New England, ME, USA
- Adam Carinci** Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital Harvard Medical School, Boston, MA, USA
- Giancarlo Carli** Department of Physiology, University of Siena, Siena, Italy
- Christer P. O. Carlsson** Rehabilitation Clinic, Lunds University Hospital, Lund, Sweden
- Susan M. Carlton** Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX, USA
- Richard Carr** Clinic for Anaesthesiology, Heidelberg University, Mannheim, Baden-Wuerttemberg, Germany
- Benjamin S. Carson** Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, MA, USA
- Brian Carter** University of Missouri at Kansas City Children's Mercy Hospital and Bioethics Center, Kansas City, MO, USA
- Kenneth L. Casey** Department of Neurology, University of Michigan Medical Center, Ann Arbor, MI, USA
- Christine T. Chambers** Departments of Pediatrics and Psychology, Dalhousie University, Halifax, NS, Canada
- Sandra Chaplan** Janssen Research and Development, LLC, San Diego, CA, USA
- C. Richard Chapman** Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, UT, USA
- Santosh K. Chaturvedi** Psychiatry, National Institute of Mental Health & Neurosciences, Bangalore, India
- Andrew C. N. Chen** Human Brain Mapping and Cortical Imaging Laboratory, Aalborg University, Aalborg, Denmark
- Hsinlin Thomas Cheng** Department of Neurology, University of Michigan, Ann Arbor, MI, USA
- Pavel Cherkas** Faculty of Dentistry, University of Toronto, Toronto, ON, Canada

**Andrea Cheville** Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, USA

**Chen Yu Chiang** Faculty of Dentistry, University of Toronto, Toronto, ON, Canada

**N. L. Chillingworth** School of Physiology and Pharmacology, University of Bristol, Bristol, UK

**Edward Chow** Department of Radiation Oncology, Sunnybrook Health Sciences Centre Odette Cancer Centre (T2-182), Toronto, ON, Canada

**Julie A. Christianson** Department of Anatomy and Cell Biology, University of Kansas Medical Center, Kansas City, KS, USA

**MacDonald J. Christie** Discipline of Pharmacology, University of Sydney, Sydney, Australia

**Jin Mo Chung** Department of Neuroscience and Cell Biology, University Chair in Neuroscience, University of Texas Medical Branch, Galveston, TX, USA

**Kyungsoon Chung** Department of Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX, USA

**Anna K. Clark** Wolfson Centre for Age Related Diseases, King's College London, London, UK

**W. Crawford Clark** College of Physicians and Surgeons, Columbia University, New York, USA

**James F. Cleary** Pain & Policy Studies Group, UW Carbone Cancer Center, Madison, WI, USA

**John De Clercq** Department of Rehabilitation Sciences and Physiotherapy, Ghent University Hospital, Ghent, Belgium

**Jacqui Clinch** Royal National Hospital for Rheumatic Diseases NHS Foundation Trust, Bath, UK

**Terence J. Coderre** Departments of Anesthesia, Neurology & Neurosurgery and Psychology, McGill University, Montreal, QC, Canada

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

**Lindsey Cohen** Psychology, Georgia State University, Atlanta, GA, USA

**Alan L. Colledge** Utah Labor Commission, International Association of Industrial Accident Boards and Commissions Central Utah Medical Clinic, South Salt Lake City, UT, USA

**Beverly J. Collett** University Hospitals of Leicester, Leicester, UK

**Lesley A. Colvin** Department of Anaesthesia, Critical Care and Pain Medicine Western General Hospital, Edinburgh, UK

**Kevin C. Conlon** Trinity College Dublin, University of Dublin, Dublin, Ireland

**Mark Connelly** Integrative Pain Management, Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA

**Brian Y. Cooper** Department of Oral and Maxillofacial Surgery, University of Florida, Gainesville, FL, USA

**Christine Cordle** University Hospitals of Leicester, Leicester, UK

**Laura A. Cousins** Psychology, Georgia State University, Atlanta, GA, USA

**Michael J. Cousins** Department of Anesthesia and Pain Management, Royal North Shore Hospital University of Sydney, Sydney, NSW, Australia

**Verne C. Cox** Department of Psychology, University of Texas at Arlington, Arlington, TX, USA

**George A. Crabill** Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, MA, USA

**Rebecca M. Craft** Psychology, Washington State University, Pullman, WA, USA

**Kenneth D. Craig** Department of Psychology, University of British Columbia, Vancouver, BC, Canada

**Richard Crevenna** Medizinische Universität Wien, Wien, Austria

**Geert Crombez** Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

**Joan Crook** School of Nursing, Faculty of Health Sciences, McMaster University, Hamilton, ON, Canada

**Giorgio Cruccu** Department of Neurological Sciences, La Sapienza University, Rome, Italy

**Michele Curatolo** Department of Anesthesiology, Division of Pain Therapy, University Hospital of Bern Inselspital, Bern, Switzerland

**Nachum Dafny** Neurobiology and Anatomy, Health Science Center, University of Texas, Houston, TX, USA

**Jorgen B. Dahl** Department of Anaesthesiology, Glostrup University Hospital, Herlev, Denmark

**Yi Dai** Department of Anatomy and Neuroscience, Hyogo College of Medicine, Hyogo, Japan

**Stefaan Van Damme** Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

**Alexandre F. M. DaSilva** Biologic & Materials Sciences, University of Michigan Dental School, MI, USA

**Steve Davidson** Pain Center & Department of Anesthesiology, Washington University School of Medicine, MO, USA

**Brian Davis** Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

**Karen D. Davis** Brain, Imaging and Behaviour – Systems Neuroscience, Toronto Western Research Institute, Toronto, ON, Canada

Department of Surgery, University of Toronto, Toronto, ON, Canada

**Richard O. Day** Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney, NSW, Australia

**Isabelle Decosterd** Pain Center, University Hospital Center and University of Lausanne, Lausanne, Switzerland

**Ruth Defrin** Physical Therapy, Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

**Antoon F. C. De Laat** Department of Oral/Maxillofacial Surgery, Catholic University of Leuven, Leuven, Belgium

**Joyce DeLeo** Dartmouth Hitchcock Medical Center, Dartmouth Medical School, Hanover, NH, USA

**A. Lee Dellon** Department of Plastic Surgery and Neurosurgery, Johns Hopkins University, Baltimore, USA

Dellon Institutes for Peripheral Nerve Surgery, Baltimore, MD, USA

**Marshall Devor** Department of Cell & Developmental Biology, Institute of Life Sciences and Center for Research on Pain, The Hebrew University of Jerusalem, Jerusalem, Givat Ram, Israel

**Perry Dhaliwal** Department of Neurosurgery, Cleveland Clinic Spine Institute, Cleveland, OH, USA

**David Diamant** Neurological and Spinal Surgery, Lincoln, NE, USA

**Anthony H. Dickenson** Department of Pharmacology, University College London, London, UK

**Hans-Christoph Diener** Department of Neurology, University Hospital Essen, University Duisburg-Essen, Essen, Germany

**Natalia Dmitrieva** Program in Neuroscience, Florida State University, Tallahassee, FL, USA

**L. F. Donaldson** School of Life Sciences, University of Nottingham, Nottingham, UK

**Henri Doods** CNS Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

**Victoria Dorf** Social Security Administration, Baltimore, MD, USA

**Michael J. Dorsi** Department of Neurosurgery, Johns Hopkins School of Medicine, Baltimore, MD, USA

**Jonathan O. Dostrovsky** Department of Physiology, University of Toronto, Toronto, ON, Canada

Faculty of Dentistry, University of Toronto, Toronto, ON, Canada

**Robyn Drach** Fairview Pain Management Center, Minneapolis, MN, USA

**Ron Dressler** Utah Labor Commission, International Association of Industrial Accident Boards and Commissions Central Utah Medical Clinic, South Salt Lake City, UT, USA

**Paul Dreyfuss** Department of Rehabilitation Medicine, University of Washington, Seattle, USA

**Peter D. Drummond** School of Psychology, Murdoch University, Perth, Australia

**Ronald Dubner** Department of Neural and Pain Sciences, University of Maryland Dental School, Baltimore, MD, USA

**Anne Ducros** Headache Emergency Department, INSERM, Paris, France

**Gary H. Duncan** Département de stomatologie, Faculté de médecine dentaire, Université de Montréal, Montreal, QC, Canada

Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada

**Mary J. Eaton** Research Service (151), Miami VA Health Care System, Miami VAMC, Miami, FL, USA

**Andrea Ebersberger** Department of Physiology, Friedrich Schiller University of Jena, Jena, Germany

**Christopher Eccleston** Pain Management Unit, University of Bath, Bath, UK

**John Edmeads** Sunnybrook and Woman's College Health Sciences Centre, University of Toronto, Toronto, Canada

**Edzard Ernst** Complementary Medicine, Peninsula Medical School Universities of Exeter and Plymouth, Exeter, UK

**Reuben Escorpizo** Swiss Paraplegic Research, Nottwil, Switzerland

Department of Health Sciences and Health Policy, University of Lucerne, Lucerne, Switzerland

ICF Research Branch in cooperation with the World Health Organization (WHO) Collaborating Centre for the Family of International Classifications in Germany, Nottwil, Switzerland

**Schonstein Eva** RehabCo, Fyshwick, ACT, Australia

**Joshua C. Eyer** Department of Psychology, University of Alabama, Tuscaloosa, AL, USA

**Marie Faaborg-Andersen** McGill University, Montreal, QC, Canada

**Keri L. Fakata** College of Pharmacy and Pain Management Center, University of Utah, Salt Lake City, USA

**Marie Fallon** Department of Oncology, Edinburgh Cancer Center University of Edinburgh, Edinburgh, UK

**Melissa Farmer** Department of Physiology / Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

**Samantha R. Fashler** Department of Psychology, University of British Columbia, Vancouver, BC, Canada

**Jean-Baptiste Fassier** Department of Occupational Health and Medicine, UMRESTTE-Université Claude Bernard Lyon 1, Lyon, France

**Charlotte Feinmann** Eastman Dental Institute London, University College London, London, UK

**Elizabeth Roy Felix** The Miami Project to Cure Paralysis, University of Miami Miller School of Medicine, Miami, FL, USA

**Bin Feng** Center for Pain Research, Department of Anesthesiology, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

**Yi Feng** Department of Anesthesiology, Peking University People's Hospital, Peking, China

**Andres Fernandez** Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, MD, USA

**Antonio Vicente Ferrer-Montiel** Institute of Molecular and Cell Biology, University Miguel Hernández, Elche, Alicante, Spain

**Perry G. Fine** Pain Research Center, School of Medicine, University of Utah, Salt Lake City, UT, USA

**David J. Fink** Department of Neurology, University of Michigan and VA Ann Arbor Healthcare System, Ann Arbor, MI, USA

**Nanna Brix Finnerup** Aarhus University Hospital, Danish Pain Research Center, Aarhus, Denmark

**David A. Fishbain** Department of Psychiatry, University of Miami, Miami, FL, USA

**Maria Fitzgerald** Neuroscience, Physiology & Pharmacology, University College London, London, UK

**Per Flisberg** Department of Anaesthesia and Intensive Care, Lund University Hospital, Lund, Sweden

**Herta Flor** Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

**Christopher M. Flores** Drug Discovery, Johnson and Johnson Pharmaceutical Research and Development, Spring House, PA, USA

**Wilbert E. Fordyce** Department of Rehabilitation, University of Washington School of Medicine, Seattle, WA, USA

**Robert D. Foreman** Department of Physiology, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

**Gary M. Franklin** Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA

Department of Health Services, University of Washington, Seattle, WA, USA

**Jan Fridén** Department of Hand Surgery, Sahlgrenska University Hospital, Gothenborg, Sweden

**Justin Friedlander** The Arthur Smith Institute for Urology, North Shore-LIJ Healthcare System, Hofstra North Shore LIJ School of Medicine, New Hyde Park, NY, USA

**Allan H. Friedman** Division of Neurosurgery, Duke University Medical Center, Durham, NC, USA

**Perry N. Fuchs** Department of Psychology, University of Texas at Arlington, Arlington, TX, USA

**Deborah Fulton-Kehoe** Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA

**Andrea D. Furlan** Institute for Work & Health, Toronto, ON, Canada

**Vasco Galhardo** Departamento de Biologia Experimental, Faculdade de Medicina, Universidade do Porto, Portugal

**Andreas R. Gantenbein** RehaClinic Bad Zurzach, Bad Zurzach, Switzerland

**I. Garonzik** Department of Neurosurgery, Johns Hopkins Medical Institutions, Baltimore, MD, USA

**Robert Gassin** Musculoskeletal Medicine Clinic, Frankston, VIC, Australia

**Robert J. Gatchel** Department of Psychology, The University of Texas, Arlington, TX, USA

**Gerald F. Gebhart** Department of Anesthesiology, Center for Pain Research, University of Pittsburgh, Pittsburgh, PA, USA

**Gerd Geisslinger** Department of Clinical Pharmacology, University Frankfurt am Main, Frankfurt, Germany



**Robert D. Gerwin** Department of Neurology, Johns Hopkins University, Bethesda, MD, USA

**Maria Adele Giamberardino** Pathophysiology of Pain Laboratory and Centre for Fibromyalgia and Musculoskeletal Pain, Department of Medicine and Science of Aging, University of Chieti, Chieti, Italy

**Stephen Gibson** National Ageing Research Institute Department of Medicine, University of Melbourne, Parkville, VIC, Australia

**Glenn J. Giesler** Department of Neuroscience, University of Minnesota, Minneapolis, MN, USA

**Philip L. Gildenberg** Baylor Medical College, Houston, TX, USA

**Myra Glajchen** Department of Pain Medicine and Palliative Care, Beth Israel Medical Center Albert Einstein College of Medicine, New York, NY, USA

**Hartmut Göbel** Kiel Migraine and Headache Center, Kiel Pain Center, Kiel, Germany

**Peter Goadsby** Headache Center, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA

**Philippe Goffaux** Faculty of Medicine, University of Sherbrooke, Sherbrooke, QC, Canada

**Ana Gomis** Instituto de Neurociencias de Alicante, Universidad Miguel Hernández-CSIC, San Juan de Alicante, Spain

**Gilbert R. Gonzales** Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, USA

**Allan Gordon** Wasser Pain Management Centre, Mount Sinai Hospital University of Toronto, Toronto, ON, Canada

**Liesbet Goubert** Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

**Jayantilal Govind** Pain Clinic, Department of Anaesthesia, University of New South Wales, Sydney, NSW, Australia

**Richard H. Gracely** Departments of Medicine-Rheumatology and Neurology, University of Michigan Health System, Ann Arbor, MI, USA

**Garry G. Graham** Department of Pharmacology, School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia

**David K. Grandy** Department of Physiology and Pharmacology, Oregon Health and Science University, Portland, OR, USA

**Thomas Graven-Nielsen** Laboratory for Musculoskeletal Pain and Motor Control, Center for Sensory-Motor Interaction, Aalborg University, Aalborg, Denmark

**Barry Green** Pierce Laboratory, Yale School of Medicine, New Haven, CT, USA

**Paul G. Green** Oral & Maxillofacial Surgery, University of California San Francisco, San Francisco, CA, USA

**Joel D. Greenspan** Department of Neural and Pain Sciences, University of Maryland School of Dentistry, Baltimore, MD, USA

**John W. Griffin** Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Cornelius Groenwald** Department of Anesthesiology and Pain Medicine, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA, USA

**Douglas P. Gross** Department of Physical Therapy, University of Alberta WCB-Alberta Millard Health, Edmonton, AB, Canada

**Sabine Grösch** Institute of Clinical Pharmacology, Clinical Center of the Goethe University, Frankfurt, Germany

**Blair D. Grubb** Department of Cell Physiology and Pharmacology, University of Leicester, Leicester, UK

**Ruth Eckstein Grunau** Pediatrics Dept, University of British Columbia Developmental Neurosciences & Child Health, Child & Family Research Institute, Vancouver, BC, Canada

**Christoph Gutenbrunner** Department of Physical Medicine and Rehabilitation, Hanover Medical School, Hanover, Germany

**Maija Haanpää** Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland

**Sherri Haas** Fairview Pain Management Center, Minneapolis, MN, USA

**Ute Habel** Department of Psychiatry and Psychotherapy, RWTH Aachen University, Aachen, Germany

**Thomas Hachenberg** Clinic for Anaesthesiology and Intensive Therapy, Otto-von-Guericke University, Magdeburg, Germany

**Nouchine Hadjikhani** Martinos Center for Biomedical Imaging, Massachusetts General Hospital Harvard Medical School, Charlestown, MA, USA

**Ole Haegg** Department of Orthopedic Surgery, Sahlgren University Hospital, Goteborg, Sweden

**Bryan C. Hains** Department of Neurology, Yale University School of Medicine, West Haven, CT, USA

**Else K. B. Hals** University of Oslo, Faculty of Dentistry, Oslo, Norway

**Darryl T. Hamamoto** Diagnostic and Biological Sciences, University of Minnesota, Minneapolis, MN, USA

**Donna L. Hammond** Department of Anesthesia, University of Iowa, Iowa City, IA, USA

**Menachem Hanani** Hadassah-Hebrew University Medical Center Hebrew University Medical School, Jerusalem, Israel

**Hermann O. Handwerker** Department of Physiology and Pathophysiology, University of Erlangen/Nürnberg, Erlangen, Germany

**George M. Hanna** Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital Harvard Medical School, Boston, MA, USA

**Jing-Xia Hao** Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

**Eleni G. Hapidou** Department of Psychiatry and Behavioural Neurosciences, McMaster University and Hamilton Health Sciences Chronic Pain Management Unit, Chedoke Hospital, Hamilton, ON, Canada

**Geoffrey Harding** Sandgate Spinal Medicine Clinic, Sandgate, QLD, Australia

**Louise Harding** Hospitals NHS Foundation Trust, University College London, London, UK

**Kenneth M. Hargreaves** Department of Endodontics, University of Texas Health Science Center at San Antonio, San Antonio, USA

**D. Paul Harries** Pain Treatment Center, Samaritan Hospital Lexington, Lexington, KY, USA

**Denise Harrison** Nursing, Children's Hospital of Eastern Ontario (CHEO), University of Ottawa, Ottawa, ON, Canada

**Steven Harte** Anesthesiology and Internal Medicine/Rheumatology, University of Michigan VA Ann Arbor Healthcare System, Ann Arbor, MI, USA

**Barbara A. Hastie** Community Dentistry & Behavioral Science, University of Florida College of Dentistry, Gainesville, FL, USA

**Jennifer A. Haythornthwaite** Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, USA

**Heinz-Joachim Häbler** FH Bonn-Rhein-Sieg, Rheinbach, Germany

**John H. Healey** Orthopaedic Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center Weill Medical College of Cornell University, New York, NY, USA

**Alicia A. Heapy** VA Connecticut Healthcare System, Westhaven, CT, USA

**Anne M. Heffernan** The Adelaide and Meath Hospital Incorporating The National Children's Hospital, Dublin, Ireland

**Geert Van der Heijden** Julius Center, Department of Epidemiology, University Medical Center Utrecht, Utrecht, The Netherlands

**Mary M. Heinricher** Departments of Neurological Surgery and Behavioral Neuroscience, Oregon Health & Science University, Portland, USA

**Robert D. Helme** Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia

**Kim Helsen** Research Group on Health Psychology, KU Leuven Katholieke Universiteit Leuven, Leuven, Belgium

Department of Experimental–Clinical and Health Psychology, Ghent University, Ghent, Belgium

**Amin S. Herati** The Arthur Smith Institute for Urology, North Shore-LIJ Healthcare System, Hofstra North Shore LIJ School of Medicine, New Hyde Park, NY, USA

**Robert D. Herbert** Neuroscience Research Australia, Sydney, Australia

**Christiane Hermann** Department of Clinical Psychology, Justus-Liebig University Giessen, Giessen, Germany

**Juan F. Herrero** Department of Physiology, Faculty of Medicine University of Alcalá, Alcalá de Henares Madrid, Spain

**Aki J. Hietaharju** Department of Neurology and Rehabilitation, Pain Clinic Tampere University Hospital, Tampere, Finland

**Karin Westlund High** Department of Physiology, University of Kentucky, Lexington, KY, USA

**Marita Hilliges** Dalarna University, Halmstad, Sweden

**Max J. Hilz** University of Erlangen-Nuremberg, Erlangen, Germany

**Burkhard Hinz** Institute of Toxicology and Pharmacology, University of Rostock, Rostock, Germany

**Anthony R. Hobson** Section of GI Sciences, Hope Hospital University of Manchester, Salford, UK

**Edward Högestätt** Department of Laboratory Medicine, Lund University, Division of Clinical Chemistry and Pharmacology, Lund, Sweden

**Tomas Hökfelt** Department of Neuroscience, Karolinska Institute, Stockholm, Sweden

**Sarah V. Holdridge** Department of Pharmacology and Toxicology, Queen's University, Kingston, Canada

**Kjell Hole** University of Bergen, Bergen, Norway

**Graham R. Holland** Department of Cariology, University of Michigan, Ann Arbor, MI, USA

**Chang-Zern Hong** Department of Physical Medicine and Rehabilitation, University of California, Irvine, CA, USA

**Minoru Hoshiyama** Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Japan

**Fred M. Howard** University of Rochester, Rochester, NY, USA

**Sung-Tsang Hsieh** Department of Anatomy and Cell Biology, Department of Neurology, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan

**James W. Hu** Faculty of Dentistry, University of Toronto, Toronto, Canada

**Claire E. Hulsebosch** Spinal Cord Injury Research, University of Texas Medical Branch, Galveston, TX, USA

**Thomas Hummel** Department of Otorhinolaryngology, Technical University of Dresden Medical School, Dresden, Germany

**Mark R. Hutchinson** School of Medical Sciences, University of Adelaide, Adelaide, SA, Australia

**Charles E. Inturrisi** Department of Pharmacology, Weill Cornell Medical College, New York, USA

**Koji Inui** Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Japan

**Koichi Iwata** Department of Physiology, Nihon University School of Dentistry, Chiyoda-ku, Japan

**Suhayl J. Jabbur** Anatomy, Cell Biology and Physiology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

Neuroscience Program, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

**Nora Janjan** University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

**Luc Jasmin** Department of Anatomy, University of California San Francisco, San Francisco, CA, USA

**Anne Jaumees** Royal North Shore Hospital, St Leonards, NSW, Australia

**Wilfrid Jaenig** Physiologisches Institut, Christian-Albrechts-Universität zu Kiel, Kiel, Germany

**Daniel Jeanmonod** Functional Neurosurgery, The Center of Ultrasound Functional Neurosurgery, Solothurn, Switzerland

**Andrew Jeffreys** Director Department of Anaesthesia & Pain Medicine, Western Health, Melbourne, VIC, Australia

**Mark P. Jensen** Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA

**Troels Staehelin Jensen** Danish Pain Research Center, Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

**Kurt L. Johnson** Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA

**Mark I. Johnson** Faculty of Health and Social Sciences, Leeds Pallium Research Group, Leeds Metropolitan University, Leeds, UK

**Mark Johnston** Hibiscus Coast Highway, Orewa, New Zealand

**Edward Jones** Center for Neuroscience, University of California, Davies, CA, USA

**Jeroen R. De Jong** Department of Rehabilitation, University Hospital Maastricht, Maastricht, The Netherlands

**Sven-Eric Jordt** Department of Pharmacology, Yale University School of Medicine, New Haven, CT, USA

**Ellen Jørum** The Laboratory of Clinical Neurophysiology, Rikshospitalet University, Oslo, Norway

**Stefan Just** CNS Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

**Timothy K. Y. Kaan** Department of Anatomy, University of California San Francisco, San Francisco, CA, USA

**Noufissa Kabli** Department of Pharmacology and Toxicology, Queen's University, Kingston, Canada

**Ryusuke Kakigi** Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Japan

**Peter C. A. Kam** Anaesthesia, Central Clinical School, The University of Sydney, Sydney, Australia

**Giresh Kanji** The Sports and Pain Clinic, Wellington, New Zealand

**Joel Katz** Department of Psychology, McGill University, Montreal, QC, Canada

**Valerie Kayser** NSERM U677 91Bd de l'Hôpital, Paris, France

**Francis J. Keefe** Pain Prevention and Treatment Research, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

**Lois J. Kehl** Department of Anesthesiology, University of Minnesota, Minneapolis, MN, USA

**Maureen Kelley** Department of Pediatrics, Bioethics Division, University of Washington School of Medicine, WA, USA  
Seattle Children's Hospital, Seattle, WA, USA

**Stephen Kennedy** Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, UK

**Edmund Keogh** Department of Psychology, University of Bath, Bath, UK

**Robert D. Kerns** VA Connecticut Healthcare System, Westhaven, CT, USA

**Sanjay Khanna** Department of Physiology, National University of Singapore, Singapore

**Kok Eng Khor** Department of Pain Management, Prince of Wales Hospital University of New South Wales, Randwick, NSW, Australia

**Mina Khoshnejad** Department of Neuroscience, University of Montreal, Montreal, QC, Canada

**H. J. Kim** Department of Life Science, Yonsei University, Wonju, Republic of Korea

**Sara King** Faculty of Education (School Psychology), Mount Saint Vincent University, Halifax, NS, Canada

**Wade King** Department of Clinical Research, Royal Newcastle Centre University of Newcastle, Newcastle, NSW, Australia

**K. L. Kirsh** Behavioral Medicine, The Pain Treatment Center of the Blue grass, Lexington, KY, USA

**Henriette Klit** Danish Pain Research Center, Aarhus University Hospital, Aarhus C, Denmark

**Ricardo J. Komotar** Department of Neurological Surgery, Neurological Institute Columbia University, New York, NY, USA

**Sungtae Koo** Division of Meridian and Structural Medicine, School of Korean Medicine, Pusan National University, Yangsan, Korea

**Rhonda K. Kotarinos** Oakbrook Terrace, IL, USA

**Katalin J. Kovacs** Department of Veterinary and Biomedical Sciences, University of Minnesota, St. Paul, MN, USA

**Malgorzata Krajnik** Chair of Palliative Care, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland

**Elliot Krane** Anesthesia and Pediatrics, Stanford University School of Medicine Lucile Packard Children's Hospital at Stanford, Stanford, CA, USA

**Ajit Krishnaney** Department of Neurosurgery, Cleveland Clinic, Cleveland, OH, USA

**Greg Krohm** International Association of Industrial Accident Boards and Commissions (IAIABC), Utah Valley University, USA

**Lawrence Kruger** UCLA Geffen School of Medicine, Los Angeles, CA, USA

**M. M. ter Kuile** Department of Gynecology, Leiden University Medical Center, Leiden, The Netherlands

**Promil Kukreja** Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, AL, USA

**Alice Kvåle** Department of Public Health and Primary Health Care, Faculty of Medicine and Dentistry University of Bergen, Bergen, Norway

**Gunnvald Kvarstein** Department of Pain Management and Pain Research, Oslo University Hospital, Rikshospitalet, Oslo, Norway

**Jean-Jacques Labat** Neurology and Rehabilitation, Clinique Urologique, Nantes, France

**Gaston Labrecque** Faculty of Pharmacy, University of Laval, Quebec City, QC, Canada

**Marco Lacerenza** Pain Medicine Center, Casa di Cura S. Pio X, Opera San Camillo Foundation, Milan, Italy

**Uri Ladabaum** Gastroenterology & Hepatology, Stanford Cancer Institute, Redwood City, CA, USA

**Marie Andree Lahaie** McGill University, Montreal, QC, Canada

**Miguel J. A. Lainez-Andres** Department of Neurology, University of Valencia, Valencia, Spain

**Robert H. LaMotte** Department of Anesthesiology, Yale School of Medicine, New Haven, CT, USA

**James W. Lance** Institute of Neurological Sciences, University of New South Wales, Sydney, Australia

**Robert G. Large** The Auckland Regional Pain Service, Auckland Hospital, Auckland, New Zealand

**Alice A. Larson** Department of Veterinary and Biomedical Sciences, University of Minnesota, St. Paul, MN, USA

**Roberta Lattanzi** Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy

**Peter Lau** Department of Clinical Research, Royal Newcastle Hospital, University of Newcastle, Newcastle, NSW, Australia

**Stefan A. Laufer** Institute of Pharmacy, Eberhard-Karls University of Tuebingen, Tuebingen, Germany

**Stefan Lautenbacher** Physiologische Psychologie, Otto-Friedrich-Universität, Bamberg, Germany

**Gilles J. Lavigne** Facultés de Médecine Dentaire et de Médecine, Université de Montréal, Hôpital Sacre Coeur de Montreal. Surgery-trauma dept, Montréal, QC, Canada



**Emily Law** Center for Child Health, Behavior, and Development, Seattle Children's Research Institute, Seattle, WA, USA

**Peter G. Lawlor** Our Lady's Hospice, Medical Department, Dublin, Ireland

**Michel Lazdunski** Institut de Pharmacologie Moléculaire et Cellulaire (IPMC) CNRS/UNS UMR7275, Valbonne-Sophia Antipolis, France

**Vincenzo Di Lazzaro** Institute of Neurology, Campus Biomedico University, Rome, Italy

**Alyssa Lebel** Boston Children's Hospital, Boston, MA, USA

**Frank Lee** Johns Hopkins University, Baltimore, MD, USA

**Maaïke Leeuw** Department of Medical, Clinical and Experimental Psychology, Maastricht University, Maastricht, The Netherlands

**Siri Graff Leknes** Research Fellow, Psykologisk institutt, Oslo, Norway

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

**Guillaume Léonard** Faculty of Medicine, University of Sherbrooke, Sherbrooke, QC, Canada

**Pauline Lesage** Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, USA

**Isobel Lever** Neural Plasticity Unit, Institute of Child Health University College London, London, UK

**Khan W. Li** Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, MD, USA

**Alan R. Light** Department of Anesthesiology, University of Utah, Salt Lake City, UT, USA

**Michael Lim** Department of Neurosurgery and Department of Neurology, Johns Hopkins Hospital, Baltimore, MA, USA

**Deolinda Lima** Department of Experimental Biology, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

**Volker Limmroth** Department of Neurology, University of Essen, Essen, Germany

**Eric Lingueglia** Institut de Pharmacologie Moléculaire et Cellulaire (IPMC) CNRS/UNS UMR7275, Valbonne-Sophia Antipolis, France

**Steven J. Linton** Department of Occupational and Environmental Medicine, Orebro Medical Center, Orebro, Sweden

**Arthur G. Lipman** Departments of Pharmacotherapy and Anesthesiology and Pain Management Center, University of Utah, Salt Lake City, UT, USA

**Richard B. Lipton** Departments of Neurology, Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

**Diana Lisi** Department of Psychology, York University, Toronto, ON, Canada

**Kenneth M. Little** Division of Neurosurgery, Duke University Medical Center, Durham, NC, USA

**Edward Littleton** Queen Elizabeth Hospital, Birmingham, UK

**Spencer S. Liu** Virginia Mason Medical Center, Seattle, WA, USA

**Anne Elisabeth Ljunggren** Section for Physiotherapy Science, Department of Public Health and Primary Health, Faculty of Medicine, University of Bergen, Bergen, Norway

**John D. Loeser** Department of Neurological Surgery, University of Washington, Seattle, WA, USA

**Joern Loetsch** Institute for Clinical Pharmacology, Pharmaceutical Center Frankfurt, Johann Wolfgang Goethe University, Frankfurt, Germany

**Patrick Loisel** Disability Prevention Research and Training Centre, Université de Sherbrooke, Longueuil, Canada

**Elisa Lopez-Dolado** Servicio de Rehabilitacion, National Hospital of Paraplèjicos SESCAM, Toledo, Spain

**Jürgen Lorenz** Faculty of Life Science, Competence Center Gesundheit, University of Applied Science Hamburg, Hamburg, Germany

**Dayna R. Loyd** US Army Institute of Surgical Research, Fort Sam Houston, TX, USA

**Daniel Lubelski** Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

**Stephen Lutz** Blanchard Valley Regional Cancer Center, Findlay, OH, USA

**Bruce Lynn** Department of Physiology, University College London, London, UK

**Ross MacPherson** Department of Anesthesia and Pain Management, Royal North Shore Hospital University of Sydney, Sydney, NSW, Australia

**Christophe Maes** Manager Innovatie AZ Alma, Belgium

**Michel Magnin** INSERM, Neurological Hospital, Lyon, France

**Bryan Mahony** Department of Anesthesiology, Ohio State University Medical Center, Mount Sinai Hospital, New York, NY, USA

**Steven F. Maier** Department of Psychology and Neuroscience, and The Center for Neuroscience, University of Colorado at Boulder, Boulder, CO, USA

**Thorsten J. Maier** Institute of Pharmaceutical Chemistry, Goethe University, Frankfurt, Germany

**Chris J. Main** Keele University, Keele, Staffordshire, UK

**Marzia Malcangio** Wolfson Centre for Age Related Diseases, King's College London, London, UK

**Paolo L. Manfredi** Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, USA

**Kaisa Mannerkorpi** Department of Rheumatology and Inflammation Research, Institute of Medicine, University of Gothenburg, Göteborg, Sweden

**Barton H. Manning** Amgen Inc., Thousand Oaks, CA, USA

**Patrick W. Mantyh** Department of Pharmacology, The University of Arizona, AZ, USA

**Jianren Mao** Department of Anesthesia and Critical Care, Harvard Medical School, Boston, MA, USA

**Serge Marchand** Faculty of Medicine, University of Sherbrooke, Sherbrooke, QC, Canada

**Paolo Marchettini** Pain Medicine Center, Scientific Institute San Raffaele, Milan, Italy

**Sarah R. Martin** Psychology, Georgia State University, Atlanta, GA, USA

**Peggy Mason** Department of Neurobiology, Pharmacology and Physiology, University of Chicago, Chicago, IL, USA

**Scott Masters** Caloundra Spinal and Sports Medicine Centre, Caloundra, QLD, Australia

**Laurence E. Mather** Department of Anaesthesia and Pain Management, University of Sydney at Royal North Shore Hospital, St. Leonards, Sydney, NSW, Australia

**Bill McCarberg** Pain Services, Kaiser Permanente, San Diego, USA

**Lance McCracken** Health Psychology/Psychology Department, King's College London, London, UK

**Kathleen McGinn** Anesthesiology & Pain Medicine, Seattle Children's Hospital, Seattle, WA, USA

**Patricia A. McGrath** The Hospital for Sick Children Pain Research Center, Toronto, ON, Canada

**Patrick McGrath** Departments of Psychology, Pediatrics and Psychiatry, Dalhousie University, Canada

**Greg McIntosh** Canadian Back Institute, Toronto, ON, Canada

**Peter McIntyre** Department of Pharmacology, University of Melbourne, Melbourne, Australia

**Elsbeth M. McLachlan** Neuroscience Research Australia, University of New South Wales, Randwick, NSW, Australia

University of Glasgow, Glasgow, UK

**Peter A. McNaughton** Department of Pharmacology, University of Cambridge, Cambridge, UK

**J. Mark Melhorn** Section of Orthopaedics, Department of Surgery, University of Kansas School of Medicine, Wichita, KS, USA

**Ronald Melzack** Department of Psychology, McGill University, Montreal, QC, Canada

**Lorne M. Mendell** Department of Neurobiology and Behavior, Stony Brook University, Stony Brook, NY, USA

**George Mendelson** Department of Psychological Medicine, Monash University, Caulfield, VIC, Australia

**Siegfried Mense** Neuroanatomy, Heidelberg University, Medical Faculty Mannheim, CBTM, Mannheim, Germany

**Daniel Menétrey** Biomédicale, Paris, France

**Sebastiano Mercadante** Pain Relief & Palliative Care, La Maddalena Cancer Center University of Palermo, Palermo, Italy

**Susan Mercer** School of Biomedical Sciences, The University of Queensland, Brisbane, Australia

**Karl Messlinger** University of Erlangen-Nürnberg, Erlangen, Germany

**Richard A. Meyer** Department of Neurosurgery, School of Medicine Johns Hopkins University, Baltimore, MD, USA

**Walter J. Meyer III** Shriners Hospitals for Children, Shriners Burns Hospital, Galveston, TX, USA

Department of Psychiatry, University of Texas Medical Branch, Galveston, TX, USA

**Björn A. Meyerson** Department of Clinical Neuroscience, Section of Neurosurgery, Karolinska Institute/University Hospital, Stockholm, Sweden

**Martin Michaelis** Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany

**Joseph Mignogna** Michael E. DeBakey VA Medical Center, Houston VA HSR&D Center of Excellence (152), Houston, TX, USA

**Judith A. Mikacich** Department of Obstetrics and Gynecology, University of California Los Angeles Medical Center, Los Angeles, CA, USA

**Kensaku Miki** Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Japan

**Vjekoslav Miletic** School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA

**Scott R. Miller** Memorial Sloan-Kettering Cancer Center, New York, USA

**Erin D. Milligan** Department of Neurosciences, University of New Mexico, Albuquerque, NM, USA

**Michael S. Minett** Molecular Nociception Group, Wolfson Institute for Biomedical Research, University College London, London, WC, UK

**J. Mocco** Department of Neurological Surgery, Neurological Institute Columbia University, New York, NY, USA

**Jeffrey S. Mogil** Department of Psychology, McGill University, Montreal, QC, Canada

**Harvey Moldofsky** Sleep Disorders Clinic of the Centre for Sleep and Chronobiology, Toronto, ON, Canada

**Robert M. Moldwin** The Arthur Smith Institute for Urology, North Shore-LIJ Healthcare System, Hofstra North Shore LIJ School of Medicine, New Hyde Park, NY, USA

**Derek C. Molliver** Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

**Robert D. Mootz** Washington State Department of Labor and Industries, Olympia, WA, USA

**Laura Mordillo-Mateos** FENNSI Group, Hospital Nacional de Paraplégicos, Toledo, Spain

**Anne Morel** Laboratory for Functional Neurosurgery, Neurosurgical Clinic University Hospital Zürich, Zürich, Switzerland

**Anne Morinville** Montreal Neurological Institute, McGill University, Montreal, QC, Canada

**Stephen Morley** Academic Unit of Psychiatry and Behavioral Sciences, University of Leeds, Leeds, UK

**David B. Morris** University of Virginia, Charlottesville, VA, USA

**G. Lorimer Moseley** Sansom Institute for Health Research, University of South Australia Neuroscience Research Australia, Adelaide, Australia

**Joachim Mossner** Medical Clinic and Polyclinic II, University Clinical Center Leipzig AöR, Leipzig, Germany

**Eric A. Moulton** P.A.I.N. Group, Anesthesiology, Boston Children's Hospital, Harvard Medical School, Waltham, MA, USA

**Francis Githae Muriithi** Department of Obstetrics and Gynaecology, Aga Khan University, Nairobi, Kenya

**Anne Z. Murphy** Neuroscience Institute, Georgia State University, Atlanta, GA, USA

**Paul M. Murphy** Department of Anaesthesia and Pain Management, Royal North Shore Hospital, St. Leonards, NSW, Australia

**Alison Murray** Foothills Medical Center, Calgary, AB, Canada

**H. S. Na** Neuroscience Research Institute and Department of Physiology, Korea University, College of Medicine, Seoul, Republic of Korea

**Daisuke Naka** Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Japan

**Yoshio Nakamura** Pain Research Center, Department of Anesthesiology University of Utah School of Medicine, Salt Lake City, UT, USA

**Barbara Namer** Department of Physiology & Pathophysiology, FAU, Erlangen/Nuremberg, Bavaria, Germany

**Matti V. O. Närhi** Department of Biomedicine/Physiology, Department of Dentistry, University of Eastern Finland, Institute of Medicine, Kuopio, Finland

**H. J. W. Nauta** University of Texas Medical Branch, Galveston, TX, USA

**Lucia Negri** Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy

**Gary Nesbit** Department of Radiology, Oregon Health and Science University, Portland, OR, USA

**Timothy Ness** Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, AL, USA

**Volker Neugebauer** Department of Neuroscience & Cell Biology, University of Texas Medical Branch, Galveston, TX, USA

**Lawrence C. Newman** Albert Einstein College of Medicine, New York, NY, USA

**Michael K. Nicholas** Royal North Shore Hospital, University of Sydney, St. Leonards, NSW, Australia

**Ellen Niederberger** Pharmazentrum frankfurt, Institute of Clinical Pharmacology, Goethe-University Hospital, Frankfurt, Germany

**Lone Nikolajsen** Department of Anaesthesiology, Danish Pain Research Center Aarhus University Hospital, Aarhus, Denmark

**Katie Nixdorf** Comprehensive Pain Center, Oregon Health and Science University, Portland, OR, USA

**Donald R. Nixdorf** Department of Diagnostic and Biological Sciences, School of Dentistry University of Minnesota, Minneapolis, MN, USA

**Carl E. Noe** University of Texas Southwestern Medical Center, Lubbock, TX, USA

**Koichi Noguchi** Department of Anatomy and Neuroscience, Hyogo College of Medicine, Hyogo, Japan

**Richard B. North** The Johns Hopkins University, Baltimore, MD, USA

**Turo J. Nurmikko** Department of Neurological Science, University of Liverpool, and Pain Research Institute, The Walton Centre NHS Foundation Trust, Liverpool, UK

**Anne Louise Oaklander** Nerve Injury Unit, Departments of Neurology and Pathology, Massachusetts General Hospital Harvard Medical School, Boston, MA, USA

**Koichi Obata** Department of Anatomy and Neuroscience, Hyogo College of Medicine, Hyogo, Japan

**Tim F. Oberlander** Division of Developmental Pediatrics, University of British Columbia, Vancouver, BC, Canada

**Bruno Oertel** Institute for Clinical Pharmacology, Pharmaceutical Center Frankfurt, Johann Wolfgang Goethe University, Frankfurt, Germany

**Andrea C. Ogbonna** Wolfson Centre for Age Related Diseases, King's College London, London, UK

**Alfred T. Ogden** Department of Neurological Surgery, Neurological Institute Columbia University, New York, NY, USA

**S. Ohara** Department of Neurosurgery, Johns Hopkins Hospital, Johns Hopkins Medical Institutions, Johns Hopkins University, Baltimore, MD, USA

**Peter T. Ohara** Department of Anatomy, University of California San Francisco, San Francisco, CA, USA

**Akiko Okifuji** Department of Anesthesiology, University of Utah, Salt Lake City, UT, USA

**Jean-Louis Oliveras** Inserm, Paris, France

**Antonio Oliviero** FENNSI Group, National Hospital of Paraplégicos, Toledo, Spain

**Sean O'Mahony** Palliative medicine, Rush University Medical Center, Chicago, IL, USA

**Peregrine B. Osborne** Dept Anatomy & Neuroscience, University of Melbourne, Melbourne, VIC, Australia

**Michael H. Ossipov** Department of Pharmacology, University of Arizona  
College of Medicine, Tucson, AZ, USA

**Tonya M. Palermo** Seattle Children's Hospital Research Institute, CW8-6 -  
Child Health, Behavior and Development, University of Washington, Seattle,  
WA, USA

**Shreela Palit** Department of Psychology, The University of Tulsa, Tulsa,  
OK, USA

**Juan A. Pareja** Department of Neurology, Fundación Hospital Alcorcón,  
Madrid, Spain

**Steven D. Passik** Psychiatry and Anesthesiology, Vanderbilt University,  
Nashville, TN, USA

**Gavril W. Pasternak** Laboratory of Molecular Neuropharmacology,  
Memorial Sloan-Kettering Cancer Center, New York, USA

**S. H. Patel** Department of Neurosurgery, Johns Hopkins Hospital,  
Baltimore, MD, USA

**Gavin Pattullo** Department of Anesthesia and Pain Management, Royal  
North Shore Hospital, University of Sydney, St. Leonards, NSW, Australia

**Kevin Pauza** Tyler Spine and Joint Hospital, Tyler, TX, USA

**Eric M. Pearlman** Pediatrics, Mercer University School of Medicine,  
The Children's Hospital at Memorial University Medical Center, Savannah,  
USA

**Elvira De la Pena** Instituto de Neurociencias, Universidad Miguel  
Hernández-CSIC, Alicante, Spain

**Yuan Bo Peng** Department of Psychology, University of Texas at Arlington,  
Arlington, TX, USA

**Jose Pereira** Foothills Medical Center, Calgary, AB, Canada

**Edward Perl** Department of Cell and Molecular Physiology, School of  
Medicine University of North Carolina, Chapel Hill, NC, USA

**Tiffany Grace Perry** Center for Spine Health, The Cleveland Clinic Founda-  
tion, Cleveland, OH, USA

**Marie Pertin** Pain Center, University Hospital Center and University of  
Lausanne, Lausanne, Switzerland

**Antti Pertovaara** Department of Physiology, Institute of Biomedicine  
University of Helsinki, Helsinki, Finland

**Peter Peter** Department of Neurobiology and Anatomy, University of  
Rochester Medical Center, Rochester, NY, USA

**Lisa M. Peters** Department of Anesthesiology and Pain Medicine, Seattle  
Children's Hospital, Seattle, WA, USA



**Pramit Phal** Department of Radiology, Oregon Health and Science University, Portland, OR, USA

**Rebecca Pillai Riddell** Department of Psychology, York University, Toronto, ON, Canada

Department of Psychiatry, Hospital for Sick Children, Toronto, ON, Canada

**Issy Pilowsky** University of Adelaide, Adelaide, Australia

**Leon Plaghki** Institute of Neuroscience (IoNS), Université Catholique de Louvain, Brussels, Belgium

**Markus Ploner** Department of Neurology, Technische Universität München, Munich, Germany

**Esther M. Pogatzki-Zahn** Department of Anesthesiology and Intensive Care Medicine, University Muenster, Muenster, Germany

**Michael Polydefkis** Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

**James D. Pomonis** Algos Preclinical Services, Roseville, MN, USA

**Dieter Pongratz** Friedrich Baur Institute, Ludwig Maximilians University, Munich, Germany

**Hayley Poole** Hadley House, Leicester General Hospital, Leicester, UK

**Frank Porreca** Department of Pharmacology, University of Arizona Health Sciences Center, Tucson, AZ, USA

**Russell K. Portenoy** Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY, USA

**Ian Power** Critical Care and Pain Medicine, The University of Edinburgh, Edinburgh, UK

**Donald D. Price** Oral Surgery and Neuroscience, McKnight Brain Institute University of Florida, Gainesville, FL, USA

**Daryl Pullman** Medical Ethics, Memorial University of Newfoundland, St. John's, NL, Canada

**Yunhai Qiu** Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Japan

**Michael Quittan** Department of Physical Medicine and Rehabilitation, Kaiser-Franz-Joseph Hospital, Vienna, Austria

**Raymond M. Quock** Department of Pharmaceutical Sciences, Washington State University College of Pharmacy, Pullman, WA, USA

**Jennifer Rabbitts** Department of Anesthesiology and Pain Medicine, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, WA, USA

**Nicole Racine** Psychology, York University, Toronto, ON, Canada