# Melatonin, Neuroprotective Agents and Antidepressant Therapy

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*Editors*

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*Editors*
Francisco López-Muñoz
Faculty of Health Sciences
Camilo José Cela University
Neuropsychopharmacology Unit
Hospital 12 de Octubre Research Institute (i+12)
Madrid
Spain

Cecilio Álamo
Department of Biomedical Sciences (Pharmacology Area)
Faculty of Medicine and Health Sciences
University of Alcalá
Madrid
Spain

Venkataramanujam Srinivasan
Sri Sathya Sai Medical Educational and Research Foundation
Coimbatore
India

Takahiro A. Kato
Department of Neuropsychiatry
Graduate School of Medical Sciences
Kyushu University
Fukuoka
Japan

Domenico de Berardis
NHS, Department of Mental Health
Psychiatric Service of Diagnosis and Treatment
Hospital "G. Mazzini"
Teramo
Italy

Department of Neurosciences and Imaging
University "G. D'Annunzio"
Chieti
Italy

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# Preface

At some point the editors of this book made the decision to work together to consider the relationship between two very classic issues, such as the pineal gland and the old melancholy, today known as depression, with most modern topics as neuroprotection in mental illness. Each of these issues separately has generated numerous scientific and clinical studies that have justified a myriad of publications. However, our interest is focused on the possible interrelationship between these topics.

Conventionally, in the research field of depression, a focus on monoamine neurotransmitters, especially serotonin and noradrenaline, has historically underpinned to understand the pathophysiology of depression and its therapeutic mechanisms. This book is a composition of cutting edge research on brain science and clinical depression with a strong focus on melatonin. In the first half of the text, we cover topics from the discovery of melatonin to its physiology, pharmacology, and expanding pathophysiology. The latest findings regarding drug discoveries that have targeted melatonin are also included. In the second half of this book moving beyond melatonin, we have included writing on the most up-to-date research topics on depression along with discussions on pathophysiology and treatment.

A complex illness, depression requires deeper understanding from a variety of perspectives. Understanding depression necessitates understanding not only of monoamine neurotransmitters, but also of neural systems with glial networks, genetic features including methylation, and other molecules focusing on neurotrophic factors, inflammatory cytokines, and free radicals. These various elements are correlated in a complex manner, creating various conditions of depression, and this is where melatonin is a crucial factor. When it comes to treatment, understanding of these various aspects is absolutely essential.

The pineal gland, the "enigmatic organ," as it was called by Van Gehuchten, is an organ that has been studied thoroughly from a historical perspective. The first chapter of the book refers to his scientific and philosophical evolution throughout human history. Since Classical Antiquity, numerous authors have linked the origin of some mental disorders to physical and functional changes in the pineal gland because of its attributed role in humans as the connection between the material and the spiritual world. Descartes proposed that it was the seat of the human soul and controlled communications between the physical body and its surroundings, including emotions. But the link between the pineal gland and psychiatric disorders was definitively

highlighted in the twentieth century. The use of glandular extracts in patients with mental deficiency, and finally the discovery of melatonin in 1958, reawakened interest in the relationship between the pineal gland and mental disorders, fundamentally the affective and sleep disorders. In the past 25 years, scientific production, both from a basic perspective as clinic, in relation to the pineal gland and melatonin has had an exponential development, as reflected in the initial chapters of this book.

Considering the important prevalence of primary insomnia in the general population, neuroimaging studies remain relatively few. In addition, little is known about the relation between pineal volume and insomnia. In another chapter of this book, the contribution of functional and structural neuroimaging to our current understanding of primary insomnia is examined.

An updated description of the basic and clinical aspects of melatonin is given in several chapters, which also discuss the interesting new clinical perspective for melatonin. One of the key contents of this book is the role played by melatonin as a neuroprotective agent, which is treated by different working groups in four chapters. Thus, the involvement of melatonin and its receptors in neuroprotection and the current status of melatonin in neurodegenerative processes are reviewed in detail. In addition, the concomitant use of melatonin with other pharmacological agents in the treatment of neurodegenerative diseases is described in detail. Furthermore, we explore the mechanism of melatonin that is associated with the role of stress as a key factor to precipitate depression and as a factor altering neurogenesis, supporting the notion that melatonin possesses anti-stress and neurogenic actions. On the other hand, melatonin shows a pleiotropic character and it is a versatile and ubiquitous antioxidant molecule with low toxicity and high efficacy in reducing oxidative damage. Furthermore, melatonin has anti-inflammatory effects by regulation of multiple cellular pathways and properties to prevent excitotoxicity, among others. In this book, melatonin's beneficial effects in hepatic injury and its marked potential for improving human health against the most widely used chemical weapons are reviewed.

The relationship between melatonin, sleep and circadian rhythms is highly known. Alterations in cascade of these parameters can lead to an alteration of mood associated with the emergence of depressive disorders. In fact, a growing literature suggests that the melatonergic system may be involved in the pathophysiology of mood and some core symptoms of depression show disturbance of the circadian rhythm in their clinical expression. In addition, alterations have been described in the circadian rhythms of several biological markers in depressed patients. These aspects are developed in different chapters of the book, highlighting that melatonin through its receptor can modulate the survival of newborn neurons in the adult hippocampus, making it the first known exogenously applicable substance with such specificity.

Fibromyalgia syndrome is a complex chronic condition with an unknown etiology and pathophysiology, causing widespread pain and a variety of other symptoms. However, abnormality in circadian rhythm of hormonal profiles and cytokines has been observed in this disorder. Several studies have reported a common comorbidity between depression and fibromyalgia syndrome. Thus, study of the role of melatonin in fibromyalgia seems justified.

Taking into account the possible pharmacological role of melatonin in different processes, various mechanisms that improve its clinical applicability have been studied. In this book some authors discuss new galenic formulations of melatonin, the possibility of using agents that act directly on melatonergic receptors, as ramelteon, and the antidepressant role of the agomelatine. This agent behaves both as a potent agonist at melatonin $MT_1$ and $MT_2$ receptors and as a neutral antagonist at 5-$HT_{2C}$ receptors. Accumulating evidence in a broad range of experimental procedures supports the notion that the psychotropic effects of agomelatine are due to the synergy between its melatonergic and 5-hydroxytryptaminergic effects.

Another important group of chapters of this book concerns the study of some lesser known characteristics of mood disorders. The contribution made by leading experts in each of the items collected in the different chapters is remarkable. In this sense, interesting aspects are analyzed as neuropsychological models of depression, the chronobiology, sleep abnormalities, hormonal dysfunction and affective temperaments of mood disorders, or bipolar disorders and biological rhythm, circadian clock gene dysfunction, and neurocognitive deficit.

Finally, a large section related to drugs for the treatment of depression—antidepressants—is discussed. This section covers from the history of antidepressants to the future therapeutic targets for the treatment of depression, as vasopressin, opioids, brain-derived neurotrophic factors, glutamatergic mechanisms, and corticotropin-releasing factor antagonists as antidepressants. We also collect particular aspects of the use of antidepressants, for example, the combination strategies in patients with treatment-resistant depression, or the use of antidepressants in elderly or in patients with chronic pain and the use of these agents and suicide risk. In addition, there is a pair of chapters related to the pharmacogenomics of antidepressant drugs.

Melatonin is an important mediator of a wide range of physiologic functions, and alterations in the melatonergic systems may be implicated in the etiopathogeny of some diseases. Several investigations have been conducted on melatonin in different psychiatric/neurologic diseases, and these preliminary positive findings with respect to disease pathology and treatment mark only the beginning of a fruitful new era in psychopharmacology.

The etiologic heterogeneity of depressive disorders does not allow to conclude on a general relationship between melatonin deficiency and depression. Nevertheless, this connection may exist in some subforms, and melatonin receptors can be a target for antidepressants. Although available drugs are effective, they also have substantial limitations. Recent advances in our understanding of the fundamental links between chronobiology and major mood disorders, as well as the development of new drugs that target the circadian system, have led to a renewed focus on this area. This book emphasizes these aspects and aims to provide a new grain of sand in the broad field of depression and its treatment.

For this purpose, we were invited to participate in the preparation of this book to an international roster of prestigious authors, who are experts in these topics. The positive response received pleasantly exceeded our expectations. This book should be characterized as a work of an integrative nature where

the context is as important as the text itself and where it is possible to contrast different visions and approaches to this field of study. This would have been impossible without an international and multidisciplinary conception of this project, in which 145 authors from 25 countries have collaborated on the preparation of the 51 chapters of this book. We thank all authors for their efforts, which have served, in a decisive manner, to make this project a reality, as well as the personnel in Springer for the interest shown in this work.

This book is dedicated to the memory of Professor Venkataramanujam Srinivasan, MSc, PhD, MAMS, whose untimely death has saddened his colleagues and the scientific community. We express our condolences to the late Professor Srinivasan who envisioned this book. Professor Srinivasan was an eminent neuroscientist, psychopharmacologist, and professor of physiology at multiple prestigious academic institutions. He founded and chaired the Sri Sathya Sai Medical Education and Research Foundation, where he donated his time and effort in the pursuit of knowledge. He devoted his life researching the physiology of sleep, chronobiology, psychoimmunology, and endocrinology. He was an internationally recognized teacher of physiology and biological psychiatry, a noted investigator of melatonin's physiological function, and a leader in the development of melatonin drugs for the treatment of medical conditions. A prolific writer, he published a plethora of his research findings in highly respected journals and books. Professor Srinivasan provided guidance, patience, and stimulus in the completion of this, his final work, allowing an encyclopedic review of melatonin's therapeutic uses and neuroprotective qualities. This book follows his previous important review of the use of melatonin and its congeners in clinical practice. Professor Srinivasan's knowledge and contributions to medical science will be greatly missed by his colleagues and medical scientists all over the world. Based on the intention of Professor Srinivasan, in addition to us four editors, and with the cooperation of the late professor's daughter Dr. Veda Padmapriya Selvakumar and family, it has finally reached completion. To all those involved, we would like to express our gratitude.

By reading this book, it is possible to grasp not only the research related to melatonin but also an overall picture of the latest research into depression. This work makes an important contribution to the development of future research of depression. We have worked with intensity on the development of "Melatonin, Neuroprotective Agents, and Antidepressant Therapy." After months of hard editorial work, this book sees the light and reaches the hands of the reader. It is hoped that this work will help to better understand the intricate mechanisms of depression and its therapeutic approach. If it benefits only one of the patients treated by the reader, we would be fully satisfied.

Madrid, Spain — Francisco López-Muñoz
Chieti, Italy — Domenico de Berardis
Madrid, Spain — Cecilio Álamo
Fukuoka, Japan — Takahiro A. Kato
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# Contributors

**Sarfraz Ahmad** Aimcan Pharma Research and Technologies Inc., Guelph, ON, Canada

**Cecilio Álamo** Department of Biomedical Sciences (Pharmacology Area), Faculty of Medicine and Health Sciences, University of Alcalá, Madrid, Spain

**Gamze Altun** Department of Histology and Embryology, Medical School, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

**Berrin Zuhal Altunkaynak** Department of Histology and Embryology, Medical School, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

**Mario Amore** Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genova, Genova, Italy

**Vanessa Areco** "Dr. Cañas" Laboratory, Biochemistry and Molecular Biology, Faculty of Medical Sciences, Universidad Nacional de Córdoba, INICSA (CONICET-UNC), Córdoba, Argentina

**Cynthia L. Arfken** Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

**Nazem Atassi** Neurological Clinical Research Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

**Pınar Atukeren** Department of Medical Biochemistry, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey

**Sofia Avissar** Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheba, Israel

**Livia Avvisati** Laboratory of Molecular and Translational Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

**Dominika Berent** Department of Psychiatry, Medical University of Warsaw, Warszawa, Poland

**James D. Berry** Neurological Clinical Research Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

**Parichart Boontem** Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Salaya, Thailand

**Nash N. Boutrous** Department of Psychiatry, University of Missouri – Kansas City, Kansas City, MO, USA

**Amnon Brzezinski** Department of Obstetrics and Gynecology, Hadassah Medical Center, The Hebrew University, Jerusalem, Israel

**J.M. Bumb** Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

**Ramón Cacabelos** Chair of Genomic Medicine, Camilo José Cela University, Madrid, Spain

EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, Bergondo, Corunna, Spain

**Caroline Caddy** Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, the Institute of Psychiatry, King's College London, London, UK

**Heather K. Caldwell** Laboratory of Neuroendocrinology and Behavior, Department of Biological Sciences, Kent State University, Kent, OH, USA

**Agata Carpentieri** "Dr. Cañas" Laboratory, Biochemistry and Molecular Biology, Faculty of Medical Sciences, Universidad Nacional de Córdoba, INICSA (CONICET-UNC), Córdoba, Argentina

Biological Chemistry, Faculty of Dentistry, Universidad Nacional de Córdoba, Córdoba, Argentina

**Valentina Casetti** Crisis, Inpatient, and Rehabilitation Services, Oxleas NHS Foundation Trust, London, UK

Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, the Institute of Psychiatry, King's College, London, UK

**Zhuoyou Chen** Department of Neurology, Changzhou Second People's Hospital, Changzhou, Jiangsu Province, China

**Paul Chu-Sin-Chung** Centre National de la Recherche Scientifique (CNRS)-UPR 3212, Institute of Cellular and Integrative Neurosciences, Strasbourg, France

**Merit E. Cudkowicz** Neurological Clinical Research Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

**Salvatore Cuzzocrea** Department of Biological and Environmental Sciences, The University of Messina, Messina, Italy

**Emmanuel Darcq** Douglas Mental Health University Institute, McGill University, Verdun, QC, Canada

**Débora d' Ávila Reis** Department of Morphology, Cell Biology Institute, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

**Gabriela Díaz de Barboza** "Dr. Cañas" Laboratory, Biochemistry and Molecular Biology, Faculty of Medical Sciences, Universidad Nacional de Córdoba, INICSA (CONICET-UNC), Córdoba, Argentina

**Marina de Barros Pinheiro** Arthritis and Musculoskeletal Research Group - AMRG, The University of Sydney, Sydney, NSW, Australia

**Andrea de Bartolomeis** Laboratory of Molecular and Translational Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

**Domenico de Berardis** NHS, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "G. Mazzini", Teramo, Italy

Department of Neurosciences and Imaging and Clinical Sciences, University "G. D'Annunzio", Chieti, Italy

**Omur Gulsum Deniz** Department of Histology and Embryology, Medical School, Ondokuz Mayıs University, Samsun, Turkey

**Massimo di Giannantonio** Department of Neuroscience, Imaging and Clinical Science, Chair of Psychiatry, University "G. D'Annunzio", Chieti, Italy

**Dimos Dimelis** Department of Psychiatry, 424 Military Hospital, Thessaloniki, Greece

**Marco di Nicola** Institute of Psychiatry and Psychology, Catholic University of Sacred Heart, Rome, Italy

**Peter Dome** Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

Laboratory of Suicide Research and Prevention, National Institute for Psychiatry and Addictology, Budapest, Hungary

**Alan B. Douglass** Royal Ottawa Mental Health Center, University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada

**Manuel Durán** Acute Inpatients Unit, Dr. R. Lafora Psychiatric Hospital, Madrid, Spain

**Kasima Ekthuwapranee** Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Salaya, Thailand

**Agata Faron-Górecka** Department of Pharmacology, Institute of Pharmacology Polish Academy of Sciences, Kraków, Poland

**Valeria Feinshtein** Department of Clinical Biochemistry and Pharmacology, Ben Gurion University of the Negev, Beersheba, Israel

**Alberto Fernández** Department of Psychiatry, Faculty of Medicine, Complutense University, Madrid, Spain

**Michele Fornaro** Polyedra Clinical Group, Teramo, Italy

Department of Education Science, University of Catania, Catania, Italy

**Judith Fosbraey** Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, the Institute of Psychiatry, King's College London, London, UK

**Anastasios Fotinos** Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

**Konstantinos N. Fountoulakis** Division of Neurosciences, 3rd Department of Psychiatry, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

**Doron Fux** Department of Clinical Biochemistry and Pharmacology, Ben Gurion University of the Negev, Beersheba, Israel

**Pilar García-García** Department of Biomedical Sciences (Pharmacology Area), Faculty of Medicine and Health Sciences, University of Alcalá, Madrid, Spain

**Valentina Gilardi** Laboratory of Molecular and Translational Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

**Moran Golan** Department of Clinical Biochemistry and Pharmacology, Ben Gurion University of the Negev, Beersheba, Israel

**Xenia Gonda** Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

Laboratory of Suicide Research and Prevention, National Institute for Psychiatry and Addictology, Budapest, Hungary

**Robert Gonzalez** Department of Psychiatry, Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA

**Piyarat Govitrapong** Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Salaya, Thailand

Center for Neuroscience and Department of Pharmacology, Faculty of Science, Mahidol University, Salaya, Thailand

**Yingjun Guan** Department of Histology and Embryology, Weifang Medical University, Weifang, Shandong, China

**Claudio Guarneri** Department of Clinical Experimental Medicine, Section of Dermatology, The University of Messina C/O A.O.U. Policlinico "G. Martino", Messina, Italy

**José Antonio Guerra** Department of Pharmacology, Pharmacy Faculty, Complutense University, Madrid, Spain

**Solange Guizzardi** "Dr. Cañas" Laboratory, Biochemistry and Molecular Biology, Faculty of Medical Sciences, Universidad Nacional de Córdoba, INICSA (CONICET-UNC), Córdoba, Argentina

**Kenji Hashimoto** Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, Chiba, Japan

**Hideki Horikawa** Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

**Felice Iasevoli** Laboratory of Molecular Psychiatry and Psychopharmacotherapeutics, Section of Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

Polyedra Clinical Group, Teramo, Italy

**Sâmia R.L. Joca** Department of Physics and Chemistry, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, São Paulo, Brazil

**Rosa Jurado** Department of Basic Psychology II, Faculty of Psychology, Complutense University, Madrid, Spain

Faculty of Health Sciences, Psychology Department, Camilo Jose Cela University, Madrid, Spain

**Shigenobu Kanba** Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

**Arife Ahsen Kaplan** Department of Histology and Embryology, Medical School, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

**Suleyman Kaplan** Department of Histology and Embryology, Medical School, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

**Takahiro A. Kato** Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Brain Research Unit, Innovation Center for Medical Redox Navigation, Kyushu University, Fukuoka, Japan

**Sefa Ersan Kaya** Department of Histology and Embryology, Medical School, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

**Brigitte L. Kieffer** Douglas Mental Health University Institute, McGill University, Verdun, QC, Canada

**Eiji Kirino** Department of Psychiatry, Juntendo University Shizuoka Hospital, Shizuoka, Japan

Department of Psychiatry, Juntendo University School of Medicine, Tokyo, Japan

**Siyona Kolatkar** Department of Clinical Biochemistry and Pharmacology, Ben Gurion University of the Negev, Beersheba, Israel

**Gianmarco Latte** Laboratory of Molecular and Translational Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

**Yu-Li Liu** Center for Neuropsychiatric Research, National Health Research Institutes, Zhunan, Miaoli County, Taiwan

Department of Pharmacology, China Medical University, Taichung, Taiwan

**Francisco López-Muñoz** Faculty of Health Sciences, Camilo José Cela University, Villanueva de la Cañada, Madrid, Spain

Neuropsychopharmacology Unit, Hospital 12 de Octubre Research Institute (i+12), Madrid, Spain

Portucalense Institute of Neuropsychology and Cognitive and Behavioural Neurosciences, Portucalense University, Porto, Portugal

**Pierre-Eric Lutz** McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Verdun, QC, Canada

**Lilly L.J. Mao** Aimcan Pharma Research and Technologies Inc., Guelph, ON, Canada

**José Luis Marco-Contelles** Medicinal Chemistry Laboratory, Institute of General Organic Chemistry (CSIC), Madrid, Spain

**Fernando Marín** Department of Cellular Biology, Faculty of Medicine, Complutense University, Madrid, Spain

**Giovanni Martinotti** Department of Neuroscience, Imaging and Clinical Science, Psychiatry, University "G. D'Annunzio", Chieti, Italy

**Monica Mazza** Polyedra Clinical Group, Teramo, Italy

Department of Health Science, University of L'Aquila, L'Aquila, Italy

**Louise Mercer** Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, The Institute of Psychiatry, King's College London, London, UK

**Yoshito Mizoguchi** Department of Psychiatry, Faculty of Medicine, Saga University, Saga, Japan

**Juan D. Molina** Acute Inpatients Unit, Dr. R. Lafora Psychiatric Hospital, Madrid, Spain

Faculty of Health Sciences, Camilo José Cela University, Madrid, Spain

**Akira Monji** Department of Psychiatry, Faculty of Medicine, Saga University, Saga, Japan

**Julio Cesar Morales-Medina** Research Center for Animal Reproduction, CINVESTAV-Universidad Autónoma, Tlaxcala, México

**Stephan Moratti** Department of Basic Psychology I, Faculty of Psychology, Complutense University, Madrid, Spain

**Ingo S. Nölte** Department of Neuroradiology, University Hospital Mannheim, Mannheim, Germany

**Nootchanart Ruksee** Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Salaya, Thailand

National Institute for Child and Family Development, Mahidol University, Salaya, Thailand

**Trevor R. Norman** Department of Psychiatry, University of Melbourne, Austin Hospital, Heidelberg, VIC, Australia

**Masahiro Ohgidani** Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

**Laura Orsolini** Academic Department of Experimental and Clinical Medicine, United Hospitals, Polytechnic University of Marche, Ancona, Italy

Villa S. Giuseppe Hospital, Hermanas Hospitalarias, Ancona, Italy

Polyedra Clinical Group, Teramo, Italy

School of Life and Medical Sciences, University of Hertfordshire, Hatfield, Herts, UK

**Mehmet Emin Onger** Department of Histology and Embryology, Medical School, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

**Zahiruddin Othman** Department of Psychiatry, School of Medical Sciences Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

**Timo Partonen** Department of Health, National Institute for Health and Welfare, Helsinki, Finland

**Andrei Pereira Pernambuco** Cell Biology Institute, Department of Morphology, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

Department of Health Sciences, University Centre of Formiga (UNIFOR-MG), Centre for Research and Extension (CEPEP), Formiga, MG, Brazil

Department of Health Sciences, University of Itaúna, Itaúna, MG, Brazil

**Giampaolo Perna** Department of Clinical Neurosciences, Hermanas Hospitalarias, FoRiPsi, Villa San Benedetto Menni, Como, Italy

Department of Psychiatry and Neuropsychology, University of Maastricht, Maastricht, The Netherlands

Department of Psychiatry and Behavioral Sciences, Leonard Miller School of Medicine, University of Miami, Coral Gables, FL, USA

**Monica Piersanti** NHS, Department of Mental Health, Psychiatric Service of Diagnosis and Treatment, Hospital "G. Mazzini", ASL 4, Teramo, Italy

**René Pita** Chemical Defence Department, CBRN Defence School, Madrid, Spain

**Giovanni Polimeni** Sicilian Regional Centre of Pharmacovigilance, C/O Unit of Pharmacology, A.O.U. Policlinico "G. Martino", Torre Biologica, Messina, Italy

**Francisco J. Povedano** Faculty of Health Sciences, Camilo José Cela University, Madrid, Spain

**Emiliano Prinzivalli** Laboratory of Molecular and Translational Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

**Gerardo Bernabé Ramírez-Rodríguez** Laboratory of Neurogenesis, Division of Clinical Investigations, National Institute of Psychiatry "Ramón de la Fuente Muñiz", México, DF, México

**Eva Ramos** Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Complutense University of Madrid, Madrid, Spain

**Zoltan Rihmer** Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

Laboratory of Suicide Research and Prevention, National Institute for Psychiatry and Addictology, Budapest, Hungary

**María Angélica Rivoira** "Dr. Cañas" Laboratory, Biochemistry and Molecular Biology, Faculty of Medical Sciences, Universidad Nacional de Córdoba, INICSA (CONICET-UNC), Córdoba, Argentina

**Timothy Roerhrs** Henry Ford Sleep Disorders and Research Center, Henry Ford Health System, Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

**Alejandro Romero** Department of Toxicology and Pharmacology, Faculty of Veterinary Medicine, Complutense University of Madrid, Madrid, Spain

**Arann R. Rowe** Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, The Institute of Psychiatry, King's College London, London, UK

**Gabriel Rubio** Psychiatry Service, 12 de Octubre University Hospital, Madrid, Spain

Neuropsychopharmacology Unit, Hospital 12 de Octubre Research Institute (i+12), Madrid, Spain

Department of Psychiatry, Faculty of Medicine, Complutense University, Madrid, Spain

**Gabriel Schreiber** Division of Psychiatry, Ben Gurion University of the Negev and Barzilai Medical Center, Beersheba, Israel

**Mamuel Sebastián-Aldeanueva** Primary Care Administration of Soria, Soria, Spain

**Gianluca Serafini** Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genova, Genova, Italy

**Kyra-Verena Sendt** Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, the Institute of Psychiatry, King's College London, London, UK

**Sukhwinder S. Shergill** The National Psychosis Unit, South London and Maudsley NHS Foundation Trust, London, UK

Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, The Institute of Psychiatry, King's College London, London, UK

**Winston W. Shen** Department of Psychiatry, Wan Fang Medical Center, Taipei Medical University, Taipei, Taiwan

Department of Psychiatry, College of Medicine, Taipei, Taiwan

**Nicola Smallcombe** Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, the Institute of Psychiatry, King's College London, London, UK

**Paola Solano** Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genova, Genova, Italy

**Venkataramanujam Srinivasan** Sri Sathya Sai Medical Educational and Research Foundation, International Medical Sciences Research Study Center "Prasanthi Nilayam", Kovai Coimbatore, Tamil Nadu, India

**Kinga Szafran-Pilch** Department of Pharmacology, Institute of Pharmacology Polish Academy of Sciences, Kraków, Poland

**Murat Terzi** Department of Neurology, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

**Farah Tiwana** Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, the Institute of Psychiatry, King's College London, London, UK

**Francisco Toledo-Romero** Psychiatry Service, "Virgen de la Arrixaca" University Hospital, Murcia, Spain

**Nori Tolosa de Talamoni** "Dr. Cañas" Laboratory, Biochemistry and Molecular Biology, Faculty of Medical Sciences, Universidad Nacional de Córdoba, INICSA (CONICET-UNC), Córdoba, Argentina

**Carmine Tomasetti** Polyedra Clinical Group, Teramo, Italy

Laboratory of Molecular Psychiatry and Psychopharmacotherapeutics, Section of Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

**Clara Torrellas** EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, Bergondo, Corunna, Spain

**Derek K. Tracy** Crisis, Inpatient, and Rehabilitation Services, Oxleas NHS Foundation Trust, London, UK

Cognition Schizophrenia and Imaging Laboratory, Department of Psychosis Studies, The Institute of Psychiatry, King's College London, London, UK

**Aysın Pınar Turkmen** Department of Histology and Embryology, Medical School, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey

**Hafize Uzun** Department of Medical Biochemistry, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey

**Alessandro Valchera** Polyedra Clinical Group, Teramo, Italy

Villa S. Giuseppe Hospital, Hermanas Hospitalarias, Ancona, Italy

Laboratory of Molecular and Translational Psychiatry, Department of Neuroscience, University School of Medicine "Federico II", Naples, Italy

**Glenn R. Valdez** Department of Psychology, Grand Valley State University, Allendale, MI, USA

**Gustavo H. Vazquez** International Consortium for Bipolar and Psychotic Disorder Research, McLean Hospital, Belmont, MA, USA

Department of Neuroscience, Palermo University, Buenos Aires, Argentina

**Xin Wang** Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

**Marcus Ward** Royal Ottawa Mental Health Center, University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada

**Gregers Wegener** Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Centre for Pharmaceutical Excellence, School of Pharmacy, North West University, Mahikeng, South Africa

**Shannah K. Witchey** Laboratory of Neuroendocrinology and Behavior, Department of Biological Sciences, Kent State University, Kent, OH, USA

**Ana Isabel Wu-Chou** Department of Psychiatry, Wan Fang Medical Center, Taipei Medical University, Taipei, Taiwan

**Ying Xu** Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York, Buffalo, NY, USA

**Mohd Jamil Yaacob** Department of Psychiatry, Faculty of Medicine, Asian Institute of Medicine, Science and Technology, Bedong, Kedah Darul Aman, Malaysia

**Xifei Yang** Toxicology Laboratory, Shenzhen Center for Disease Control and Prevention, Shenzhen, Guangdong Province, China

**Murat Yuce** Department of Histology and Embryology, Medical School, Ondokuz Mayıs University, Samsun, Turkey

**Kıymet Kubra Yurt** Department of Histology and Embryology, Medical School, Ondokuz Mayıs University, Samsun, Turkey

**Rahimah Zakaria** Department of Physiology, School of Medical Sciences, University Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

**Han-Ting Zhang** Department of Behavioral Medicine and Psychiatry, and Department of Physiology and Pharmacology, West Virginia University Health Sciences Center, Morgantown, WV, USA

**Edward W. Zhou** Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

**Yongjin Zhu** Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

# History of Pineal Gland as Neuroendocrine Organ and the Discovery of Melatonin

1

Francisco López-Muñoz, Fernando Marín, and Cecilio Álamo

## 1.1 Introduction

The pineal gland is one of the anatomic organs that have generated most controversy and speculation throughout history. Its anatomical localization in the crossroads of the central nervous system (CNS) and its uneven nature in an environment of double structures together with its morphological appearance have attracted the attention of numerous scientists. Thorough and complex physiological theories have been proposed connecting this structure with the human body functionality, including philosophical postulates that relate to its spiritually. In fact, this cephalic gland, also known as epiphysis or "superior excrescence" in order to distinguish it from the hypophysis or "inferior excrescence," has gone through historic periods of absolute oblivion, deemed as a mere rudimentary vestige, but also through splendorous periods in which it even came to be considered the anatomic jail of the human soul.

In any case, until the middle of the twentieth century, the pineal gland was regarded as an "enigmatic organ," as Arthur van Gehuchten (1861–1914) rightly said [1]. This "enigmatic organ" was historically ascribed important responsibilities, as that of being the link between the body and the spirit in the human body. As a matter of fact, this function had already been considered in the Hindu philosophy and its Vedic literature from ancient times. One of the most popular legends in this culture tells how Parvati, God Shiva's wife, covered his eyes, submerging the world in the darkness. Fortunately, a third eye appeared on his forehead, thus saving the world from an inevitable disaster (Fig. 1.1) [2]. In this regard, according to the ancient Hindu traditions, the human beings would have a "third eye" or mystic organ (the pineal gland), corresponding to

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López-Muñoz F, Marín F, Alamo C. El devenir histórico de la glándula pineal. II: de sede del alma a órgano neuroendocrino. *Revista de Neurología* 2010; 50: 117–125.

F. López-Muñoz (✉)
Faculty of Health Sciences, Camilo José Cela University, Villanueva de la Cañada, Madrid, Spain

Neuropsychopharmacology Unit, Hospital 12 de Octubre Research Institute (i+12), Madrid, Spain

Portucalense Institute of Neuropsychology and Cognitive and Behavioural Neurosciences, Portucalense University, Porto, Portugal
e-mail: francisco.lopez.munoz@gmail.com; flopez@ucjc.edu

F. Marín
Department of Cellular Biology, Faculty of Medicine, Complutense University, Madrid, Spain

C. Álamo
Department of Biomedical Sciences (Pharmacology Area), Faculty of Medicine and Health Sciences, University of Alcalá, Alcalá de Henares, Madrid, Spain



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**Fig. 1.1** Artistic impression of one of the legends about the appearance of Shiva's third eye

the sixth *chakra* (*ajna*), which would provide them with some sort of window to their own spiritual life and which would hold the key to their own mental power [3]. It would then be the organ of clairvoyance and meditation [4].

This mediatory role of the pineal gland between the material and spiritual worlds reached its highest relevance in the seventeenth century, the time when Modern Science was born, thanks to one of its most prominent prime drivers, René Descartes (1596–1650) who hypothesized that this anatomic structure was home to the soul. For Descartes, the pineal gland was not only the material seat of the divine spirit but was also responsible for the appropriate communication between the human machine and its environment, being the intimate spring that controlled the exact functioning of the human body [5].

Finally, from the second half of the nineteenth century on, the definitive breakdown of this prescientific stage of "pinealogy" started, and the period of scientific analysis (as we know it today) on the nature of this organ began, culminating in the obvious confirmation of its endocrine nature following the isolation of melatonin, in 1958, by team of Aaron B. Lerner (1920–2007). To deepen the historical development of the pineal gland, see López-Muñoz et al. [6, 7].

## 1.2 Galen's *Conarium*: The Pineal Gland in the Classic Antiquity

In Western culture, the first express mention of the pineal gland must be looked for in the classic Hellenic antiquity and, more specifically, among the members of the so-called Alexandrian School. This medical trend of thought emerged in Egypt during the Ptolemaic times and resulted in a new anti-Hippocratic physiology that would serve as basis for the doctrinal body of Galenism. Its two most eminent representatives, Herophilos of Chalcedon (325–230 BC) and Erasistratus of Ceos (310–250 BC), considered, respectively, by some authors as "the Father of Anatomy" and "the Father of Physiology," took up the stoic legacy of the Neumatism, promoted centuries back by Diogenes of Apollonia (fifth century BC) and theories of Anaximenes of Miletus (585–524 BC) on the air as a vital principle. They elaborated their physiological theory about animal spirits, in which the pineal gland would play an important role. For these authors, the air, once inside a living being, would be transformed into *pneuma* (*spiritus*, in Latin). Erasistratus tells how the air (cosmic *pneuma*) once transported from the lungs to the heart is changed in the cardiac organ into *pneuma zootikon* (*spiritus vitalis*, in Latin), in order to be, subsequently, carried through the bloodstream to the brain, where it would be then transformed inside the brain ventricles into *pneuma psychikon* (*spiritus animalis*, in Latin) [8]. In this historic frame, according to Ariëns-Kappers' [4] opinion, Herophilos of Chalcedon could well have been the true discoverer of the pineal gland, ascribing its functions in valvular control, as a sphincter, regulating the flux of the *pneuma psychikon* from the third ventricle to the posterior ventricle [9]. However, there is no direct evidence backing up these claims, given the fact that the writings from the Alexandrian anatomist

were completely lost and we only find reference to them in the works of Galen, who stated that the "ancient anatomists" knew about the pineal organ.

It is precisely Claudius Galen (131–200) who completes the first detailed description of this organ that has survived until modern times [10]. Galen gathered the philosophical-physiological Greek legacy, modified the pneumatic theory, and elaborated a physiological doctrine that would last for more than fifteen centuries [11]. Thus, according to the master of Pergamo, the blood that pneumatized in the heart would be conducted to the *rete mirabile* of the brain, originating in the lateral ventricles (considered by Galen to be only one paired ventricle, named anterior ventricle) the psychic pneuma or *spiritus animalis*. This pneuma, comprised of very subtle material substances, would then pass to the spinal cord and the nerves (regarded empty spaces) as a *dynamis psykhiké*-inducing agent, resulting in a muscular action [12].

Even though Galen did never dissect human corpses, he used to humanize by analogy the results from the study of the body of multiple animal species, mainly pigs. The name *Konareion*, with which the pineal gland was designated, comes from his quill (*kônos*, pinecone in Greek), due to the similarity between this fruit and the epiphysis he studied (*conarium*, in Latin). Galen described in deep detail the conarium's anatomy in his *De anatomicis administrationibus*, but consigned its functional role to a mere pseudoglandular lymphatic organ that would serve as fastening to the mass of cerebral veins that go all over the posterior and dorsal faces of the diencephalon. He defended this hypothesis in the eight book of his work *De usu partium*. Galen considered that, in its flux through the ventricular system, the superior cerebellar vermis and not the pineal gland, as Herophilos used to think, was the anatomic structure that acted as a sort of valve able to close the aqueduct of Sylvius avoiding the passing of the psychic pneuma to the fourth or posterior ventricle, seat of memory [13]. A source of confusion inherent to this theory could be the synonym employed by Galen to designate the *vermis superior cerebelli*, which is interchangeably referred to as *epiphysis*, a term designated to the pineal gland in modern times. According to Galen, the pineal gland would be an extracerebral organ lacking self-motility, and therefore, it could not exercise valvular work. For that reason, he would name those defending the pineal theory "stupid" and "ignorant." While he gives no names, he probably refers with these qualifiers to Hippolytus of Rome (ca. 170–235), later Saint Hippolytus, who in his work *Refutatio omnium haeresium* also discusses the role of the pineal gland and the spirits flux [14].

The galenic organization of the brain functionality suits a model that could be called "pneumatic-ventricular model," with a notorious hydraulic nature [15], as the brain is considered as some kind of bomb that distributes the psychic pneuma coming from the sensitive nerves from the lateral ventricles towards the fourth ventricle, in order to propel them later on through the motor nerves [16]. As Spillane [17] highlights, Galen's theory of the spirits will be the longest-lasting throughout the whole history of science.

## 1.3 The Valvular Function of the Pineal Organ and the Three Cell Medieval Theory

Galen's psychophysiological postulates were slightly modified by the following authors, mainly in relation to the ventricular localization of the psychic functions. This way, Posidonius of Byzantium (ca. 370), by the end of the fourth century, established the seat of imagination in the anterior part of the brain, memory in the posterior part, and reasoning in the third ventricle, while Nemesius (ca. 390) positions these three faculties in the anterior, third, and posterior ventricles, respectively, giving rise to the "Three Cell Theory" [15], very much in vogue throughout the Middle Ages (Fig. 1.2). Likewise, Augustine of Hippo (Saint Augustine) (354–430), in his neuropsychological writings, takes the nervous system organization defend by Erasistratus: "*Et aer*, *qui nervis infusus est*, *paret voluntati*, *ut membra moveat*, *non autem ipse voluntas est*" ("The air infused into the nerves is obedient to the will, and

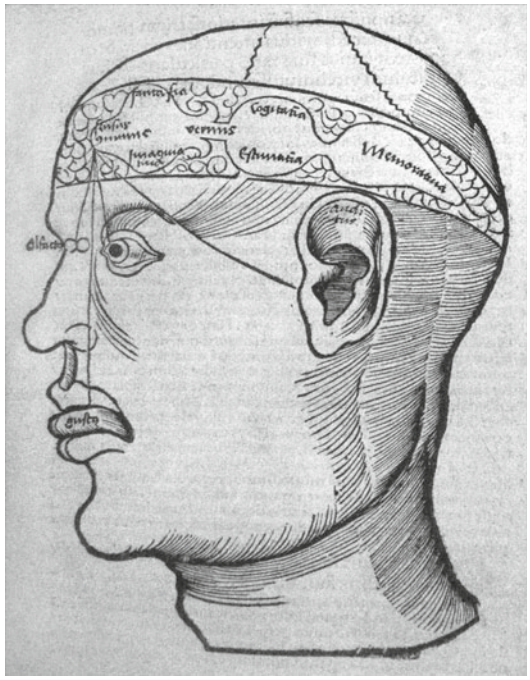


**Fig. 1.2** Illustration of the work *Anathomia* by Mondino de Luzzi, in which the vermis is shown controlling the passage between the anterior and third ventricles. This drawing is, in turn, one of the most popular representations of the three ventricular cells theory and the localization of brain functions

makes the limbs move in the absence of the aquiescence of the very will") (*De Genesi ad Litteram*, 401–415). Finally, the Arabian author Qusta ibn Luqa (Costa ben Luca or Constabulus) (864–923) combined Galen's and Nemesius' theories in his work named *De differentia inter animam et spiritum*, in which he defended the existence of a sort of "memory valve" (the vermis and not the pineal gland) as a kind of sphincter that would regulate the flow between the third and the posterior ventricles (Fig. 1.3) [18].

In this sense, and although the theory giving the pineal gland a valvular role in the ventricular flux of the spirits had already been discarded by Galen, this hypothesis regained strength in the late Medieval times. This could have been the result of a new misconception, as several medical texts from that time, such as the *Liber de oblivione* by Abu Ja'far Ahmad bin Abi Khalid Ibn al-Jazzar (ca. 900–980), or the *Speculum Majus* de Vincent de Beauvais (1190?–1267?), would employ the term "*pinea*" in order to designate the

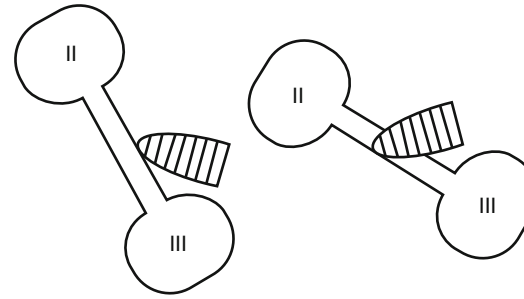


**Fig. 1.3** Schematic reconstruction of the theory by Qusta ibn Luqa on the role of the vermis as a valve between the third ventricle (II) and posterior ventricle (III), seat of memory, preventing the flow of the animal spirits (Reprinted with permission from the online Stanford Encyclopedia of Philosophy (Descartes and the pineal gland)).

cerebellar vermicular appendix to which Galen attributed the control of the spirits flow to the posterior ventricle [19].

## 1.4 The Pineal Gland in Its Anatomical Context

Renaissance thought, mainly platonic, allowed the comeback of modern science and the abandonment of the Medieval Scholastics, still robustly anchored among the university faculties [20]. In the field of medicine, Andreas Vesalius (1514–1564), Father of Modern Anatomy, supposed an inflection point. Vesalio still considers the cephalic organ as the side to the classic *dynámeis* and defends the previous neurophysiological aspects, as the conduction of the animal spirits through the nerves [21]. However, Vesalio refuted all the classical theories about the ventricular localization of the psychic functions, as well as the ability of the *rete mirabile*, the net of blood vessels located at the base of the brain, to produce the animal spirits [22].

With respect to the pineal organ, the theory stating its role as the "guardian" of the flux of the animal spirits continued to be defended during the Renaissance period by authors of the standing of Giacomo Berengario da Carpi (c.1460–c.1530), Jean Fernel (1492–1558), and even, later on, William Harvey (1578–1657) himself in his work *Praelectiones Anatomiae Universalis* (1626). Berengario published in 1522 his *Isagogae breves*, in which he describes the brain ventricles,

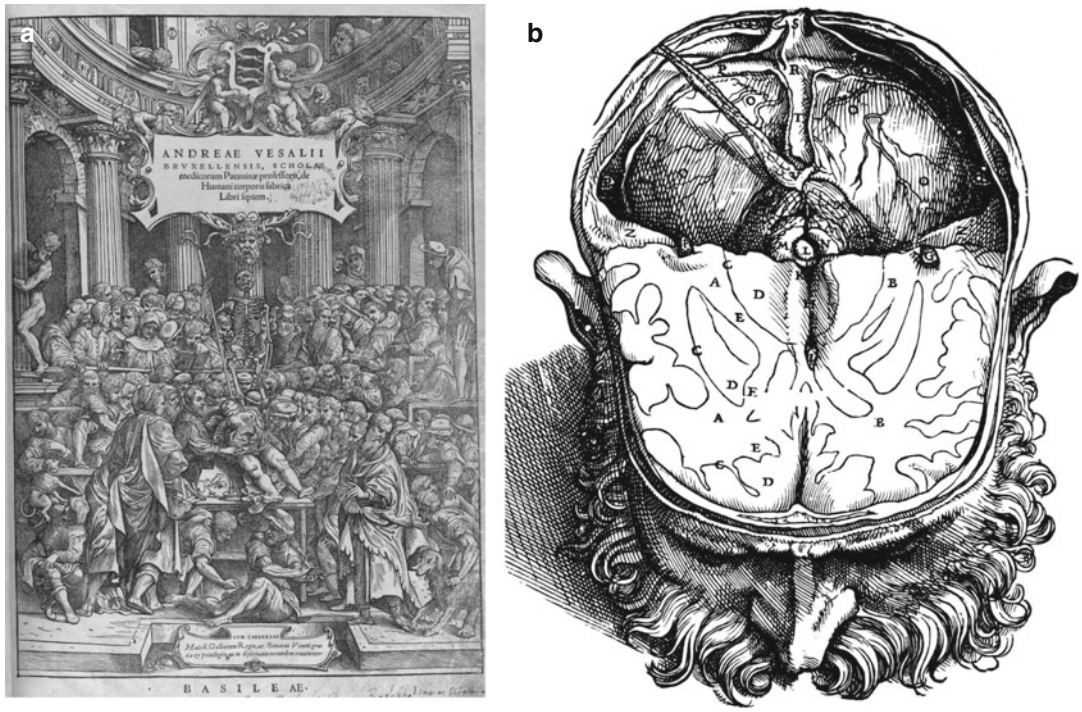


**Fig. 1.4** Frontispiece of the famous work by Andreas Vesalius *De Humani Corporis Fabrica…* (Basel, 1543) (**a**), and illustration of the brain (**b**) corresponding to the second edition of this work (1555), in which the location of the pineal gland (L) is shown, right in the center of the cranial cavity

the choroid plexuses, and the pineal gland, which he denominated "the appendix of thought" [23]. The great contribution of Berengario with respect to the *conarium* was to also ascribe it a role as a filter of cerebrospinal fluid. On the other hand, Fernel, modern exponent of the galenic medical system (*Universa Medicina*, 1554), also defends the valvular concept of the epiphysis, although Lokhorst and Kaitaro [14] are of the opinion that the anatomic structure to which Fernel refers is not the pineal gland itself but rather the cerebellar vermis (as Galen and Ben Luca postulated). In the same way, the Italian physician Girolamo Fracastoro (1483–1553) pointed out that the existence of an odd-numbered brain organ was required in order to integrate and coordinate the sensitive perceptions received by the organism. For Fracastoro, this organ should be the *conarium*, in his opinion seat of reasoning. Nevertheless, from a functional perspective, some Renaissance authors considered the conary organ to be just a mere anatomical support to the neighboring vascular structures.

All these authors' contributions were pointing to a change in the prevailing ideological conception in relation to the pineal organ, which was embodied in the person of Andreas Vesalius. In his masterpiece, *De humani corporis fabrica* (Basel 1543), he ridicules every preceding anatomy treatise, and in his VII book (Fig. 1.4a), in which he analyzes the cephalic organs, a detailed description of the human epiphysis can be found (Fig. 1.4b). According to Bargmann [11], the first graphical representation of the history of the pineal gland is due to Vesalius. Two years later, Charles Estienne (1503–1564), one of the members of the famous family of publishers of that name in Paris, aptly illustrated the epiphysis relationships in his book *De dissectione partium corporis humani* (1545). From a physiological perspective, Vesalio definitely rejected the valvular conception of the pineal gland, as well as that of other anatomic structures, such as the *vermis superior cerebelli*, according to Galen and Qusta ibn Luqa's proposal, or the choroid plexus, whose valvular role was proposed by Mondino de Luzzi

(1275–1326) in his *Anathomia* (1316). Still, the mechanical hypothesis of the spirits flux regulation during Renaissance continued to be stood up for and, once assimilated to the cerebrospinal fluid, lasted even to the times of the genial François Magendie (1783–1855), who, in a piece of work published in 1828 (*Mémoire physiologique sur le cerveau*), affirmed that the pineal gland was "a valve that opened and closed the brain aqueduct" [25]. Possibly, in the opinion of Ariëns-Kappers [26], the last author defending the role of the pineal organ as a regulator of the ventricular flux of cerebrospinal fluid at the level of the aqueduct of Sylvius was Élie de Cyon (1842–1912), nothing less than in the year 1907.

## 1.5 The Pineal Gland as the Seat of the Soul in the Philosophical and Physiological Cartesian Approaches

The role of the pineal gland in the human physiology gained great significance in the seventeenth century, the time of the birth of modern science, thanks to one of its leading proponents, René Descartes (Fig. 1.5a), who said that the seat of the soul resided within it [5, 27]. On the basis of the Greek philosophical analysis, although within the borders of the Catholic faith he always professed, Descartes, who cultivated not only philosophy but also mathematics, physics, astronomy, music, and physiology [28], unleashed the Platonic idea of a human duality, that is, body-soul [29, 30]. Thus, Descartes distinguishes the soul and intelligence (*res cogitans*), as well as a transcendent and free God, from the rest of the cosmos, which includes the human body (*res extensa*) and the animals, which would be subject to the laws of mechanics and mathematics.

Although Descartes always defended the originality of his philosophical hypotheses, when it comes to physiological and anatomical terms, he adopted much of the prevailing theories from classical antiquity, mainly the proposals of the Pneumatic Alexandrian school in relation to the so-called animal spirits (*copula animae* cum *corpore*), later "christianized" by St. Augustine [31]. In this sense, according to Descartes psychophysiological approaches, the placid harmony

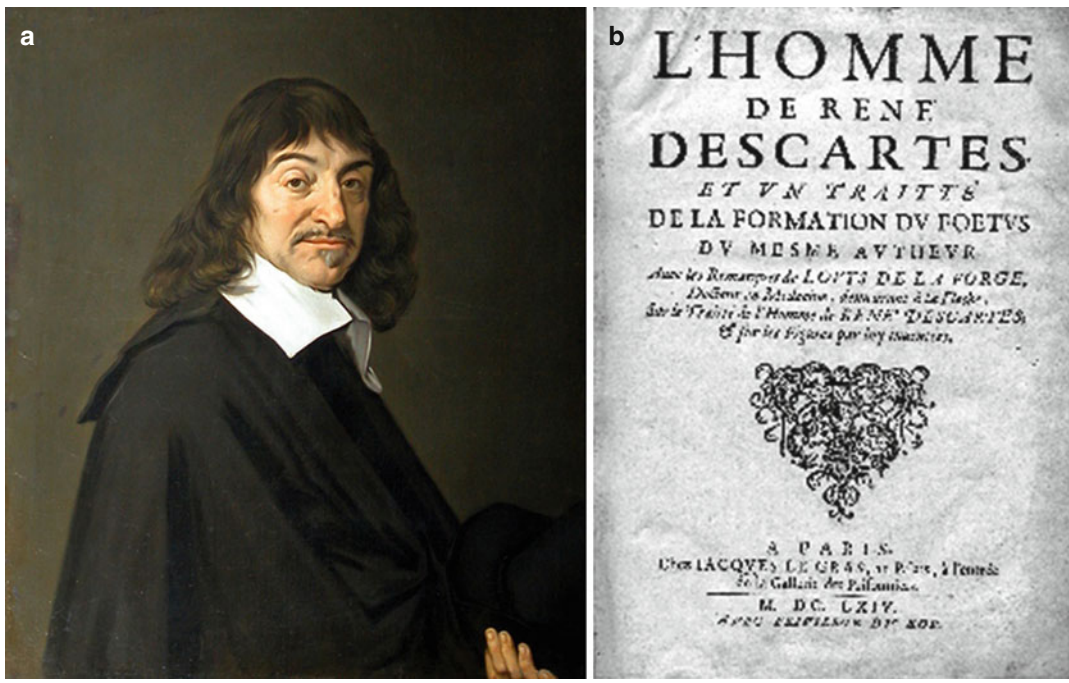


**Fig. 1.5** Portrait of René Descartes, painted by Frans Hals, in 1648 (Musée du Louvre, Paris) (**a**) and cover of the second edition of the *Treatise of Man* (first in French), entitled *L'Homme de Rene Descartes et un Traité de la formation du foetus* (Paris, 1664) (**b**)