# Psychiatry and Neuroscience Update

## From Translational Research to a Humanistic Approach - Volume III

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*Editors*

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*The present volume is dedicated to the memory of*
*Prof. Sandra Del Vecchio († 2017)*

# Foreword

The king of Corinth was the most cunning man of his time. But his tricks and cheating defied the gods until he was punished to an eternal hard labor, pushing uphill a great rock only to see it fall just before reaching the top.

Myths remind men of their fate. Most human endeavors are an endless search for truth or happiness. If the goal is an ideal, by definition, it is not possible to succeed; death will find the hero still in the path. It seems that human science cannot reach complete knowledge and has to keep endlessly toiling. But classical Greeks considered euthanasia the heroic death in battle. And the best life is that spent seeking beauty and truth for love.

When Springer asked us to update studies bridging the gap between psychiatry and neuroscience, an enthusiastic group of experts volunteered. Hard work and many hours of reading and selecting valuable papers laid the foundations for state-of-the-art conclusions.

The first volume had a good acceptance, and in the next year, Volume II covered a *translational approach.* When Springer asked for another update, we thought that maybe every 5 years could be reasonable. In the end, however, the final answer was that 5 years are too full of changes.

Learning and leading with technology is the new approach needed for teaching and working in investigation. But more demanding and an ethical obligation is continuous medical education. E-portfolio is the name we have to include with our familiar books and instruments. Technology has made simulators a new teaching facility unavoidable in many medical specialties. Videos and Gesell cameras help psychology and psychiatry.

Biotechnology is defying ethical boundaries, and posthumanism is proposing super humans in the near future. Microchips implanted in the brain enhance abilities present or lost. Temptation to be like gods forgets the spiritual dimension of human personality.

In spite of the evident difficulties and complexity of the task, this foreword is repeating our commitment to humbly keep up our efforts in aid of excellence in knowledge and the practice of medicine.

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# Preface

The present book constitutes a new effort aiming to approximate basic translational research, clinical psychopathology, psychiatry, and humanities. Like in the previous volumes, four parts are displayed.

In Part I, epistemological considerations about the study of normal and abnormal behavior are proposed. In the first chapter, Professor Juan Ernesto Calderón analyzes the concept of truth in psychiatry and neurosciences. Starting from classic conceptualizations of truth, Calderón lucidly analyzes the contributions of Heidegger and Gadamer to the idea of Plato regarding these ideas as germinal proposals of Western thought. Meanings of the Greek word *a-letheia* are profoundly analyzed. The meaning of this word is *uncon-cealment*, and its implications in psychiatry and neurosciences are rigorously examined. Hermeneutics and scientific knowledge are profoundly studied. The impact of these points of view is analyzed in a bright manner.

In the second chapter, Professor Miriam Dolly Arancibia analyzes the notion of freedom. She follows the studies of Leonardo Polo, who proposes a transcendental anthropology. Changes of values during different history points are clearly analyzed, following modifications in their values. Ideas such as autonomy and freedom are studied in this context. The role of Kant in education and his proposal of autonomy are matters of a subtle and interesting analysis in this study. The implications of these ideas in the context of authority and table of values are displayed in an original manner. The counterbalance due to pedagogy and recent neurosciences is proposed. This chapter is an example of creativity and originality, in a rigorous context. It gives relevant cues to philosophers, psychotherapists, and teachers in the classroom.

Chapter 3 is dedicated to a humanistic perspective of pain. Offered by Pablo Rodolfo Brumovsky, Carly Jane McCarthy, Mariana Malet, and Marcelo José Villar, the neurobiology of pain is summarized following a humanistic perspective. Definition of the International Association for the Study of Pain (IASP) is analyzed, and its implications are highlighted in an interesting and original manner. That this experience is predominantly emotional is considered an important cue to understanding this phenomenon. The role of previous painful experiences as evoking pain is considered, and the interrelation between pain and emotions is analyzed in a bright manner. Mechanisms connecting peripheral and central neurons and the way in which

The original version of the book was revised: Copyright page text and Preface has been updated. The correction to the book is available at https://doi.org/10.1007/978-3-319-95360-1_35

they are interrelated and processed constitute a very interesting and transcendent chapter of this book.

In Chap. 4, Professor Luis Echarte proposes a wide analysis of implications of the so-called *lie detector*. Controversies related to this machine are detailed in a very interesting manner. Its application to national security, job recruitment procedures, and divorce disputes is analyzed in an original and detailed way. Attention paid to detection of self-lies is an interesting matter of discussion. Trajectory of the lie detector from 1921 to the present is interestingly displayed. In the same way, a proposition of authors is related to the fact that new phenomenological and neuropsychological approaches to inauthentic experiences could be considered as an appropriate tool aimed at understanding and detection of these self-lies.

In the fifth chapter, Professor Rocco Genaro is dedicated to review evidences regarding brain damage and some psychopathological entities. Cognitive deficits in pathologies like hemispatial neglect, agnosias, amnesia, and somatoparaphrenia are studied. The role of neural substrate of specific functions is explained, and the role of brain damage is deeply analyzed. Interesting considerations about mental processes and consciousness and its relation with the brain are studied in a detailed manner. The condition of possibility that the brain grants to the so-called superior functions is rigorously posed. Projections to conceptions of mind are drawn and discussed. Interesting consequences on metaphysics of consciousness are proposed and discussed in a bright manner.

In the next chapter, Juan Francisco Franck studies the double challenge of naturalistic understanding of the mind. His proposal is mainly related to the study of correspondence between physical and organic processes generating or corresponding to a given experience or phenomenal feeling. A satisfactory explanation for the gap between the physical and the mental processes is interestingly attempted. A critique study about the concept of emergence and its possibility to contribute conceptually closing the gap is done. The contrast between phenomenal experience and the mental acts that reach the objective truth is pointed out, thus proposing the existence of timeless principles and propositions. The contributions of Edmund Husserl and Thomas Nagel are analyzed, in a very interesting contribution.

Chapter 7, written by Consuelo Martínez Priego, analyzes the meaning of "neuronal correlate" in mind-brain relationship. The term "correlation" is analyzed following the close relationship between neural activity and mind or consciousness. The proposal of this chapter, as it was established by the author, is to show the real scope of the term in this field. In this context, three possible meanings are established for this term. The first is the existence of a causal-efficient relationship. The second possibility is a psychosocial parallelism. The third would be a terminological not real dualism between the conceptual systems. The author proposes the analysis of other levels. The difference between "causality" and "condition of possibility" is clearly, elegantly, and lucidly delimited.

In Chap. 8, a work team directed by Prof. Dr. José Murillo and integrated by Gonzalo Arrondo, Nathaniel Barret, Francisco Güel, and Javier Bernacer proposes new ways for a fruitful translation between neuroscience and psy-

chiatry. The beneficial role of methods of neuroscience to psychiatric research is highlighted. The problem of reliability of neuroimaging research is commented and discussed. The role of translational neurosciences and mental symptoms is exhaustively discussed. The necessity of critical stances of brain imaging and a more complete epistemological model of mental symptoms are discussed in an interesting manner. The possibility of an integration between neuroscience and psychiatry is commented and discussed in an original manner.

The second part is dedicated to topics coming from basic neurosciences and reaching dynamics of human brain. In Chap. 9, a solid team directed by Prof. Dr. Claudia Bregonzio and Prof. Dr. Gustavo Baiardi writes about vascular alterations in mental disorders, focusing on angiotensin II role. This group includes Leticia Delgado, Osvaldo Martin Basmadjian, Victoria Belén Occhieppo and Natalia Andrea Marchese. They describe that prevalence of mental disorders is here considered taking into account that approximately 25% of the population worldwide will develop a mental illness at a moment of his life. Inflammation and vascular alterations are being related today with some kinds of mental illnesses. The role of microvasculature in essential functions as oxygen delivery is overlighted, and microvascular alterations like capillary ultrastructural abnormalities, deficient perfusion, and blood-brain barrier disruption are here related to schizophrenia, depression, and Parkinson's and Alzheimer's diseases. The possibility of new therapeutic resources is suggested in this way.

In Chap. 10, the group of Daniel Vigo, Leonardo Nicola Siri, and Prof. Dr. Daniel Cardinali proposes the heart rate variability as a tool to explore the dynamics of autonomic nervous system (ANS) activity. They propose to study it in health and disease. The ANS is conceived here as a structural and functional interface between the forebrain and the internal and external environment variables, allowing to regulate energy, matter, and information exchanges. Authors describe recent studies in which a systematical exploration of subtle relations between ANS activity and heart rate variability (HRV) was done. Its importance in pathophysiology of metabolic disorders, cardiovascular diseases, and psychopathological disorders such as anxiety and depression is clearly exposed. This chapter constitutes an interesting study of ANS activity as a physical substrate of psychiatric disorders.

In Chap. 11, Prof. Dr. José Burgos proposes Pavlovian blindsight and masked conditioning as a neural network model. The effects of hippocampal lesions on Pavlovian conditioning are studied and discussed. It is postulated that a primary role of the hippocampus during Pavlovian conditioning is to send a diffuse discrepancy signal. This signal appears to modulate synaptic efficacies in sensory association areas. In the present chapter, it is postulated that this signal decreases negative effects of the non-reinforcement and reinforcement of weak cues on such efficacies. It is concluded that hippocampal damage affects hippocampal more long-delay than short-trace conditioning and backward more than contiguous-trace conditioning. Furthermore, evidences are offered regarding that context reinstatement is disrupted by hippocampal lesion. Future research lines are proposed and discussed.

Chapter 12 is an interesting contribution of the group directed by Prof. Dr. Bruno Cavagnaro. The workgroup is integrated by María Inés De Rosa, Leonor Deis, Liliana Martínez, Martín Durán, and Emiliano Malovini. In this study, the role of anthocyanins is described regarding nutrition, biochemistry, and health benefits. Since now an important attention has been paid to natural foods like vegetables and fruits, the study of its nutritional components is very relevant. It is the case of red grape berries. They constitute an important study target because of their high phenolic contents. These substances include anthocyanins that play a major role in their nutraceutical properties. His presence in grape berries and wine is reviewed in a complete form. Metabolism of these compounds is described, and its possible effects on health is commented and discussed in a documented and solid chapter.

The same workgroup directed by Prof. Dr. Bruno Cavagnaro proposes in Chap. 13 important health effects for resveratrol, a very promising molecule present in grapes and wine. This group, integrated by Liliana Martínez, Martín Durán, Emiliano Malovini, María Inés De Rosas, and Leonor Deis, offers evidences regarding the beneficial effect of this molecule in cardiovascular protection, antiplatelet aggregation effect, antioxidant and anti-inflammatory effects, and blood glucose lowering. It is also proposed an important role in cancer prevention, anti-aging, and anti-obesity activities. It has been also proposed that resveratrol have anti-inflammatory, anxiolytic, and antidepressant effects. The attempts to produce grapes and wines with higher concentration of resveratrol are mentioned, and future applications are proposed. It is a very interesting chapter related to natural products.

Chapter 14 is dedicated to study the role of oxidative stress in neurodegenerative diseases. The contribution of this group, directed by Prof. Dr. Claudia Beatriz Hereñu, and integrated by Macarena Lorena Herrera, Eugenia Falomir-Lockhart, Franco Juan Dolcetti, Nathali Arnal, and María José Bellini, is very relevant and interesting in the area of pathophysiology of neurodegenerative diseases. An important number of research lines regarding these illnesses are detailed. The main part of the chapter focuses the implication of the oxidative stress, aging, and inflammation processes on neurodegenerative alterations. It is sustained that these factors lead to neuronal dysfunctions, tissue disturbances, and motor-cognitive disorders. The role of neurotrophic factors preventing the degeneration and enhancing recovery is proposed. Among these factors, insulin-like growth factor 1 (IGF-1) is mainly considered. It is strongly induced by microglial cells after insults of different types. It may be considered an emerging and powerful neuroprotective substance, and it is here postulated as a key neuroprotective and neuromodulator molecule.

In Chap. 15, the workgroup directed by Benjamin Yee and integrated by Joseph Leung, Way Lan, and Benson Law studies the link of melatonin to adult neurogenesis. A proposal of a novel target for the treatment of depression and anxiety is drawn. An actualization about melatonin and his functions precede the body of the chapter. Its role as regulator of the circadian rhythm and the sleep-wake cycle is enriched by other physiological roles, such as its antioxidative and free radical scavenging functions. This workgroup presents also evidences on melatonin as an important modulator of the anti-inflammatory response. They suggested that it may be mediated by the immune-pineal axis.

Different melatonin receptors are presented and their implications in several functions commented. The role of dysregulation of brain melatonin signaling as a causal risk factor of neurodegenerative and mood disorders is postulated also. The use of melatonin and its synthetic analogues like agomelatine for the treatment of depression and anxiety is proposed.

Prof. Dr. Fabian Mohamed and Prof. Dr. Verónica Filippa review in Chap. 16 the effect of lithium (Li) therapy in the reproductive system. Its use in manic pole of bipolar psychoses is mentioned and its mechanism of action wide and clearly exposed. Its action on neurotransmission and modifications of cAMP signaling and phosphoinositol pathways is explained and evaluated. The action on GABA and glutamate is explained in the context of a mood-stabilizing effect. Additional effects on the circadian rhythm and neuroendocrine functions are described. Toxic effects on hypothalamic-pituitary gonadal axis, reproductive system, and, therefore, human sexual functions are also mentioned and described. The chapter has a very relevant clinical impact.

In Chap. 17, Ane Murueta Goyena, José Vicente Lafuente, and Harkaitz Bengoetxea propose an important role of interneurons in cognitive impairment in schizophrenia. Loss of inhibition of pyramidal cell activity is considered as the start point of the evidences. A cognitive impairment due to perturbed excitatory/inhibitory balance or abnormal disinhibition is postulated as the origin of schizophrenic cognitive impairment. The role of interneurons governing the complex interactions between principal cells and coordination of network operations is conceived as the main alteration involved in these disturbances. The notion that interneurons might be engaged in different stages of acquisition and storage of information is postulated. It is conceived that these neurons may be target of future treatment schedules. This rigorous chapter opens interesting doors to future research.

Chapter 18 was written by our team. This workgroup, integrated by José Ignacio Hernández, Santiago Márquez Herrero, Osvaldo Soler, Manuel Alejandro Guevara, and Pascual Ángel Gargiulo, presents a review about animal models of depression. In this first chapter, the group considers validation criteria and relevance of these models in translational experimental neurobiology. The departure point is epidemiological evidences, considering the existence of refractory patients. The increasing role of translational approaches is valued. Some analytical tools for validating the methods are exposed. Results coming from experimental findings are commented and critically analyzed. Evaluation criteria for translational research are matter of exhaustive analysis. It is considered that the main objective of this chapter is to provide an analytical and critical elaboration of the validation criteria of animal models of depression. Additionally, a comparative confrontation between the most recent paradigms and their most classical conceptions is done.

In Chap. 19, the same group, preceded by Santiago Márquez Herrero, proposes a classification of animal models of depression. Starting from the pioneer approaches of Paul Willner and his classical concepts about validation criteria, some approaches are considered mainly following the notion of imitation of the etiological processes. The use of genetic variables is considered, and environmental stress is also taken into account. The possibility of a combined treatment is also considered. The relevance of an abbreviation of dis-

tance between basic research and clinical practice is proposed. Mutual concessions and possible potentiation possibilities are proposed, aiming to use research resources in a mutual advantage. Present knowledge should be opened to modifications in the field, trying to conciliate translational models to human psychopathology.

Chapter 20 constitutes an effort between Prof. Dr. Sergio Tufik, head of the workgroup, and the colleagues that work under his direction, Gabriel Natán Pires, Katsumasa Hoshino, and Mónica Levy Andersen, aiming to correlate sleep, their main field, and aggressive behavior. A complete and interesting review is presented in a solid and lucid manner. His proposal starts with the fact that relationship between sleep and behavior has been studied in the context of several fields, like both cognitive and behavioral comorbidities. These findings include aggressive behavior. This relationship between sleep and aggression has been examination matter from different angles. It is presented in a concise manner, and then a summarized discussion is drawn presenting laboratory and clinical findings. The role of sleep deprivation inducing aggression is commented. On the other hand, the role of an aggressive behavioral phenotype inducing a sleep alteration is also discussed. The neurobiological relevance of these findings is adequately and brightly presented in this chapter.

The third part includes chapters in which neurosciences, learning, teaching, and the role of the social environment are related. In Chap. 21, the group of Belén Mesurado, María Cristina Richaud, Lucas Marcelo Rodríguez, and María Paulina Guerra realizes a meta-analysis about the effectiveness of social behavior effectiveness. Prosocial behavior is defined as a voluntary act intended to help or benefit another individual or group of individuals. It has been postulated that prosocial behavior inhibits aggressive behavior, and in this way, a proposal is suggested. An important number of studies about interventions in children and adolescents were included. Only studies that utilized a randomized controlled design were considered aiming to evaluate impact of the interventions in promoting prosocial behavior and reducing aggressive behaviors. The present chapter is an interesting proposal of social actions destined to modify social conditions related to learning and teaching.

The group integrated by Lucas Marcelo Rodríguez, Belén Mesurado, and José Moreno writes Chap. 22. In it, they explain the role of ethical position, empathy, and prosocial behavior. They delimitate the contributions of these factors presented as an interaction model to be applied in prevention and psychotherapeutic approaches of antisocial disorders. The role of penalizing acts, ethics, and empathy are analyzed in a subtle and original manner. The influence of ethic positions is analyzed in the context of the influences exerted on prosociality and penalization of acts. A positive effect on penalization of acts was attributed to nonrelativistic position and empathy. The influence and relevance of empathy-inducing prosocial behaviors is sustained. Its role as an individual developmental variable and other variables such as socio-moral development and prosociality is highlighted. The applications of these facts to psychiatry constitute an interesting proposal of this group.

In Chap. 23, the workgroup of María Cristina Richaud, Vanessa Arán Filippetti, and Belén Mesurado draws some lines aiming to bridge cognitive, affective, and social neuroscience with education. They refer detection of grow-

ing interest in applying to the field of education (reading, writing, mathematics) recent knowledge about the functioning of the human brain. The same knowledge should be applied to study relations between emotions, social functioning, and decision-making. Authors refer that there is a gap between the inner workings of the brain and the practical application of this knowledge. They affirm that this gap must be resolved aiming to promote an effective teaching and learning. Some research results on the effect of IQ and executive functions on mathematical skills are presented. Furthermore, the role of executive functions on written composition is described, and the problems in affective development affecting cognitive and school performance are also discussed.

Chapter 24 is dedicated to reflexive considerations about the treatment of emotional problems. The chapter is written by a team integrated by Ángel José Martín Gargiulo, Augusto Pascual Ítalo Gargiulo, Nicolás Cristy, and Paula Soledad José Quintero. These authors sustain that suffering is part of having a valuable life. In this context, emotions and thoughts are, in many cases, causes of that suffering. A special attention is paid to the context in which we live, which is here referred as responsible of the experiential avoidance linked to suffering. This context emits signals according to a negative value of suffering, as an abnormal experience. In an automatic manner, psychotherapies tend to reduce suffering, sometimes before studying the meaning of the concrete suffering offered by the patient. Authors describe a series of sequential mistakes leading to equivoque treatment schedules. The way of understanding emotions in each case is considered as an opportune criterion. Equivocal medication of these kinds of problems is analyzed. This chapter constitutes an original and bright part of present update.

In Chap. 25, Prof. Dr. Gilberto Gamboa Bernal develops a description of intelligence of emotions as a path to discover. Professor Gamboa offers an interesting and profound analysis of the consequences of the "boom" that the emotions experienced along last years. The author points that it may be related to the informative literature proclaiming "emotional intelligence." It must be taken into account considering that emotional intelligence and intelligence of emotions are not synonymous. Maturating in the clinical setting, psychology has taken different paths related to emotions. Recent scientific advances have contributed to enhance our knowledge of emotions and its brain correlates, documenting the neural areas involved. An important future in these research lines is postulated. The chapter is an interesting and documented study about an area of growing evidences.

The fourth part is mainly dedicated to explain human pathological behaviors. It presents a group of evidences regarding how brain pathological conditions induce psychiatric disorders. In Chap. 26, Dr. Rose Emily Nina-Estrella actualizes the notion of mild cognitive impairment, suggesting diagnostic criteria and reviewing possible treatment attempts. She starts considering that mild cognitive impairment (MCI) represents an intermediate stage between normal aging and the development of pathologic aging and dementia. Etiology is considered heterogeneous. It is proposed to divide MCI in amnestic or non-amnestic forms. Since the progress to dementia is relevant, it is considered a very important task to detect people in early MCI stages, mainly after 65 years old. The importance of this detection is postulated as a very

important task for public health planning and preventing strategies. The use of biomarkers, neuropsychological tests, and neuroimaging screening is proposed. This chapter has a relevant application in public health.

In Chap. 27, our group proposes neurocognitive assessment for diagnosis and treatment of schizophrenia spectrum disorders (SSD). This group is integrated by Guillermo Alfonso, Bruno César Franco, Mauricio Cervigni, Paola Buedo, Celina Graciela Korzeniowski, and Pascual Ángel Gargiulo. The role of cognitive alterations was detected since the early descriptions of the illness, but recently an additional attention has been paid to it, receiving evidences from the neuroscience advances, allowing to objectively study the evolutionary course of the disease. A review of the most frequent cognitive alterations in SSD is displayed. In a parallel manner, corresponding research strategies are proposed. These studies involve also its relation with behavioral and positive symptoms, personality variables, and social difficulties. We believe that this chapter could be interesting, aiming to orientate new research projects. But also, it may serve to encourage clinical application of functional neuro-evaluation tasks and neuro-rehabilitation protocols. It may be an interesting additional goal.

Chapter 28 is dedicated to study up to date and detail policy, services, and statistics overview about demented patients care in Argentina. The workgroup, directed by Prof. Dr. Ricardo Allegri, is integrated by Pablo Bagnati, Fabián Román, Marcela Bonafina, and Andrew Blake. A historic consideration about caring of elderly in Argentina is initially presented. The chapter updates local resources for dementia contention and treatment. It also refers to resources associated with cognitive impairment detected in elderly people. Public and private sectors intervene with professionals and diagnostic resources concentered in the largest cities. The role of different diagnostic and family support centers and societies is detailed. The initiative of the Argentine Neurological Society launching the first dementia diagnosis and treatment guideline in 2011 is commented. The next activities are also referred. This chapter is an interesting review of present actions on dementia screening and care in Argentina.

In Chap. 29, the workgroup, directed by Prof. Dr. Francisco Barrantes, and integrated by Santiago Pérez Lloret and Viviana Bernath, develops an interesting review on genetic factors that influence neuropsychiatric symptoms in Parkinson's disease (PD). The role of genetic and environmental factors is recognized, and the interaction between gene mutations and phenotypic characteristics of the disease is interestingly proposed. The role of different genes in dementia and PD, and genes related to increased risk of cognitive impairment, dementia, and visual hallucinations are considered. Significance and clinical and epidemiological relevance are exposed in a bright manner. The possible role of gene mutations in cognitive impairment and PD psychotic states is displayed in a precise and documented manner. It makes the present chapter a relevant and interesting contribution of neurosciences to clinical psychiatry.

Chapter 30 is dedicated to actualize the neuroimaging studies in psychotic disorders. This workgroup is integrated by Nicolás Fayed, Carlos Torres, Humberto Morales, and Laura Viguera. The neuroimaging techniques provide significant data in psychiatric disorders research. Higher resolution in these complementary diagnostic methods led to a transcendent result improvement. Impact of these new imaging tools in the last two decades like high-resolution three-dimensional magnetic resonance and conventional magnetic resonance imaging (MRI) has clearly optimized resolution. By this way, they have allowed the detec-

tion of abnormalities in several parameters, like blood flow, metabolism, and neurotransmitter receptor function. Present findings lead to a better explanation of molecular biology related to psychiatric disorders. The possible role in new treatments is proposed. The registered role of some brain areas in different psychopathological conditions is reviewed and discussed. The present chapter constitutes simultaneously an interesting systematic exposition about preceding findings and, simultaneously, a transcendent guide for future research ways.

The same group in Chap. 31 proposes objective neuroimaging patterns for post-stroke depression. Nicolás Fayed, Humberto Morales, Carlos Torres, and Laura Viguera present interesting findings regarding this point. This study starts considering prevalence of stroke after depression and considers it in a level of 33%. The critical situation implicated in a low detection and treatment is registered. Some considerations are done regarding quality of life, rehabilitation, and mortality. The relevance of early treatment and rehabilitation is proposed. Antidepressant treatment is postulated as a possibility of reduction in mortality. The multifactorial etiology of post-stroke depression is interestingly detailed. Some factors, such as white-matter disease, cerebrovascular dysregulation, altered neuroplasticity, and changes in glutamate neurotransmission, are related to etiology of post-stroke depression. An important number of neuroimaging methods are studied regarding possible brain areas involved in these pathologies. Present chapter represents a very interesting approach to correlations of brain functions and psychopathology.

In Chap. 32, the group directed by Svetlozar Haralanov and integrated by Evelina Haralanova, Emil Milushev, and Diana Shkodrova studies and proposes a locomotor movement pattern analysis trying to consider it as an individualized objective and quantitative approach in psychiatry and psychopharmacology. It is here proposed an easy-to-perform objective and quantitative approach to the individual motor behavior. Authors propose a method for evaluating movement patterns as an objective biomarker of psychiatric and neurological illnesses to be used in everyday practice. Furthermore, they propose subsequent treatment effects as a mode to evaluate them. The method consists mainly in an equilibriometric quantification of movements (head and body) during execution of specific locomotor tasks. Present procedures were validated in a data base involving more than one thousand patients and healthy controls along 20 years. Its use aiming to separate subgroups within nosological entities is also proposed, and pharmacological uses are also suggested. The present chapter constitutes a very original and interesting proposal in the field of objective biological markers in psychiatry.

Chapter 33 is written by María Graciela López-Ordieres, a prestigious argentine researcher in schizophrenia. She analyzes, taking into account historic approaches to schizophrenia treatment, different theories regarding neurotransmission, pathophysiology, and present therapeutic evidences in this field. The role of functional brain networks in these psychotic states and its relation to clinical manifestations, like psychotic symptoms, negative symptoms, and cognitive impairment is carefully reviewed. The possibility of contact with reality, delusions, and hallucinations are detailed in a close linking with pathophysiological evidences. Neurodevelopmental and epigenetic theories are also detailed and lucidly presented. The role of neurotransmitters misbalances and new therapeutic possibilities related to them are brightly proposed. The present chapter constitutes an interesting actualization about schizophrenia and related therapeutics schedules.

The last chapter, written by Prof. Dr. Daniel Cardinali and Dr. Daniel Vigo, is dedicated to an efficacy comparison between melatonin and benzodiazepine/Z drugs. The present chapter starts pointing evidences on relation between melatonin and sleep. Authors point that increase in sleep propensity and sleep-promoting effects of exogenous melatonin constitutes an important argument regarding the role of this substance in sleep regulation. This affirmation is also based in consensus and meta-analysis agreement, giving credibility to the melatonin use in sleep disorders. Mechanism of action is attributed to $MT_1$ and $MT_2$ melatonin receptors. They are present in the hypothalamic suprachiasmatic nucleus (SCN) but also in other brain areas. An interaction between melatonin- and GABA-containing neurons is postulated. Furthermore, benzodiazepine (BZD) antagonism blunts melatonin behavioral effects, including sleep. Due to the hangover effect observed after benzodiazepines and Z drugs, postulated advantages of melatonin in sleep regulation are analyzed. This leader group gives here new evidences to sleep disturbance treatment.

Finally, we would like to express the satisfaction that the continuity of this update gives to all of us. We wish that these periodical books constitute a point of encounter and dialogue between the various disciplines that enable a better understanding of man and his sickness in a scientific and open-minded way. We would like to express our gratitude to Springer for this exceptional opportunity.

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**Part II From Basic Neurosciences to Human Brain**

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# Part I

# Epistemological Considerations About the Study of Normal and Abnormal Human Behaviors

# 1 The Truth in Psychiatry and Neurosciences

Juan Ernesto Calderón

## Introduction

The Philosophy of Science points out an important difference between the classic and contemporary version related to the degree of truth or certainty which science can reach. However, in both stages scientists assume that their reflections are true or that they are associated in some way with truth, understood as the correspondence of the intellect to the thing. This relation between science and truth takes place, but it is not normally reflected upon. Martin Heidegger first and Hans Georg Gadamer later sustained that the conception of truth as the correspondence or adequation of the intellect to the thing was established in a germinal of the Western thought, specifically in Plato's work. This definition of truth replaces the original meaning of the Greek word a-letheia, meaning 'unconcealment'. The adequation is understood as concordance of intellect and thing; but for Plato the idea is conceived as the pattern which defines what is correct. For this reason, this correction can be clearly seen in the possibility of representing the thing and that the thing be like the idea, but not in promoting that the thing be unconcealed. The scientific thought follows this tradition and emerges as the parameter and the supreme form of human knowledge, leaving the other expressions behind. The distinction between science and pseudoscience is similar to the distinction between true knowledge and false knowledge. This distinction is in crisis nowadays. What science and pseudoscience are remains unclear. Phenomenology and Hermeneutics tackle both problems: the concealment of things through a hegemonic method and the so-called absolute character of scientific knowledge.

On this basis, the present contribution proposes another definition of truth which can be useful for scientific research and practice. In particular, [1] the definition of truth as 'unconcealment' posed by Phenomenology and Philosophical Hermeneutics is analysed; [2] the usefulness of this notion in the fields of Psychiatry and Neurosciences is demonstrated. For this purpose, this paper will deal in the first place, with the problem of method and understanding in Hermeneutics and the rigour which scientific knowledge can reach. Then, the notion of truth according to the hermeneutic conception will be developed. Finally, the impact of this difference in the conception of truth for scientific practice will be analysed, placing special emphasis on Neurosciences.

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## The Problem of Method and Understanding in Hermeneutics

Method means way, a path of knowledge capable of being repeated to go in search of something [1]. Once found what was being searched, it is apprehended in order to take it as a new point of departure because the method is intrinsically progressive. The fact that the method is progressive is essentially matched with the fact that it is also productive, that is to say, which serves 'to' solve problems. This is the idea of method inherent to the naturalistic model. Gadamer [2] points out the inadequacy of the naturalistic model of science in the so-called Human Sciences. The naturalistic model of science begins in the seventeenth century with Galileo who, departing from submitting nature to a mathematical construction to a quantitative analysis, obtains a new concept of natural law. In the nineteenth century, this model of science, proposed initially by the natural sciences, is transformed into the hegemonic model of science. In other words, the model of natural sciences had to be followed in order to have access to the category of 'science'.

The problem of method-generated answers to the various schools of thought, among which is Hermeneutics, is included. For this current of thought, the problem of the method must be included within the problem of comprehension. Comprehension is a basic phenomenon in men's existence and cannot be reduced to the field of science. Science has been imposed as the only way and the only path for knowledge. For this reason, Phenomenology first and Hermeneutics later state that the analysis of the analytical existential dimension of men must be previous to the methodological analysis itself. Science is one of the possible ways but definitely not the only way of understanding.

The existential analysis reveals the prestructure of comprehension. For Heidegger ([3] p.142) understanding is projecting. When we understand, we make a projection of sense. 'Meaning is that a wherein the intelligibility of something maintains itself'. 'The concept of meaning includes the formal framework of what necessary belongs to what interpretation that understands articulated'. 'Meaning, structured by fore-having, fore-sight, and fore-conception, is the upon with of the project in terms of which something becomes intelligible as something' ([3] p. 142). Sense is the condition of a possibility by which something appears as something. The act of comprehending projects sense and opens possibilities. This act of projecting is essentially determined by the act of finding oneself. 'Dasein' is always a 'being-in-the-world'. The 'Dasein' projects and comprehends; but this act of projecting departs from 'there'. That means signifying the factuality and historicity of the whole understanding. The 'Dasein' is already within a determined 'world', immersed in determined possibilities. 'Dasein' factically exists; it is never past but is always already having-been in the sense of 'I-am-as-having-been'. And only as long as Dasein is 'can it be as having-been', the Dasein '… always 'finds itself' only as a thrown fact'. 'The primary existential meaning of facticity lies in having-been' ([3] p. 301).

Comprehension is always projecting, but this act of projecting is done about a particular 'world', starting from certain prejudices. The notion of prejudice and Gadamer's rescue of this notion, in the face of the contempt it suffered during the *Enlightenment*, forms a central part in Philosophical Hermeneutics. The negative sense of the prejudices imposed by the *Enlightenment* is still in force nowadays. Our experience and everyday language give a clear example of this idea: a prejudice is a false judgement or at least a not appropriately justified one. However, a prejudice by itself does not necessarily mean a false judgement. A prejudice can be valued in a positive or negative way. '… the prejudices of the individual, far more than his judgments, constitute the historical reality of his being' ([4] p. 278).

The notion of comprehension has the circular figure of the whole and the part [5]. When we begin reading any text, we grasp a first sense, and then, through this first sense, we are able to grasp the sense of the whole. The comprehension of the text consists in the elaboration of the previous project, in the anticipation of sense. As long as we advance in the reading, the sense is being

proved because it is subjected to revision in contact with the text itself, and in this way, we start to deepen the sense, broadening our understanding. A hermeneutically formed conscience must be ready to accept the alterity of the text. It does not mean self-censorship or neutrality, but I place myself in relation to what was transmitted. For that, it is necessary for every interpreter to start reflecting on their preconceived ideas because the anticipation of sense is determined by the community, which join us to the tradition. The anticipation of sense is not an act of mere subjectivity but what we project from a specific world which constitutes us and makes us be who we are. Being susceptible of receiving the text is relevant for us to enrich ourselves with what is incorporated in the reading of the other ([4] p. 293).

The critical question of Hermeneutics arises at this point ([4] p. 298): how can we distinguish the positive prejudices which enlarge our understanding from those negative prejudices which cause misunderstandings? To solve this problem, Gadamer takes the concept of temporal distance. Contrary to the supposition of Historicism, which poses the necessity of putting temporal distance aside to achieve a 'pure' understanding, that is to say, an understanding separated from prejudice and from any subjective burden. In a contrary manner, Gadamerian Hermeneutics sees temporal distance as a positive and productive possibility of understanding. Distance in time must not be overcome (in fact, distance is impossible to surpass). What we should do is recognizing in distance the possibility of having an improved vision, through broadening of our understanding.

Frequently, the lack of temporal distance influences our understanding in a negative way. Events too near to us appear distorted to the extent inasmuch as uncontrollable prejudices operate. Gadamer sets the example of contemporary art ([4] p. 296). Questions (such as the following: is it really art? what value does it have? among others) cannot be answered correctly because the works of art are too near us that we cannot appreciate them in their actual magnitude. Another case is historical research ([1] p. 295). Thanks to the temporal distance, the interpreter can have access to tradition as bearer of sense, and in that way, he can question the prejudices in order to distinguish the positive from the negative ones. Temporal distance allows us to broaden our horizon. Gadamer ([4] p. 301) defines horizon as '… the range of vision that includes everything that can be seen from a particular vantage'. To take a visual example, a similar case would be the observation of a building. To observe it in a correct way and in its totality, the best way is not to be so near but to a distance which allows to see the building in perspective. It is almost impossible to understand the construction if we are very close to it. Only distance opens the necessary horizon for understanding.

Broadening our horizon is the way by which man can value and comprehend in a correct way. When man does not have horizon, he values the present wrongly because he does not have the necessary perspective for understanding ([4] p.302). It is precisely in the contact with tradition where we can shape and widen our horizon confronting it with the horizon of tradition. Gadamer ([4] p. 302) calls this process a fusion of horizons. Our horizon, our range of vision, is not the product of an absolute subject. On the contrary, our present horizon is essentially constituted by the horizon of the past, by tradition, and it is in this contact with tradition where we broaden our horizon bringing the prejudices which guide our understanding into light. All understanding must begin with the interpreter's reflection upon his preconceived ideas, not to deny them but to be conscious of them, testing them with what tradition transmits. Every understanding of a text means validating the sense of such text. It involves applying the text to the interpreter's situation. For Gadamer ([4] p. 305) the problem of application is inner to every understanding. Testing our prejudices, in the task of interpreting a text, is the basis for widening our horizon. The interpreter must never suppressed himself or pretend to eliminate his situation. The key to understanding is to be able to relate the text to us in order to understand it ([4] p. 321). In understanding, we do not part from scratch. For this reason, Hermeneutics invites us to take conscience of our own historicity and consequently of the historicity of all understanding.

## Truth as Unconcealment and Rigour in Science

Inside Philosophy many ways and doctrines about truth arise [6, 7]. In scientific practice, truth is considered the 'adequation of the intellect to a thing'. Bertrand Russel and George Edward Moore are the authors of the current version of the doctrine of truth as correspondence [8]. However, this conception of truth recognizes antecedents in Plato and Aristotle and is used throughout occidental history, with relevant key milestones such as Thomas Aquinas, René Descartes and Immanuel Kant. Over the course of centuries, many schools and versions within this way of understanding the truth have appeared. That is to say, truth has been regarded as a property involving a relation between a statement and a portion of reality. The members of these schools joined by the same general principle regarding truth speak different terms ('correspondence', 'conformity', 'congruence', 'copying', 'picturing', 'signification', 'representation', 'reference', 'satisfaction'). These diversities of terms used for this relation point out the great amount of nuances within this position. The different nuances make impossible to understand this position in a monolithic way, but 'family resemblances' in Ludwig Wittgenstein's words come out [9] (§66).

For Hermeneutics, understanding is mediating between the past and the present to develop a continuous series of perspectives. For this reason, truth cannot be understood as the 'adjustment of the intellect to the thing' but as 'unconcealment' [1]. Martin Heidegger [10] sustains that truth as adaptation was conceived in a germinal moment of occidental thought, specifically in the Plato's work. This definition of truth displaces the original meaning of the Greek word *a-letheia*, which means 'unconcealment', putting correction in its place. Correction is manifested in the possibility of representing the thing, but not in letting the thing manifest. Heidegger analyses this change in the Cavern Allegory ([11] 514a–518b). This part of the Republic does not deal primarily with truth but reveals the primacy of the correction of representation with the idea of the concealment of the thing itself. In the Cavern Allegory, the chained slaves only know truth when they are out of the cavern. Outside the cavern the sun light, as a supreme idea, makes the truly real become visible. Nevertheless, the real is the idea. The truth cannot be found in the thing but in the idea since it is the pattern to which all things must conform in order to be true. For this reason, the unconcealment, understood as a restricted meaning of adjustment, means making the thing agree with the idea, not making the thing manifest and unconceal.

According to Heidegger [10] the doctrine of truth as an adequation has been hegemonic in occidental thought and is still in force nowadays. To demonstrate its place, Heidegger does a historic journey which starts with Plato, continues with Aristotle, Thomas Aquinas and Rene Descartes and ends with Nietzsche ([12] 493, 1885), to whom he cites: 'Truth is the kind of error without which a definite kind of living species would not be able to live. The value for life decides at the end'. If truth is a kind of error, then its essence is in the way of thinking which makes things false. It turns them into false or hides them because it fixes the intense historical path in a static representation. Truth understood as correspondence fixes something which must not be fixed but submitted to constant mutation and change.

Phenomenology, with its central motto 'to the things themselves', sheds light into to this problem. Scientific thought rises as the parameter and supreme form of human knowledge, making the thing adequate to the intellect and not making the thing show itself. The crisis of fundamentals in science at the end of the nineteenth century and at the beginning of the twentieth century is a key element for understanding the appearance of Phenomenology and Hermeneutics. Both currents mark not only the crisis of the fundamentals but also the neglect of the 'lifeworld' [13, 14]. The principal motto of Phenomenology, 'to the things themselves', puts the emphasis in a basic problem of the naturalistic model of science: the object does not mind; only the applied method does. In this view, the how appears to determine the what, generating a serious difficulty when dealing with problems which do not correspond or which cannot submit to the same method.

Paradoxically, the method in science was said to be fully objective, when really what does is imposing a way of understanding: only the method could determine the accuracy of knowledge by submitting the object to its parameters. This is similar to the case of Procrustean bed, understood as 'a scheme or pattern into which someone or something is arbitrarily forced' [15].

The image of the Procrustean bed is not only reflected in the methodological question but also in the degree of certainty which scientific knowledge can effectively reach. Ancient science searched knowledge for the knowledge itself. Modern and Contemporary Science, however, relates scientific knowledge to the production and modification of nature (Bacon's phrase 'knowledge is power' summarizes this change). Nevertheless, besides this well-known difference, ancient and modern science has something in common which indicates a continuity between both conceptions: the idea of rigour and certainty which knowledge must reach to be called scientific.

The ideal of rigour in science until the mid-twentieth century can be summarized in the attitude of some geographers mentioned by Jorge Luis Borges [16], in his paper called 'The rigor in science'. According to Borges' account, some geographers tried to make a map similar to the empire. The task failed because the map can never be 'equal' to the empire; it can only represent it. The problem in this attempt told by Borges was forgetting that reality can never be completed covered by a map. The ideal of these geographers is similar to the way of understanding science from Plato to Kant. This way becomes canonical since Aristotle and can be expressed formally in the following way:

$$_{\mathbf{sf}}h_1,_{\mathbf{sf}}h_2,\ldots,_{sf}h_n \vdash_{\mathbf{sf}} c$$

'*C*' is perfect or sufficient (**sf**), when its premises '*h*' are true and the transition rule '⊢' is perfect, by which truth is maintained [17].

The basic problem of this type of scientific rationale is that it does not explain the real history of science. Pretending that science has a perfect foundation is not acknowledging its history in both factual sciences and formal sciences. In both types of sciences, well-funded rational beliefs are found, but not absolute in the etymologic sense of the word, that is to say, free from ties and valid and independent of all restriction. Science only wants theories to be 'good conjectures': good conjectures which are rationally well-funded beliefs or which can reach a good foundation but never a sufficient foundation [17]. For this reason, today a possible rationale can be achieved through what is called 'dialectical syllogism' (SD), formally expressed:

$$\mathrm{SD}:_{\mathrm{sf}} h_1,_{\mathrm{sf}} h_2,\ldots,_{\mathrm{if}} h_i,\ldots,_{\mathrm{sf}} h_n \mid\sim_{\mathrm{if}} c$$

This rule has the following characteristics:

1. At least the premise 'ifhi' is insufficiently founded, and for that reason it is the minimally founded of the class of premises $h_1$, $h_2$, ..., $h_n$.
2. The conclusion 'ifc' is founded upon the premises $h_1$, $h_2$, ..., $h_n$ through a rule of fallible basis, which we symbolize with '|~'.
3. The degree of foundation of the conclusion $_{\mathbf{if}}c$ en SD is insufficient and, according to the rules of formation, is at best as founded as and in general less funded than the premise $_{\mathbf{if}}h_i$.

A dialectical syllogism of this kind is not fallacious because it only ensures that the premises found the conclusion fallibly' [17].

## Truth in Psychiatry and Neurosciences

In the case of Neurosciences, an important distinction between Philosophy of Neuroscience and Neurophilosophy can be found. Neurophilosophy aims at using the tools of Neuroscience to understand traditional philosophical questions as what is an emotion? [18] What is the nature of desire? [19]. How is social cognition made possible? [20] What is the neural basis of moral cognition? [18]. What is the neural basis of happiness? [21]. Philosophy of Neuroscience, however, deals with the traditional questions of Philosophy of Science: Which kind of investigation and which type of

explanation is made in Neurosciences? These enquiries can be answered from a descriptive or from a normative perspective, whether we attempt to explain how Neurosciences proceed in fact or how they should proceed [22].

The Philosophy of Neurosciences has problems when framing its activity in relation to the general framework of sciences and its classification. Taking into account the nature of the object of study of Neurosciences, starting from a normative framework or applying the categories of science and pseudoscience according to falsifiability has not been productive [23]. Rachel Cooper [24] states the distinction between falsifiable and unfalsifiable becomes even more confusing since the Duhem-Quine thesis, which demonstrates the impossibility of forcefully falsifying the statements. For this reason, Cooper states that in Psychiatry before debating about the character of science and pseudoscience, we must answer concrete questions about Pathology and possible treatments instead of answering to the traditional rules of science. As John Pickstone [25] and Cooper [24] point out, the methods used in Psychiatry are not always the same in a strict sense but vary historically. For this reason, instead of asking if Psychiatry is a scientific investigation, we must ask about the method which has been used to study the case in hand.

Fallible foundation and truth as unconcealment are interesting elements when dealing with Psychiatry and Neurosciences. Some questions in which Hermeneutics help scientific reflection are the following: is science and its method the only effective way of tackling with reality? Is not science and its method the only way of concealing reality instead of unconcealing it? These questions are relevant for science in general but above all for those branches of knowledge which are not between the clear boundaries of traditional science or study objects which are difficult to tackle with the same method. We have already mentioned the case of Human Sciences. The method in Natural Sciences proved to be insufficient to the extent that it does not allow to widen the understanding of an object without 'forcing' the object into a given mould.

At methodological level also, like in Philosophy of Neuroscience, unconcealment serves to uncover elements inside the scientific method. For this reason, Gadamer [26] sustains that hermeneutic reflection cannot modify scientific method; it can only reveal problematic dimensions exposing the preconceptions which remain concealed in the method. In this way, problematic dimensions of every methodological dimension are dismissed. Releasing preconceptions, starting from the idea of unconcealment, makes therapeutic practice not only a mere application of recipes but a true disclosing. Unveiling involves leaving things come out and not being subsumed beforehand under determined ways of understanding reality. The scientific method, applied to facts which do not allow or resist standard fixation, runs the risk of being concealed for the sake of methodological correction. Psychiatry and Neurosciences can find in this way of understanding the truth an interesting method to analyse their practices. The question is not finding correction but enclosing. This way of approaching the truth can be operative and can provide important elements in the fields of Psychiatry and Neurosciences.

Several humanistic-existential therapies are based on Phenomenology and Hermeneutics [27].These schools take and assimilate at a therapeutic level of the serious problems which therapies based on the scientific model must confront, where an integral and humanistic view did not have a place at all. To use schemes which reduce or prevent understanding is useless since opening our understanding is what matters. The productivity of the distance in time is relevant for Psychiatry and Neurosciences. The distance in time opens our horizon allowing to widen and unconceal. In fact, Fredrik Svenaeus [28] states that Hermeneutics is not only useful for reading texts. 'Hermeneutics is thus not only and not primarily a methodology for text reading, but the basic aspect of life. To be -to exist- means to understand'. In clinical practice, the possibilities given by Hermeneutics are clearly seen. 'Biological explanations and therapies can only be applied within the dialogical meeting, guided

by the clinical understanding attained in service of the patient and his health. Gadamer's philosophy of hermeneutical understanding, which has mainly been taken to be a general description of the pattern of knowledge found in the humanities, might thus be expanded to cover the activities of health care, I argued' [28].

This way of enquiring and investigating in Neurosciences contradicts the more accepted norm in Neurosciences according to which '… good explanations in neuroscience are good mechanistic explanations, and good mechanistic explanations are those that pick out invariant relationships between mechanisms and the phenomena they control' [29]. The analysis of the historicity and the collective character (being always with others) opens new horizons to Neurosciences. The 'has been', the 'been with' others of being-in-the-world, shows the intersubjective patterns which configure understanding. Dan Lloyd [30, 31] and Rick Grush [32] have caught our attention on the uses of the tripartite character of time as a basic element in the construction of mental representations in Neurosciences. This structure consists in the present subjunctive, an immediate past and an expectation for the immediate future. If conscience detects the tone of a musical note, this is only understood as long as it happens in a present which is retained, the present which I am feeling and the expectation for the future. The experience to be explained flows in time, which makes difficult to explain the continuity of the experience without resorting to a tripartite model of time and above all to a pattern of representation which allows us to understand this fluidity of the temporal experience and the resulting melody when the tone is in tone [29].

Thinking is an activity which is not done in vacuum. That is why unconcealing, opening problematic dimensions is necessary. The capacity of receiving the alterity of the other plays a central role in Psychiatry, both at clinical and at investigation level since sticking to rigid patterns make us lose opening of mind. The distance in time or, better, the temporal distance teaches us about the importance of gaining perspective and horizon. This is the only way of understanding the facts, in the sense of unconcealing them. It is not a question of suppressing our prejudices but making them productive for understanding.

## Conclusion

Truth is always present in the fields of Science and Philosophy. Maybe it is mentioned so many times because it seems something simple and natural. However, in moments of crisis, basic notions are important. Crisis arises due to supposedly solid knowledge or the appearance of areas of knowledge which cannot be circumscribed to established canons, because the areas do not conform to them or because they imply an interdisciplinary approach. What is understood by truth is one of these relevant notions. Traditionally, truth has been understood as an adequation of the intellect to the thing. Phenomenology and Hermeneutics present another way of understanding truth: truth as unconcealment. This way of comprehension allows to open new perspectives which give new answers about areas of knowledge which resist to be treated in the same way to the sciences which have served as a model. Trying to use a single method in Neurosciences, being an open field to multiple influences, reduces understanding. On this basis, introducing the notion of truth as unconcealment is crucial for understanding where the innovation of the hermeneutical approach lies and why it can provide a new way of access to reality. The key is unconcealing and not making the object fit into fixed patterns. Psychiatry also requires a methodological openness. The existential therapies are a proof of the possibility of taking concepts from Phenomenology and Hermeneutics and apply them in therapeutic practice. However, all this change cannot be fulfilled without a change in the notion of truth. For this reason, the usefulness of the notion of truth as unconcealment in the fields of Psychiatry and Neurosciences is clearly demonstrated.

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# 2 The Notion of Freedom According to the Transcendental Anthropology of Leonardo Polo

Miriam Dolly Arancibia

## Introduction

The majority of Western societies have conquered in our century a political model based on freedom; however, abuses and false understandings about its cabal meaning have led to a situation that is difficult to contain. After many years have passed in coexistence democratic, the respect by the others has not been attained still. The xenophobia, the discrimination by sex, social class, or religion, continues acting as prejudices that hinder the encounter with the neighbor.

The school has a high degree of responsibility. It is the place where is replicated the models and social parameters. In fact, it is not fortuitous that, in an era where freedom is declaimed, the school violence emerges as a scourge that affects all levels of education and all social strata.

This is why freedom is one of the major themes in the educational debate. From there emerge pedagogical and philosophical theories that act as guiding axles or, on the contrary, as distorting on basic and essential notions on the subject of education, of the authority and of the limits of liability.

The way of conceiving to educational subject underlies in all pedagogical strategies. Therefore, anthropology occupies a central place in a philosophical reflection on education. Nowadays, multiple disciplines, Pedagogy and Neuroscience among them, revive the old philosophical questions as freedom or determinism. Kantian notions of "autonomy" and "freedom" occupy a prominent place in the plans of teaching. The autonomy of the subject is understood as "self-determination of the freedom from the law or standard" [1].

So the proposal of Kant continues despite having affirmed freedom as absolute and the existence of imperatives that compel universally. Kant deepened the gap opened by nominalism that carries to the ethical relativism and to the agnosticism.

Terms such as "random" and "need" appear frequently in the ontological context; on the other hand, the term "freedom" emerges in the ethical and anthropological field [2].

The Greeks claimed that for well choosing is necessary the control of yourself. Taking wise choices depend on from the inside of the man. Getting right is being faithful to yourself [3]. The not teleological need appears as a disorder, such as hazardous. In this sense Arana says that the random was conceived as the dehumanized cosmic need [2, p. 17].

Plato gives a moral character to the need that governs the world. In Aristotle random refers to the marginal of the ontology, the *ens* per accidens. According to Arana, the Aristotelian contribution is ordered primarily to the establishment of the

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bases of a speech about the freedom, but less to the effective understanding of it as a factor of ontological determination. From there the philosophy of the freedom of Aristotelian inspiration is opposed to convert the freedom in something defining or essential of the human being; it appears rather as consequence that is adjectival to its nature [2].

Meanwhile, Polo points out that for Aristotle, the free man is *causa sui*, Lord of their acts. This means that freedom is framed in a space defined by the rules that guide to man.

Instead, in the old modern, its freedom is conceived as power exercised in an unlimited space. Scientific development increases the chances, and the scope of freedom seems even more. The philosophy of the Renaissance knocks down the teleological vision of the nature, and the freedom is designed as force of domination, "the man filled that teleological void with an undeniable constructive capacity" [3, p. 212]. Polo warns that to identify freedom with the power of technic is the lack of control. Is, just like that, what the Greeks named *hybris*, i.e., an excess of independence that causes alienation?

The relationship between need, freedom, and random substantially changes. The random suffers an eclipse which will last until well into the nineteenth century. The freedom becomes a priority of the reflection, both about God and about man. And the need is limited to the lesser extent possible, both in the epistemological and in the anthropological domain [2, p.18].

From that perspective Kant is involved in the modern debate on the knowledge, dominated so far by the continental rationalists and the British empiricists. Faced with the possibility of tilt for the dualism or for the monism, Kant proposes the construction. Only what is built is known.

Consequently, the study of the nature of the knowledge is focused on the relationship between subject and object. Universal knowledge have the character of the internal need; they must be clear and certain in themselves, regardless of experience, i.e., a priori, while what is taken from the experience is known only retrospectively or empirically.

Kant places limits on the reason to make possible the free self-determination. The notion of autonomy and freedom is derived from agnosticism by Kant in the *Critique of Pure Reason*. He considers his transcendental idealism as an intermediate position against the idealism and empiricism, although he forges a solid link between idealism and transcendental idealism [4, p. 201].

"The Kantian synthesis had an immense impact. In fact, we are still enjoying – or suffering – its effects. But as on so many other occasions, its consequences were very different from those that the author had wanted and expected" [2, p. 18].

Joseph Tischner appreciates Kant for the legacy of his radical criticism, because he considers that through him one arrives to the base of the certainty and the thought can approach to the truth. In this sense, to the aspiration of the philosophical thought of high hopes, as the existence of God, Kant adds the certainty. The positive side according to Tischner is that Kant leaves open the possibility of tension between the high hopes and the continuous possibility of losing those [5, p. 55].

On the contrary, Leonardo Polo is more critical concerning Kant. He realizes the difficulties that entail this conception of the freedom. Polo affirms that one of the major drawbacks of interpretation of Kant about freedom is that the autonomy as absolute cannot be intersubjective.

The problem is the notion of transcendental subject. In Kant the transcendental subject is a forgetfulness of the notion of "person," which corresponds to the question by whom. If we cannot speak of whom is the man, no one can speak of one whom with respect to other whom, and the intersubjectivity may not be formulated.

Therefore, the objective of this review is to discern contributions from the transcendental anthropology in order to achieve an integral understanding about freedom. Of the various approaches, this anthropology offers the key to discover solutions and answers to many of the problems that have today teachers in the classroom.

This conviction is based on the proposal of Leonardo Polo which is directed to privacy. As all his philosophy, his anthropology is provocative, changes structures, and requires of a change radical in our mode of thinking.

This is the reason why Polo is not easy and awake reticence if it is read superficially or briefly. Read and understand Leonardo Polo supposes leaving aside the comfort of schemes that

already were acquired and start again. We have to rethink what we thought know; we have to think the same issues from a new perspective, but, in addition, it means that we are open to the metaphysical challenge.

## Main Features About Transcendental Anthropology

Let's start by outlining the thesis on which rests the anthropological proposal of Leonardo Polo. For it is necessary to consider the following distinctions.

Polo distinguishes four capital features of privacy taking into account the classic distinction between essence and act of being and focuses on the act of being or human person. He exposes the real distinction between the characteristics of the act of human being (personal coexistence, freedom, knowing, and loving) and the other features of the human essence (the apex of the human essence conformed by the I and its two slopes: the will and the intelligence) [6, p. 7]. Thus he distinguishes two human dimensions, an upper, called *transcendental*, and an inferior named *essential* [7, p. 11].

**First Thesis:** The anthropology is not a regional ontology or a chapter of metaphysics; then, it concerns about the personal being, and this is not limited to the sense of being studying metaphysics. To this personal being corresponds the transcendental whose permission to expand these discovered by classical philosophy.

**Second Thesis:** That enlargement has been attempted by modern philosophy but not properly. The claim of know intuitively the subject in the object, as proposed by the idealism, involves the removal of the intentional value of the object. But precisely there Polo discovers the usefulness of idealism, because that in this way it helps the detection of mental limit.

**Third Thesis:** If you want to access to the human person, a new method in order to find new notions that are not metaphysical should be used. One of the main dimensions that reach such a method is the character of the person which Polo called character of *being more*. This indicates that in the object thought not is the person. This is the method required to achieve human coexistence [8, p. 106].

The theory of the transcendental arises in the Greek philosophy [9]. According to Polo, "though Aristotle does not use the word 'transcendental', which is a medieval invention, the doctrine of transcendental exposed by Tomás Aquino found their bases on the Aristotelian approach" [7, p. 52].

Polo refers to transcendental metaphysics to discuss the question of its ordering according to the different types of philosophy. He names them metaphysical for distinguishing them from other transcendental that he calls personal.

The expansion of the transcendental is necessary because metaphysics concerns of being as a principle, but this sense does not include freedom since being principle does not mean to be free. "If the first philosophy concerns of first thing and first thing is the principle, and main being excludes freedom – is not equivalent to it: the freedom is not the principle-, the freedom is regarded as purely categorical" [7, p. 22]. The consequence of assimilating freedom to the order of categories is that human reality remains limited to the condition of property of voluntary acts.

Here is where Polo inserts the need for a new method that allows reaching the realm of the transcendental. This method is named *abandonment of the mental limit*, through which, in one of its dimensions, warns the metaphysical theme, that is, the first principles, but in another, the higher, it reaches the personal transcendental.

The basic elements on which is built the new method are: "Limit" is the concealment that is hidden. It is a "true concealment that the thought carries I get, and that is hidden in the same measure in that the thought is objective" [7, p. 23]. "Detection": Polo retains the metaphorical sense of the term theoretical information attained by having arrived to play, but it gives to the same time a concrete technical sense. The limit is not a sensitive element but must get to notice him, despite his concealment, not to stay with him but to leave it. "Abandonment of the limit": it means

to try to find out the metaphysical value of the same limit and thus detect it. Now leaving the limit of thought after carrying the thinking to it means to reduce the difference in a realistic, not idealistic sense.

If it identifies the object itself of the knowledge objective as the *quidditas rei sensibilis*, the transcendent is understood as trans-objective or as beyond what is captured as an object thought [7, p. 24]. On the other hand, if immanent operation of knowing is taken into account, also one will say that this is not transcendental, and you should discover a sense of it transcendental that you must reach over it, not transcending only the object, but also the operation.

The transcendental which are detected when the object thought is abandoned are metaphysics. The transcendental reached when the immanent operation goes beyond is named personal or anthropological.

Consequently, leaving the mental limit it warns the *trans-objective* theme. And if the limitation of the operation is detected, the *trans-operational* thematic is reached. The first corresponds to the metaphysic, the second to the anthropology.

The operation of knowing is not extramental, but as the operation does not is the higher act of knowing, above it is not the trans-physical or metaphysical, but it is the trans-immanent, the spiritual reality.

In this direction proposes Polo the possibility of reaching the freedom as anthropological transcendental trans-operational and other transcendental human personal [7, p. 24]. Transcending the operation not leads to the trans-physical, but carries to transcend in the line of the spirit.

Like this flows in a transcendental anthropology, different of the metaphysical at which is not reduced because the human being is more than exist or being, where is co-being or co-exist and, therefore, being-with.

## Freedom

According to Leonardo Polo, the first understanding of freedom is not transcendental but essential; we first experience that in the free acts, not in the person. We can distinguish personal freedom (or transcendental of the order of the *actus essendi*) and essential freedom (explicit freedom or freedom in the order of to avail of). The essential freedom not is personal and is an extension of the personal freedom [7, p. 62].

The person is the intrinsic perfection, achieved according to intrinsic habits. Its essence consists in to avail of which is equivalent to manifest. Then, according to Polo, being free means not being subject to the empire of the need, but to be able to manifest, which is consistent with the transcendental privacy. The manifestation of privacy is free. The personal manifestation, the *essentia*, is not available; because the human person is different of the *esse*, the human person has not replica.

The Polo proposal is a clear challenge for a deeper conception of freedom, not only in theoretical terms but also with vital implications. First at all, Polo distinguishes between native freedom and freedom of destination; thus, freedom of intelligence and finally the freedom of the will. In this way, he proposes an integral perspective of freedom because this distinction has many implications.

We will continue analyzing this topic.

### Liberty Native and Freedom of Destination

Native freedom is the methodical sense of freedom; it is the methodical character value of additionally.

Freedom of destination is the thematic value that becomes with the intellectual search and the search for love.

In other words, the native freedom refers to the radical in man; freedom of destination to its horizon. As usually happens in the Polo texts, the reader must rethink the commonly accepted. Thus, the freedom defined before primarily by the act of choice, Polo warns that if that choice rests with banalities, and if it is restricted to light decisions, then freedom is reduced to a purely psychological interpretation.

On the contrary, the native freedom implies a greater use of freedom, as it moves toward the

radical, i.e., it starts of the person and faces to the person [10, p. 244]. Thus understood, the liberty faces to the aporia, i.e., being free is being caught in the midst of enormous complications with obstacles that must be overcame. Freedom is "linked to commissions" [10, p. 245].

Polo applies the analogy of the heroic myth in which distinguishes four elements: the subject, the reception of a commission, the adversary, and the beneficiary. The hero is who accepts a task (a commission) to another, i.e., the beneficiary will always be another, not the same. So says Polo "a hero is not free for itself" [10, p. 245], thus reaffirming the interpersonal nature of freedom.

The way in which we assume the commission, such as personal gain or for benefiting to another, will depend on how that freedom is experienced as banality or with responsibility toward a higher target defined by the encounter. What we find is the truth, not in theoretical terms, but as the impetus for their practice.

"Without truth, there is no freedom" [10, p. 249], these words of Polo acquire a very particular sense because we live a time in which the truth has been relativized to the point of being desecrated. If this is the case and the truth is relativized, then freedom is also. It is no coincidence that in times in which abound the declarations of human rights and rhetorical proclamations by a free world, however, abound also egregious violations, new forms of racism and xenophobia.

The scope of the Polo judgment goes further still: it highlights that truth fills an act as immense as it is the event. It means, the truth that one is found must be a loving truth, must be integrated to one's self. It is love of reality that comes to meet; therefore the man decides to embark and engage, and this is freedom of destination [10, p. 250].

The truth is also hope, thus connecting with the freedom which lives in hope: "one hopes to be free, and to be free more expected: more truth" [10, p. 251]. Polo highlights the approach that should guide the search for the truth, since is the more optimistic vital goal: requires sincerity of life, not for being skeptical, not for renouncing the task of looking for and serve to the truth. The encounter with the truth means to discover it as such and not only the particular truth of one or another thing.

Although it may seem utopian and unattainable, the search for truth must be constant. The first attitude that drives the search is the admiration which does not yet possess the truth, but it is the start for meeting the truth. This feature becomes something of special relevant in the field of education, because the ability of admiration is opening the door to a world of unknown matters. However, it is currently the most difficult of stimulating due to the rule of the immediacy and saturation of the vertigo of images.

The truth is therefore a metaphysical transcendental. With reference to the man the truth has to be understood in relation to the Transcendental Anthropology and in particular with the personal knowing, because without this no is such truth. From this perspective, the truth not is mere copy or reflection or '*adaequatio*' [11, p. 201].

The personal truth is a reality offering a gift whose consummation is impossible if it does not exist in other person; so from there emerges the notion of coexistence. According to Polo, it is not only to seek the truth but also fulfilling yourself from it in accordance with the character effusive of the human being and the donor nature or transcendent of its freedom. "If the man had no effusive character, finding the truth would be sterile, because the truth is destined at the encounter, due to the character of in additionally of the person" [11, p. 202].

Therefore, the formal truth is not the highest sense of truth. To find the truth is more than to know it. For finding it, the freedom is necessary, and in this sense, the truth is inspiration. Current constructivist theories affirm the truth as a result of mental construction process, while Polo emphasizes the importance of the encounter with the truth and its discovery.

The scope of the expression "encounter with the truth" is deep; hence Polo derives a third sense of the truth. In addition to that affirmed by tradition, the ontological and logical have now added the sense suprarational, personal.

This implies that the truth is displayed starting from the encounter and since it is found by being free, it has a place also in falling in love.

Freedom carries the truth beyond, thanks to the inspiration of love.

As corollaries emerge, first of all, that truth and love are attached prior to the distinction in operations of different faculties [11, p. 204]. It arises also an idea of the freedom that seeks the beautiful notion of vocation that should be lived more than the pragmatic success.

Understood in this way, the truth and freedom open broad framework of educational possibilities aimed at deeper goals involving the single notion of construction. They are not easy to inspire students loving the truth and contributing to the discovery of their vocation with the addition of encouraging them to live them. They are challenges for any educator of this century.

It is a challenge because they assume one greater commitment, not only by part of the student but also of the educator. To inspire, to make yourself fall in love, and to live the vocation, the own educator must feel it, experience it, and express it in those small moments of its pedagogical task.

Polo considers understanding that the truth is essential in human life. "Without the encounter with the truth the man does not develop as such" [12, p. 162]. The truth is a condition of sociability and is more than the virtue of veracity. This virtue grows to the extent that you discover that there is truth.

The educator can collaborate with that discovery, if he does not start from subjective or relativistic theories, which reduce the existence of the truth to the contingency and to the conventionalism.

In *The Human Person and Its Growth*, Polo says that subjectivism is a frequent and observable fact but it is not a general phenomenon [11, p. 31]. His optimism is justified by the date of this paper and then reissued in the mentioned book. Unfortunately, the subjectivism is today one of those phenomena more generalized in the theories underlying in the most of the educational policies.

Polo designates as symptoms of such subjectivity, first, the shortening of the radius of interest. "How much is more person, more is interested; to interest more, takes more responsibility and therefore become more responsible; being more responsible, is more engaged" [11, p. 31].

This sentence contains a keyword: the being responsible for. On the contrary, nowadays there is an escape to everything that means responsibilities. Subjectivism became selfishness precisely to flee responsibility. The words "forever" have lost their meaning; already not run big risks; the promises have lost validity. It is not just a matter of matrimonial promises; it is not worth it the fulfillment of promises vocational. Those ways of life that meant a total surrender and forever, as they were religious vocations have been demystified. On the contrary, it is imposed with much force the principle Heraclitean nothing is for always [13, p. 44].

Another symptom is the lack of interest by the truth, by be honored, by be consistent. By the contrary prevails an interest by the immediate things and justifies mediums that serve to achieve it, especially "in the character pulsating of the interest in the field sexual" [11, p. 31].

Another field in which is experiencing the lack of interest is the politics. The purely selfish interpretation or political subjectivity that causes the anemia of political activity predominates. In the subjectivism each encloses in himself and loses interest of others.

The application of this observation is wide, since one of the main factors of the global economic crisis is the corruption and loss of interest for the common benefit. On the contrary, a search unscrupulous for greater individual revenue predominates.

Polo considers as pathological symptoms of the subjectivism a set of features that, unfortunately, happens currently with much frequency in the classrooms. The decrease of the capacity of communication, the poverty of vocabulary which has arrived to alarming levels, causes a decrease in the skills of writing, reading, and understanding of texts, what Polo calls "crisis of the expressiveness" [11, p. 33].

In the affective order, the triggering mass of the affectivity predominates. Its feature is the overflow of feelings and their lack of control. The affection changes from the apathy to the exaggerated manifestation. The affectivity is shown

to such an extent that it is trivialized; the more intimate experiences of people are disseminated through the media impoverishing the interiority of people.

In religious sphere, the sentimentality prevails causing deterioration of the transcendent sense of the religion. The religious experience is reduced to such an extent that it is equated with the merely human emotional experience and the love is restricted to the satisfaction of individual desires.

In its *transcendental anthropology*, Polo indicates that love is a personal transcendental, which is converted with the other transcendental of the act of the personal being but is superior to the others, because the highest sense of being is to give [7, p. 211].

This means that the act of being in its highest sense is not a transcendental closed. It could convert neither with the truth nor with the good. In this way, Polo extends the traditional perspective for which truth and good are relative, being the first transcendental, absolute and closed. On the other hand, the conversion of the transcendental metaphysical requires the opening discovered by transcendental anthropology.

The human person is co-action of being which denotes opening. Such opening is net in the personal love, because this is equivalent to give and because to give without acceptance does not have sense. The character of additionally is equivalent to the accepting and to the giving created, "If the person does not accept its being personal created it is annihilated" [7, p. 211]. Thus, to love and to the being accepted it must be added the love.

The freedom is measured by the importance of the reality to which aims. The degrees of the freedom, and similarly of the love, have their scale. That is why it is important that man finds a proper reference. Otherwise, freedom is frustrated. "What justifies our situation of men free is the reality to which we are opened" [7, p. 211].

Therefore, freedom is also a proof of the existence of God, since He is the highest reality to which the free acts of man tend. In God, love is personal, in man it is in his works.

Loving to God is transcendental because the person prefers to God, but the love not is a human transcendental. That is why freedom extends to the essence and to wanting I, the subsequent voluntary acts and habits of the will [7, p. 219].

The wanting is constitutive of the voluntary acts. Polo understands the will following with the classical tradition; the voluntary acts put true control over the cognitive operations. The moral not is of transcendental level but derives from the personal transcendental and appears as the man acts. The moral teaches to respect the essence of the man which is the available – not available or reserved to God [7, p. 220].

## Freedom of Intelligence

As it has been said before, our first acquisition of liberty is essential, not transcendental and then it is where it is first understood not in person but in free actions, hence the distinction between human freedom (freedom in the order of the *actus essendi*) and freedom of man (freely available, manifest freedom).

The human essence is distinct from the essence of the universe because the man acquires habits. The nature is beginning of operations but not is free; the essence is an acquired perfection: the dimension by which human freedom takes contact with nature is the habit, "for them we are essence and not only nature" [14, p. 61].

According to this perspective, the essential freedom not is personal but is an extension of the personal freedom. Freedom appears in habits, as freely available, as privacy free demonstration. The essential freedom is freely effusive leaving the possibility that the man refuses. Hence, there is also an elective freedom, but this is not the personal freedom but a derivative of it. Unlike the classical tradition, Polo reiterates that only elections did not define freedom.

From these prolegomena emerges, as far as intellectual habits are concerned, that, if these are acts and perfections of the faculty, and then they are illuminations of operations on the part of the intellect agent. Here Polo introduces a very Aristotelian topic, but he will give his own imprint.

First, the agent intellect is personal: is to know in act; it is the transcendental personal from which are derived the habits. According to

Aristotle, human knowledge begins with experience, "there is nothing in the intellect which has not first passed through the senses" [15]. But the cognitive ability is not limited to the empirical field; it comes from the knowledge of essences. To explain the passage from the sensitive to the intelligible, Aristotle provides the notion of "species printed" of the intelligence. The intelligence cannot be perturbed by the corporeal since it is disembodied, and their own printed species do not come from organic faculties. The agent intellect is that lights the ghosts providing printed species to intelligence.

Polo adds that the intellect agent is not only illuminating the ghosts but that operations are also illuminated [14, p. 62]. The operation knows the object but it is not objectified, it is not known objectively, i.e., it is not reflective. Therefore, the operation is just known if it is illuminated; such lighting, while intrinsic act of the faculty, it is a habit.

Applying the Transcendental Anthropology, the mental edge is the operation. We abandon the limit, thanks to the habits, that is, to illuminate the operation, we obtain a knowledge superior to operative, and we can go beyond. Additionally, the notion of lighting means that the habit is not caused, that it is above the cause, and that therefore the common knowledge is free. The operation is not free, only the habits which are extension and manifestation from freedom to the intellective power.

Now, the freedom not manifests itself only in the intelligence, but also at will. Polo moves away from the traditional position, and he refuses the principle according to which "we are free because we exercise voluntary acts free" [14, p. 64].

Polo is provocative, as on many other occasions. He preserves the tradition at the same time he extends it. This aspect will be developed in the next section.

## The Freedom of the Will

On the traditional conception of will, Polo warns the inadequacy of Greek view, because the will is more than the desire, the deliberation, and decision. He rescues the difficulty pointed out by Thomas of Aquino on the voluntary intention insofar as it is not the intention of similarity but one intention of other, of otherness. Indeed, the will does not refer to reality by similarity, but it goes directly to the reality. Both intentions are irreducible, because the reality is another and has reason of another. Finally, he takes the notion of curvature: unlike the intelligence, the voluntary act is reflective or quasi-reflective.

Nevertheless, Polo goes beyond because he completes these notions, since he considers that the characteristic of the will is to accompany vision that emerges from the character of *additionally*. From there it follows that the company of the subject to the will is more closely than on intelligence, and it is also the company that is the other. From transcendental anthropology, the notion of otherness thus acquires a new meaning. It establishes a difference that does not mean isolation.

*Intendere* according to the otherness does not imply imperfection. The will cannot be isolated of the action. It needs active use. The freedom of the will is then understood from the point of view of the addition, of the otherness, "the free will is that holds any downpour that it is still freedom in the most frozen Northern steppe and requests help" [14, p. 106]. The will is a faculty that reunified.

Polo remembers that the will not has a purpose separate from the intelligence, because otherwise this would appear as an illusory world. Therefore he considers that the willfulness as this of Schopenhauer acquires existentially negative characters: "the hegemony of the will leads to the irrationality of the suffering and the absence of reality of the representation, to boredom" [16, p. 17].

According to classical Greek thinkers, the will was understood as scarcity or lack of perfection; it belongs to temporary being, not to eternity. The Christianity claims that the will should be interpreted in a full sense, since God is love, therefore, the will must be placed in God. This means that the will is more than a mere desire.

On the other hand, according to Ockham, the modern voluntarism has carried out a negative and

critical derivation of the will that ruins the whole nature of this ability. Polo says that the confusion of knowledge and desire is characteristic of modern rationalism and German idealism [16].

Thus, for example, for Descartes, will and thought are the two faces of the same currency, the first is active and the second is passive. The principle of his philosophy, the doubt universal, lies in the will. Polo considers that the doubt is voluntary, since it consists of wanting to. The trial is a voluntary act; the analysis is another voluntary act; the will has active priority over the thought.

The Cartesian position is thus equivocal: "hold that reality is consecutive of the will, it is a degradation of the fullness of being." The reality is considered a posteriori with respect to the will: "If omnipotence consists exclusively in will, as Ockham says, it is confused with nothing" [16, p. 19]. The will is remaining open to nothing when their priority overrides that of being and of the understanding.

Polo underlines that being considered the will as spiritual trend in proportion with the reason then appears the notion of medium and the possibility to choice of means. In this area, "the man as a *causa sui* controls its own living to a certain extent, because he can get wrong" [16, p. 31].

As we can appreciate, Polo takes up the Aristotelian definition of the freedom as *causa sui* or domain on the own acts. The man owns his acts when he understands, selects, and pursues them. Freedom, according to which man is better essentially, is the moral freedom, in turn closely related with pragmatic freedom [14, p. 62].

According to Aristotle, the man is not a purely natural being but that there is something more than the animated being. Freedom is the dominion over the very acts, because it is impossible to consider the reality of the same will. In other words, the substance is not limited to continue in the "nature."

On the other hand, what makes to the man essential is the habit. The exercise of freedom is considered in relation to the improvement of man. This is what Polo describes as moral freedom. The man is essential if he acquires virtues; thus he needs freedom. He has more freedom, while more intrinsic perfections are achieved. The moral freedom is in the order of human growth. In terms of Leonardo Polo, man is the "perfectible perfectionist."

The man not only has the ability to perfect himself but also to produce if we consider it in the order of action. Polo distinguishes the notions of "cause" and "lead." To produce is exclusive of the essence; it is creating a symbolic world. This is called freedom pragmatic.

In conclusion, Polo emphasizes that man grows in its natural character but is perfected beyond of the organic. "Our humanity is in our hands so we can always be more like humans" [14, p. 84].

## The Optimization or Personal Growth

Freedom is not only a property of man but is also a vehicle for the progress. According to transcendental anthropology that we aspire to freedom means it is a goal, something that we not have but we desire [11, p. 38].

Freedom is not something that it is achieved as an object, is not known as one object, and is necessary to exercise it. Not all who manifest desire for freedom have clear what is this human reality.

So, there are some attitudes that ultimately are a denial of freedom. Such is, for example, the existentialist position, according to which "we are condemned to be free," "not obliged to charge our own exist" [11, p. 40]. In this perspective, freedom is defined as a heavy burden, as a grueling task or as desperation or as something so difficult and uncomfortable that finishes being somewhat useless.

Other conventional perspective about freedom is that this is finite, i.e., it has a limited character. In the first place, the reality physics is already a limit to the freedom. In the second place, the human liberty is a freedom embodied, "within my constitution, as the entity that I am, in reality that I am, there are many aspects; there are many dimensions that are not free" [11, p. 43]. And thirdly, it's a liberty situated; it has to take into account others.

Since man is born, he is inserted in a social environment that conditions him. A type of restriction of freedom, widespread in the current postmodern societies, is the confusion between experience or consciousness of freedom and its experience. However, define it only as experience, it is equivalent to reduce it, then we fall in the frivolity since is it limited to the flat of the pure feeling.

Polo defines freedom as the ability of self-determination. This does not mean indeterminacy but the absence or to stand above the determinations external.

As freedom is embodied and is not present at lower levels, it is the apex, which completes the constitution of the human being. By that Polo says that the freedom of the man is personal.

Such freedom is not something static, can be deployed, and therefore is capable of growth.

Here it shows that it has a reflective nature; you can return to the psychophysical constitution, i.e., there is a domain of the man about his body and his psyche. From here is clear that has a character reflective, but only the Christian warns that, to overcome the lust, reaches the release with regard to the I inert, included in the privacy.

Polo differentiates between the notions of "progress" and "growth." There are three types of growing life:

1. Growth of multicellular organisms of the body. It presupposes the genetic code which is a structure, a way with regulatory value of life processes. Growth is related to reproduction, but it is superior to reproduction because it continues in view of living unity.
2. In the cognitional growth, there is no known out of it, and it is known that knowing unifies. Intellectual knowledge is an infinite growth. Meanwhile, the habits of the will, the moral virtues help to be always growing.

The growth is, ultimately, spiritual, and therefore the person is irreplaceable "The greatest thing in this world is the living human in growth" [11, p. 107]. Polo believes that the best antidote against the culture of masses consists in helping to grow. From the beginning, since the human being comes to the world, is the growth of being person what will allow to stand above the individualism and the selfishness.

Thus, since notions as rich as those of "freedom" and "growth," Polo arrives at a definition of education. According to Polo, the student can improve, teaching to think is equivalent that he can do by himself.

This implies a guideline that does not mean a pure transmission of knowledge, but the achievement of learning. The student should act; of the activity derive those habits. Thus understood, the educational process is conceived as collaboration, i.e., as joining a task in common that involved students and educators.

## Conclusion

The transcendental anthropology asks about who is the man, not about what is. In fact, the response about the sense of the body and of the human sexuality depends on the response to the question about whom and for who is the man.

We cannot speak of sense of sexuality or sexual education without discovering the meaning of the human person. According to the anthropology of the privacy, or transcendental, the human sexuality is the biological typology of incarnate of the human natural.

From this anthropology, the sexual release neither responds nor respects the true freedom personal since it is submitted to the slavery of the sensitive passions. If the sexuality belongs to the area of the demonstration, it is thus incompatible with the personal privacy. It would be a deep depersonalizing.

In the incessant search of answers for a more just social order people go nowadays to philosophical positions that in some cases reduce the question to economic determinism or seek the explanation only in the permanent game of control and domination.

However, in those positions, the long-desired freedom escapes them, because they do not see output beyond the purely natural and human. Such is the case of Foucault, who in his work, *Discipline and Punish*, analyzes the technical that is put in game to

achieve the domination and with the power. Foucault reduces the human being to their impulsions [17].

On the contrary, the anthropology of privacy offers a look that transcends those natural limits based on a truly unitary vision of the person and with a deep sense of radical freedom. The human being is called to authentic liberation. According to Leonardo Polo, this means recognizing the dependence. The person is beginning or irreducible.

Polo affirms that the man is a symbolic animal, and this lies in the language as *continuation naturae.* This is the nature of the culture, and by this raises questions such as: In what world do we live in according to our capacity of corporeal possession? Do we live in a natural world or in cultural world? What is the real human world, the physical realities, or symbols?

In the continuation of the nature, man is a quasi-creator. Instead, the animal will find the vacuum if is opened more beyond of it natural. The man is in this world to cultivate and to add something new. That is the culture and the symbolic, and there is where man lives. In this way, the man survives in an intermediate area that is his habitat according to customs and symbols.

However the man does not form part of the natural world, he transcends it. The man is more than nature and shows that he is spirit. In this way, a different human sense is rescued by the transcendental anthropology, the spiritual dimension, and the body. Therefore, it offers possibilities of understanding of reality with a look of hope on the person and its social reality.

We arrive to a central point of this article: the importance of the integral vision of the human being and the role of freedom. The human dignity requires to be recognized as a complete unity, spirit and body, and unrepeatable identity.

It is not by chance that this subject acquires special interest currently. Nowadays, the human being lives immersed in times of conflicting changes by which intends to make *tabula rasa* of the principles and values that before guided the process of enculturation in Western societies.

The massification generated by modern rationalization processes is generalized. In the education dominate strategies leveling in pursuit of a thought uniform.

The exacerbated individualism is the flip side of the same coin. Lack a vision balanced, because it has broken a deep vision of person.

Therefore, the absence of recognition is the logical consequence leading to loneliness and frustration. With the notion of "recognition," many others are interlaced, as the notion of "authenticity," "respect," and "identity." From the personal identity, we have access to the transcendental freedom in reference to the origin and destination of personal being.

The freedom, together with the understanding, privacy, and gift, forms the personal transcendental. The privacy means depth for achieving for growing and for developing. The word "growth" acquires a special connotation in the framework of the transcendental anthropology; thus it is not only a quantitative growth but also growth as optimization.

The personal being is full in the measure that is growing. By that the notion of growth is inseparable of the notion of love. In other words, the gift by which the person shown and delivers its privacy. By virtue of this, a dialogical relationship is established between the givers and giving.

To give is to desire the good to others who have to accept. The gift is self-transcending, leaving it to him. In this way, the transcendental anthropology responds to controversial issues from extreme ideologies such as the so-called gender ideology that seeks to justify the abortion and a reductionist vision of the woman, which derives in an exacerbated materialism. This ideology promotes an exteriority without limits of the emotions, the private acts become public "The instances of education of feelings (family, educational centers) are today replaced by impersonal media of communication which offer skewed and superficial information with an excessive burden of insignificant stimuli" [18, p. 121].

As Leonardo Polo warned, reign even in the sphere of the universities "fashions theoretical, ephemeral accumulations that are happen one to others without any articulation" [11, p. 108].

It is expected that the horizon will be as optimistic as Polo announced: "probably, and we are working in this, the creative process will repeat and the confusion reigning in the theoretical order will disappear" [11, p. 108].

To achieve this so inspiring objective, we need to recover the deep sense of person and its freedom.

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# Neurobiology of Pain: A Humanistic Perspective

3

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## Introduction

Pain maybe understood as a complex sensory manifestation composed of two (perhaps artificially defined) distinct components. The first component is neurobiological, relating to the neuronal transmission and processing of sensory signals, providing information such as localization and intensity (and curiously not always associated to consciousness), and at a higher processing scale, supplying the sensation of pain, its conscious, emotional, cognitive, and social dimension. The second component, not immediately obvious, is more ambiguous and subjective and relates to the fact that it is not at all clear if pain is just the sum of all neurological processing involved or should be understood as an emergent property instead. So important is the distinction that today great efforts are being made to understand how these two components interact, addressing challenging questions such as if "there is a purely biological core to pain experience" [1].

In the following sections, we will discuss these two components and establish the humanistic perspective that makes pain one of the most fascinating features in human life, one that can also be challenged by disease and influence (both negatively or positively) the very core of a person.

## Defining Pain

Perhaps the first logical step in a chapter addressing pain is to ask the question: what is pain? It may seem trivial as we all believe to know what we mean when talking about pain. But the truth is we can refer to pain without the need to define it. In fact, "pain" and "love" fall into the category of concepts that are defined according to the general acceptance of a determined social group, regardless of our capacity to define their scope within the limits imposed by words.

The word pain comes from the Latin *Poena* meaning a fine or a penalty. There have been various definitions of pain depending on the conceptualization made of the phenomenon; these include thinking of pain as a sensation or an emotion or even describing it as a behavioral response that manifests during a painful situation. The first to attempt a definition were Hippocrates, suggesting that pain was strictly a physical perception, and Aristotle, proposing pain as an emotion that predominated over all rational process/reasoning (see [2]). But the path to achieve an

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acceptable definition began with Sir Charles Sherrington, one of the great English physiologists of the early twentieth century who understood that pain was part of a mechanism to protect the individual [3]. Furthermore, for Sherrington pain was a neural function of which perception, that is awareness of its existence, is separate from the neural processing of pain itself.

Thus, Sherrington distinguished between a pain reflex of protection and the conscious perception of pain. He also proposed the use of the term "nociception" to refer to the underlying neuronal processes of the painful experience (see below). Nociception in this way does not necessarily imply pain, but the sequence of neural events that allow pain sensation, whether its conscious perception exists or not. Interestingly, such a notion allowed the rational analysis of pain and the neural processes that trigger it in animal and humans under the effect of anesthesia, or in isolated cells or tissue cultures when measuring nerve impulses, that is, when there is no real pain. Thus, the study of nociception is the study of how stimuli are detected, transmitted, and eventually processed in higher-order neural structures, without necessarily implying the full knowledge of pain as experienced (see [2]).

Much more recently, the International Association for the Study of Pain (IASP) stated the most up-to-date definition, indicating that "pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [4]. The strengths of such a statement are the recognition of the psychological components of the experience of pain and providing pain with a medical-biological perspective. This definition also establishes that although injury is frequently associated to the experience of pain, there is no invariable dependence. Moreover, it recognizes the emotional component as a constituent of the painful reality and not as a secondary reality. However, an even newer definition has been recently proposed: "Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components" [5]. This newly suggested definition, which has now to be put to the test of time and peer judgment, pursues three objectives: (1) to acknowledge cognitive and social components; (2) to better describe the experience of pain, changing the rather mild word "unpleasant" for "distressing"; and (3) to provide a higher relevancy to nonverbal behaviors, as prominent sources of information when the subjective experience cannot be communicated [5].

## Neurobiological Participants in the Processing of Pain

### Primary Afferent Neurons and Nociceptors

The type of pain that keeps us alive and helps us avoiding most preventable injuries is called nociceptive, being defined by IASP as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors." In turn, nociceptors are defined as "high-threshold sensory receptors of the peripheral somatosensory nervous system that are capable of transducing and encoding noxious stimuli."

Nociceptors are produced by a subpopulation of primary afferent neurons called nociceptive neurons, located either in the trigeminal ganglion and supplying the head and face or in the dorsal root ganglion (DRG) and innervating the rest of the body. Both trigeminal and DRG primary afferent neurons are classified as pseudomonopolar neurons, meaning that they have a short axon that will soon divide into a peripheral projection innervating bodily structures, and a central projection terminating in the spinal cord. It is the ending of the peripheral projection of nociceptive neurons that is described as nociceptor which, in contrast to non-nociceptive receptors such as those sensing touch or pressure, do not have a specialized receptive structure and simply terminate as free nerve endings in, for example, the skin, muscle, or ligaments [6, 7].

Two main types of nociceptors are found, based on their axonal caliber and conduction velocity: (1) Aδ fibers, characterized by a very thin myelin sheath and transmitting at a speed of 5–30 m per second; and (2) C-fibers, with no myelin sheath, and transmitting very slowly, at a rate of less than 1 m per second [8]. For the most

part, Aδ nociceptors are activated by mechanical stimuli and in some cases also by thermal stimuli, whereas C-nociceptors tend to be responsive to multiple stimuli (i.e., mechanical, thermal, and/or chemical) and are called polymodal [9, 10]. However, some modality-specific C-nociceptors exclusively responsive to noxious mechanical (intense pressure or traction), noxious heat (more than 40 °C), or noxious cold (less than 10 °C) stimuli also exist (see [10, 11]). These two types of nociceptor-associated fibers have a wide distribution across the skin and deeper tissues and act in a coordinated way. For instance, when hitting one of our fingers while using a hammer, we immediately feel a first intense pain that is followed by a duller, diffuse, prolonged, and sometimes burning type of pain. The first pain is transmitted by Aδ fibers after activation of mechanical and some thermal nociceptors. The second pain is transmitted by C-fibers and following the activation of polymodal nociceptors.

Finally, a subpopulation of neurons called silent neurons that are unresponsive to mechanical or thermal stimuli in normal conditions, but subject to sensitization upon tissue inflammation, has also been identified [12–15]. Sensitization, however, is not only a feature of silent nociceptors. In general, nociceptors are sensitized by the occurrence of inflammatory processes (see [16]). In such event, the cellular destruction in injured tissues results in the release of a variety of chemical substances such as bradykinin, histamine, leukotrienes, prostaglandins, acetylcholine, serotonin, and also substance P (SP). The concerted action of all these substances ultimately leads to the sensitization of nociceptors by reduction of their activation threshold.

Most Aδ and C-fiber nociceptive neurons projecting to the spinal cord synthesize the excitatory neurotransmitter glutamate, which upon secretion acts onto AMPA and NMDA glutamatergic receptors expressed by projection neurons and interneurons (see below). Nociceptive neurons also express other neurotransmitters such as peptides. In particular, the excitatory SP (11 amino acids) and inhibitory neuropeptides such as galanin (29 amino acids) and neuropeptide tyrosine (NPY, 33 amino acids) have been widely analyzed in the context of pain transmission and modulation. Interestingly, one nociceptive neuron can produce and subsequently release neurotransmitters with opposing actions, exposing the complexity of pain processing already at the level of primary afferent neurons [17]. The end result is transmission of painful information toward projection neurons, with SP potentiating the excitatory effect of glutamate and galanin and NPY attenuating it [18].

Upon activation, nociceptors undergo a series of changes ultimately leading to signal propagation through the peripheral and central branches of DRG neurons, to end in the dorsal horn of the spinal cord.

## The Spinal Cord

The first relay site of all sensory information, including pain, is the dorsal horn of the spinal cord. The dorsal horn, composed of six cytoarchitectonically different laminae [19], receives the central projections of nociceptive neurons that make synaptic contact with second-order neurons called projection neurons, giving rise to ascending pathways in the spinal cord. Another type of spinal neuron receiving inputs from primary afferent neurons are hundreds of interneurons, largely establishing neuronal networks and modulating in an inhibitory or excitatory fashion the interaction between afferent input and projection neurons. Finally, descending inputs from specific nuclei located in the brainstem establish contact with all three above, adding one more step of inhibitory modulation. Thus, the dorsal horn becomes a key convergence site, where sensory information is integrated, subjected to local and supraspinal regulation, and finally retransmitted to areas of the brain where it finally becomes conscious.

The central projections of nociceptive neurons. have very specific termination patterns in the dorsal horn. Thus, the majority of the information transmitted by Aδ- and C-fibers enters lamina I (LI) [20–24]. Lamina II is subdivided into external and internal [25] and receives principally C-fibers [21, 24, 26, 27], although Aδ fibers also terminate in lamina IIe [28] and A β mechanoreceptors also terminate in LIIi by way

of LIII [27, 29–33]. Finally, the main afferent input of LIII-VI is Aα-fibers [21, 30, 32–34].

Despite their relevance, projection neurons only represent a minor proportion of all neurons in the spinal cord. For instance, only 5% of all neurons present in LI are projection neurons [35]. However, the great majority are dedicated to the transmission of nociceptive information toward upper levels of the central nervous system. In contrast, neurons located in deeper layers such as LV are called wide dynamic range and respond both to noxious and innocuous stimuli [36]. Most projection neurons are excitatory, based on their lack of the inhibitory neurotransmitters gamma-aminobutyric acid (GABA) or glycine [37, 38] and their expression of glutamate [39]. Many also express the neurokinin-1 receptor, being thus the target of substance P-expressing primary afferent nerve endings and interneurons [39]. While the thalamus is their principal destination, most LI nociceptive projection neurons also terminate in the parabrachial nucleus in the brainstem. In turn, the parabrachial nucleus provides a quick access to limbic structures such as amygdala and hippocampus, likely involved in conferring pain its emotional component. Other nociceptive projection neurons project to the periaqueductal gray, the reticular formation, the hypothalamus, and the thalamus [40–42] while collateralizing to other multiple supraspinal sites [35, 43].

Interneurons are characterized by their short axonal and dendritic projections, participating in the establishment of a complex circuitry involving other interneurons, projection neurons, and afferent nerve endings. Morphologically, interneurons can be divided into islet, central, radial, and vertical [44] and according to their neurochemistry, in excitatory and inhibitory. Excitatory interneurons, expressing the vesicular glutamate transporter type 2 (VGLUT2) [45, 46], are a heterogeneous group of neurons under the control of different transcription factors [47], determining different subpopulations based on the expression of, for instance, protein kinase C gamma (*PKCγ*) [48], μ-opioid receptor (MOR) [49–51], neurotensin [52], somatostatin [53], and neurokinin B [54]. In contrast, inhibitory interneurons utilize GABA and/or glycine as principal neurotransmitters [55]. Inhibitory interneurons can also be divided into subpopulations expressing NPY, galanin, parvalbumin, or neuronal nitric oxide synthase [56].

Altogether, interneurons, projection neurons, and central nerve endings of nociceptive neurons, tightly regulated by descending projections (to be described later), process and retransmit nociceptive inputs toward higher levels of the brain.

## The Gate Theory

Before addressing the next step in pain stimuli transmission, it is important to address the gate theory, proposed in 1965 by Ronald Melzack and Patrick Wall, as a mechanism controlling the flow of nociceptive information at the spinal cord level. The theory proposed that innocuous stimuli "blocked" the flow of nociceptive information, preventing its access to upper levels of conscious processing. Thus, it explained how innocuous sensations such as touch or pressure, transmitted by thick Aβ myelinated fibers, could block pain transmitted by thin, unmyelinated C-fibers, in an injured part of the body. Such effect was thought to take place through stimulation of axons conducting tactile and pressure stimuli and suggested interference mechanisms in the transmission of pain (and thus justifying the idea of a gate) [57]. While this theory was extremely influential on advancing pain research, it soon became obvious that pain regulation is a lot more complex than a simple balance between the activities of Aβ- and C-fibers [58]. However, its impact is still held as seminal for the development of modern pain research.

## Ascending Nociceptive Pathways and Descending Pain Modulation

Once received, modulated, and "re-elaborated," the still unconscious nociceptive information, either normal or pathological, "departs" the spinal cord by way of a number of ascending fiber systems: the spinothalamic, spinoreticular, spinomesencephalic, and spinohypothalamic pathways [59].

The spinothalamic pathway, the most voluminous, is formed by projection neurons whose axons cross the midline in their way toward the ventroposterolateral nucleus of the thalamus. The electrical stimulation of the spinothalamic nucleus produces pain, and its sectioning results in a marked reduction in the perception of pain, in both cases, opposite to the injury (due to the midline crossing).

The spinoreticular pathway is formed by fibers produced by projection fibers in the spinal cord that ascend and terminate in the reticular formation in the brainstem. Most of these fibers do not cross the midline.

The spinomesencephalic pathway comprises fibers produced by spinal projection neurons terminating in the reticular formation, but most especially in the periaqueductal gray, a very important mesencephalic area involved in pain regulation. In fact, early experiments in rodents showed that stimulation of the periaqueductal gray results in profound analgesia and prevention of the aversive reflex due to a pain stimulus [16], without compromising the sensitivity to touch, pressure, and temperature [60–62]. Importantly, morphine and other opioid-like drugs have the same effect on the periaqueductal gray. However, it was soon understood that the effect is indirect and involves several relay stations. Thus, the opioid-dependent activation of periaqueductal gray neurons projecting to the nucleus raphe magnus or several pontine nucleuses including the locus coeruleus results in activation of serotoninergic [63] and noradrenergic [62] neurons that in turn project toward the dorsal horn of the spinal cord, determining what is called descending pain modulation (and being the basis for the placebo effect to be described later). Serotonin and noradrenaline release from this descending input acts by blocking the activity of the synaptic contacts of afferent nerve endings onto projection neurons. As expected, noradrenergic and serotoninergic receptors are heavily represented in the dorsal horn of the spinal cord [62]. Finally, this pathway is also very relevant because it connects, through alternate relays, with the limbic system, the area in the brain involved in the processing of emotions. It is precisely this pathway that is thought to provide, at least in part, the affective component to pain perception.

Finally, the spinohypothalamic pathway is in charge of transmitting painful information from the spinal cord toward the hypothalamus. This is an important connection, relaying nociceptive information to the autonomic nervous system, ultimately responsible for the vegetative responses commonly observed during painful events such as, for example, cardiovascular responses.

## The Thalamus

The thalamus acts as the gateway to cortical-bound somatosensory information [64]. Most nociceptive information targets specific thalamic nuclei, among them the ventral posterior (VP), posterior (PO), intralaminar (IL), medial dorsal (MD), and midline nuclei [65–68]. Terminations from spinothalamic (direct nociceptive) or spinoreticular, spinomesencephalic, and medial lemniscus (indirect nociceptive) pathways target specific nuclei, also showing a certain degree of somatotopy (see [64]).

Pain consistently elicits the activation of the thalamus, as shown using functional imaging analysis [69] and electrophysiological recording of thalamic activity in a variety of animals, including rodents and monkeys (see [70]). Its involvement in pain transmission has also been confirmed by analysis of the effect of experimental injury and deep stimulation (see [64]). In particular, vascular alterations in the thalamus have exposed the importance of the thalamus in pain processing, in what is called the thalamic syndrome, characterized by ongoing burning pain, mechanical and thermal allodynia, and hyperalgesia [71–75].

Recent work also suggests that the lateral thalamus is “the” brain region “transmitting or sharing pain magnitude with the rest of the brain” [76] and in agreement with a more than a 100-year-old assertion by Head and Holmes [77] that the thalamus is “the” brain region specific for pain representation and not the neocortex. Thus, the lateral thalamus projects to nonspecific cortical regions, conveying nociceptive information toward areas

associated either with the processing of the sensory dimension of pain (intensity, duration, localization) or its experiential, cognitive, and emotional nature (see [64, 76]). Moreover, magnitude of chronic pain has been associated to enhanced activity in subcortical structures such as the thalamus and the basal ganglia, in contrast to lack of relation with cortical areas activity [76].

### The Cerebral Cortex

Initially, it was thought that the cerebral cortex had no relevant role in the processing of pain. In fact, for a very long time, it was virtually impossible to establish a "primary pain cortical area" [78]. Such a conclusion was based on the seminal work by Penfield and Faulk [79], who after analysis of electrical stimulation to various regions of the human cortex in awake patients, including the occipital, parietal, frontal, temporal, insular areas, and several regions in the inner face of the hemisphere, were unable to elicit painful sensations [78]. Subsequent work by the Mauguière group [78] showed that even though a pain response occurs very rarely after intracortical stimulation, painful somatic sensations are obtained in about 1.4% of all stimulated cortical sites and exclusively concentrated in the medial part of the secondary somatosensory (SII) cortex or in the posterior and upper part of the insular cortex. However, a very recent analysis of local field potentials in the human posterior insula in participants stimulated with nociceptive, vibrotactile, auditory, or visual stimuli showed posterior insula cortical activity that could not be distinguised among each stimulation protocol [80]. Thus, a primary cortical area responding to specific pain inputs and where focal stimulation evoked pain remains missing and may even be inexistent.

## The Higher Processing of Pain

### The Pain Matrix

So, if no particular area in the brain appears to act as a primary pain region, how is pain processed in its whole dimension? An early categorization of pain as an experience by Melzack and Casey [81] discriminated between three dimensions: sensory-discriminative, cognitive-evaluative, and motivational-affective. Almost intuitively, one can understand that these three dimensions cannot only involve one but many cortical and subcortical areas. The core of such understanding materialized in what has been called the "pain matrix," understood as a group of brain structures activated by nociceptive stimuli. With the advancement of technology and the availability of functional imaging studies, the pain matrix begun to emerge as composed of several cortical regions that include the insula, the SII, the anterior and mid-cingulate cortex, the primary somatosensory area, the anterior frontal and posterior parietal cortices, and the supplementary motor area [82–84]. This matrix is thought to act as a network integrating "several pain-associated functions such as pain intensity coding, pain localization, emotional and vegetative reaction, and motor withdrawal from a painful stimulus" [78].

The description of a pain matrix represented a very important conceptual advance that moved away from the concepts of pain-related emotions and cognitive phenomena as reactions, to become components of pain. Such conceptualization also debunked the idea of a "brain pain center." It also reduced the impact of sensory inputs as the only sources of pain [85]. However, what is the pain experience? In trying to answer this question, three orders of processing have been established: (1) nociceptive cortical matrix, (2) perceptual matrix, and (3) from perception to memory of pain matrix [85].

The nociceptive cortical matrix, including the posterior insula, the medial parietal operculum, and the mid-cingulate cortex, is targeted by the ventral posterior, centrolateral, mediodorsal, and posterior group nuclei of the thalamus, which in turn receive inputs from laminae I, V, and VII in the primate dorsal horn (see [85]). Thus, stimulation of the posterior insula and the inner operculum in the human brain triggers acute pain [86, 87], and their injury results in neuropathic pain (see [88, 89]). In addition, "full pain experiences" are reported when stimulating thalamic areas

projecting to the abovementioned areas [90]. However, and despite their clear involvement in nociceptive information processing, the matrix described so far does not provide the conscious dimension to human pain, since its activation persists during sleep, coma, and vegetative states (see [88, 89]). Therefore, a second level of cortical cooperation appeared as necessary to bring pain to consciousness: the perceptual matrix.

The perceptual matrix involves the following areas: the mid- and anterior insulae, the anterior cingulate, the prefrontal and posterior parietal areas, the striatum, the supplementary motor area, the hippocampus, the cerebellum, and the temporoparietal junction. None of these areas receive direct thalamocortical inputs, direct stimulation does not evoke pain, selective destruction does not induce analgesia, they are also activated by other non-pain stimuli, and their contribution to the pain matrix goes from nothing to all, depending on the context in which noxious stimuli are applied [85]. The mid and anterior insulae are constant participants of the pain matrix, and it is suggested that the flow of sensorimotor nociceptive information between these areas participates in their transformation into vegetative reactions and associated internal feelings [91–93]. In contrast, the anterior cingulate, in association with the prefrontal and parietal posterior areas, seems associated to sustain attentional and evaluative processes of anticipation, learning, and cognitive control. Activity in this second-order pain matrix seems to provide top-down modulation of nociceptive inputs (see [85]). More importantly, it is at this level that painful sensations become conscious, after the nociceptive input has been shared in a broader sense [94, 95]. In other words, painful sensations become known to the person when parietal temporal and prefrontal cortices are involved. This is not surprising, since the manifestation of pain often requires some form of declaration, for which the frontoparietal network is essential [96].

A third level in the pain matrix relates to the conversion of pain sensations into memories of pain. Here the perigenual cingulated cortex, the orbitofrontal cortex, the temporal lobe, and the anterolateral prefrontal cortex appear to take a leading role, as suggested by their activation when observing other's suffering and the consequential subjective enhancement [97–99] or their activation during pain-relieving situations such as placebo, self-control, or strong religious beliefs (see [85]).

Altogether, three processing levels of pain would compose the pain matrix: nociceptive, perceptive-attentional, and reappraisal-emotional [85], not too dissimilar to the sensory-discriminative, cognitive-evaluative, and motivational-affective categories described by Melzack and Casey [81]. The nociceptive matrix, involving regions receiving spinothalamic input, process the somatic-specific quality of the sensation. Joint activation of the perceptive-attentional matrix triggers the activity of the parietal, frontal, and anterior insular circuits and facilitating conscious perception, modulation by vegetative reactions, and internal feelings by way of anterior insular networks, attentional modulation of sensory gain, and access of nociceptive information to declarative consciousness. Finally, reappraisal as a function of affective states and previous memories by modulation at higher-order networks provides pain its subjective quality and establish its long-term memory storage. It is important to mention that these different activities and activated regions do not work independently or in sequence, but provide the perception of pain its quality of active process, "continuously reconstructing itself by integration of sensory inputs with ongoing memories and internal representations" (see [85], and references therein).

## The Humanistic Perspective of Pain

Oscar Wilde may have once said, "I don't mind pain, so long as it doesn't hurt" [100]. To hurt, especially after long periods of times, leads to suffering, and "it is suffering, not pain, that brings patients into doctors' offices. Suffering is an emergent property of the human brain and is dependent upon consciousness" [101]. Beyond all the complex neuronal circuits and relay stations briefly described above (most of which we are now beginning to unravel and understand),

nociception is only an event leading to a much higher outcome, an outcome that can even be influenced by emotions experience and social interaction. Moreover, it is clear that pain is subjective, only fully attainable to the person that is suffering it, with self-report being the most accurate way of access [1]. Such a realization has led to the fair question, "is there a purely biological core to pain experience?" [1]. How can a sensorimotor function like pain, especially when chronic, acquire such profound features leading to suffering and yet be only dependent on neuronal outcome? In truth, this is not yet known. However, efforts are and have been made to understand the neurobiological mechanisms behind such occurrence.

In the following sections, we will address the complexity of pain, with origins in an objective event (nociception) although with private or public manifestations typical of a subjective experience, all rooted in the fascinating neurobiology that resides in the human brain, but with features that appear as emergent and not always easy to reduce to mere neuronal function.

## The Pain We Need or "Good" Pain

Pain is an experience, an essential warning mechanism, that we need to survive [102, 103]. To evade an injury and the suffering that the injury produces or to eliminate them quickly is typical and a normal behavior pattern in any of us. Moreover, all our daily behavior is guided by this principle because we consider, in the depths of our being, that we have the right to a life free from pain. However, we should not confuse this with the puerile illusion of achieving an ideal theoretical state in which we could be totally insensitive to all forms of pain. This aspect is fundamental to understand the value of pain and its protective function, essential for our existence. One thing is to go through our lives trying to diminish or to avoid stimuli that generate pain and another, to go through life not fearing pain due to not knowing what it is, its significance, or how it feels. The punitive experience of pain does not occur in the latter case, but neither does learning.

Two rather dramatic scenarios can serve to exemplify the importance of pain. One is a congenital genetic disease leading to insensitivity to pain, characterized from birth by a variety of sensory deficiencies including the inability to perceive pain or temperature. Although it is a disease that is not directly fatal, the life expectancy of sufferers is less than 25 years, mainly as a result of traumatic injuries with infections that are not adequately treated. The lack of pain is one of the reasons why these injuries are not valued in their real dimension and are not put in perspective of their danger to life. Another condition that includes among its symptomatology insensitivity to pain, in varying degrees, is leprosy. A challenge in the case of lepers with neuropathies in the limbs is trying to restore the ability to perceive pain, which although difficult to achieve is not impossible. What is surprising with this treatment is that even when physical pain has been restored, its persistence and unpleasantness has not. This has led Paul Brand (1914–2003), one of the drivers of this therapy in leprosy, to make the following statement "pain is the most valuable sensation we have. Never minimize its value. Never suppress pain unless we know the cause and we can treat the root of the problem. We must work with painful sensations, not against them. Pain is the way cells speak to us, we have to listen and obey… one must take special care of those who suffer without pain" [104].

The fight against pain is today in full development in the world at many levels, particularly scientific and medical. This statement makes us think about whether all the paraphernalia of treatments that are currently in fashion and development are not leading us toward a risky situation where we ignore the alarm signals that our organism relies on, for example, headaches or joint pain.

## The Pain That We Do Not Need or "Bad" Pain

After supporting that pain is advantageous, it should be made clear that this is true for what we call normal pain or "good pain" but it is not true

on a great number of occasions where there is abnormal pain or "pathological pain."

Just as the total absence of pain is not good, nor is its excessive persistence, something which affects countless people. Therefore, when the intensity and quality of the pain ceases to be directly related to an apparent injury to the body and this pain persists beyond 3 months, the pain is pathologic and chronic [105]. This is also true for pain that is described as vague or in unusual terms such as "electric" and for pain that is triggered by a mild stimulus such as a gentle caress.

Chronic pain affects 20–30% of the world's population [106], and recent epidemiological studies show that the incidence of pain is very high, even when it is compared with other important diseases such as diabetes, cancer, or heart disease [107].

For the purpose of the present chapter, we will focus on neuropathic pain, one form of chronic pain caused by direct injury or disease of the somatosensory system [108–111]. Patients suffering neuropathic pain present a variety of sensory disturbances, including symptoms such as allodynia (pain induced by normally innocuous mechanical or thermal stimuli) or hyperalgesia (exaggerated pain responses resulting from normally noxious stimuli) [112, 113] and stabbing, burning, or electric shock sensations [113, 114]. In addition, patients experience a progressive decay in health and quality of life, severe depression, and sleep and appetite disturbances [115–117], all leading to altered interpersonal relationships, reduced productivity, important expenses for the patient and its family, as well as translating onto the public health system [117–122].

At the core of the events ultimately leading to neuropathic pain is the concept of neuronal plasticity. Not long ago, the brain was still thought as a static structure, that once developed, would only suffer degenerative changes during aging. However, in the last decades, this idea changed, in view of abundant evidence suggesting that the nervous system changes, new neurons are born, and the structure of neuronal interconnections changes due to experience, learning, and also sickness. Neuronal plasticity is in fact fundamental, for instance, in our capacity to learn or modify our behavior. This plasticity is very intense during childhood and in young adults but still persists in adulthood. Moreover, its persistence during adulthood has been associated to recovery of motor function after, for example, peripheral nerve injury.

Pain conditions such as neuropathic pain due to traumatic injury of peripheral nerves are perfect examples of plasticity. In fact, it has long been recognized that nociceptive neurons react dramatically to injury of their peripheral axons. As mentioned before, nociceptive neurons are the primary relay neuron transferring information from peripheral tissues to the spinal cord. These neurons can be subdivided, among others, by their content of neuropeptides into peptidergic and non-peptidergic. Peptidergic neurons synthesize peptides such as SP or calcitonin gene-related peptide (CGRP) and transport them toward their terminals for their release. During a peripheral nerve injury, severing of the peripheral projections of nociceptive neurons induces a profound alteration in the synthesis of several markers, including neuropeptides [123]. For instance, in normal conditions, nociceptive neurons express considerable amounts of CGRP and SP and virtually undetectable levels of two other neuropeptides, galanin and NPY. However, after injury of peripheral nerves, a dramatic downregulation of CGRP and SP [18] and upregulation of galanin and NPY are observed in DRG neurons. Such phenomenon is not limited to neuropeptides, and it has been demonstrated for a variety of other neurotransmitters and neurotransmitter receptors, both in ganglionic nociceptive neurons and in the spinal cord.

In a similar fashion, descending fibers may also experience plastic changes after injury, potentially altering the mechanisms of inhibitory modulation by endogenous peptides. Finally, comparison of whole-brain functional connectivity between healthy subjects and patients with chronic pain (low back pain or osteoarthritis) has exposed functional plasticity also in the brain. Thus, decreased functional connectivity between the lateral "nociceptive" thalamus and multiple cortical regions involved in the processing of beliefs, recall, episodic

memory, and calculation was seen in patients with chronic pain, in direct correlation with the magnitude of the pain. Interestingly, the above-mentioned cortical areas appear to be "important for evaluating internal states, processing of memories and performing cognitive tasks" [76].

## Pain and Suffering

The association between pain and suffering seems very obvious. In fact, the two terms are often used indiscriminately, as if they were synonymous. However, suffering refers to the emotional consequence of physical pain. It is a feeling of vulnerability, abandonment, and loneliness in pain which can lead to a loss of meaning and purpose in life. Suffering can reach very deep levels in which the person is challenged with their identity, self-esteem, and integrity as an individual, which can in some ways affect their future abilities. Suffering can lead to disruption of the person's relationships and cause occupational problems that affect economic stability. It can affect many variables associated with the perception and impact pain can have in a person's life. Altogether, even though suffering emerges from pain, it is not related to the nociceptive phenomenon, but to the subjective aspect of the pain process.

## Pain and Mental Structure

One of the pioneers in the multidimensional treatment of pain, John Bonica (1917–1994), set up the first interdisciplinary pain treatment clinics to treat war veterans in the United States. In one of his many works in the mid-twentieth century, he states, "The crucial role of psychological and environmental factors in causing pain in a significant number of patients only recently received attention. As a consequence, there has emerged a sketch plan of pain apparatus with its receptors, conducting fibers, and its standard function which is to be applicable to all circumstances. But... in doing so, medicine has overlooked the fact that the activity of this apparatus is subject to the constantly changing influence of the mind" [124].

There are numerous anthropological and psychological studies that show that the intensity of pain is not simply the result of the extent of an injury in a given area in the organism. Rather, the amount, duration, and type of pain, the relation to previous experiences and how they are remembered, as well as the ability to understand the consequences of an injury beyond pain itself. Even the culture in which we develop and the education we receive can play an important role in how we feel and respond to a particular pain. Thus, the study of pain also involves the analysis of the enormous plasticity of the nervous system and the psychological differences between individuals that can make each of us respond differently to the same stimuli.

Cultural values also significantly affect the way that a person perceives or responds to pain. One of the most striking examples of this is the ceremony that still takes place in some parts of India where a person is hung from hooks nailed to the skin [125]. The ceremony derives from an ancient practice whereby an elected member of the community, the "celebrant," is suspended from metal hooks nailed on the skin of their backs, in order to bless the children of that community and those of neighboring communities and also to give thanks for the food of a particular period of the year. What is surprising is that the people thus suspended and freely swinging over the crowds show no signs of pain but find themselves in a certain state of ecstasy. There are many reports that relate similar experiences, such as operations without anesthesia and individuals being able to walk on hot coals that have been filmed and actually cause more of an impact in the observer than on those individuals participating in the ritual or show. There is no reason to suppose that these people are different in any way. Quite the contrary, their culture, the expectation of being cured of an eventual chronic pain, confidence in healers, desire to go without anesthesia, as well as other psychological factors seem to be the reason for this lack of perception of pain.

When the physical evidence is unsupportive, and the explanations given to patients and the treatments that are administered do not give the expected results, it is not uncommon to appeal to psychological causes as an explanation. However, the role of psychological factors that may determine pain requires proper identification and not just be the consequence of failure to identify physical explanations. In summary, it is important to take into account concomitant factors, both psychic and physical, to understand and treat the pain that a patient refers. The personality of the patient must also be considered, although thus far there are no references of objective studies that have reliably demonstrated this influence. However, there is no doubt that there are a lot of differences between individuals, and it is not original to state that there are people who are more apprehensive or fearful than others or are simply hypochondriac, manifesting, or respond in a different way to pain.

Finally, in current times, the concept of psychological pain, and its comparison with physical pain, has gained interest in the scientific community. Psychological pain refers to "a lasting, unsustainable, and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self" [126]. Psychological pain is a lasting feeling that takes time to resolve and can result from a variety of situations that include the inability to protect oneself from injury or disease, or as a consequence of lost autonomy due to a pervasive illness [127]. Interestingly, chronic pain often features such situations suggesting a correlation between the two types of pain. In support, there appears to be a certain overlap in some cortical and subcortical areas involved in physical (insula, anterior cingulate cortex, prefrontal cortex, thalamus, primary and SII [83, 128]) and psychological pain (especially the insula, the anterior cingulate cortex, the prefrontal cortex, and the thalamus). Other more secondary areas showing some overlapping activity are the cerebellum, the basal ganglia (putamen, caudate), and the posterior cingulate cortex [127]. In particular for the later, its activation was ascribed an appraisal role, also present in the higher hierarchical processing of physical pain (see [85]) that seems to be fundamental for psychological pain (see [127]). Altogether, it should be kept in mind that physical chronic pain and psychological pain can coexist, with consequences such as depression.

## Emotions and Pain

As already established, pain is not only a sensory experience but is also unpleasant and therefore an emotional experience. The affective issues linked to pain include a variety of emotions, often negative. When pain is chronic, it is often associated with depression and anxiety. Anger is one further emotional manifestation in chronic pain patients [129].

In fact, research suggests a relatively constant relationship between chronic pain and depression. In the majority of cases, depression seems to be a consequence of the patients' strenuous struggle to get out of their situation. Interestingly, unlike what might be expected, the severity of pain does not seem to be directly related to the existence of depression [76]. On the contrary, depression has more to do with cognitive aspects and the patients' appreciation of their condition. However, the question remains, how is it that not all patients with chronic pain undergo depression? The truth is that no matter what the cause of depression is, both pain and depression itself require special attention. On the other hand, the fear of not being able to avoid painful experiences is crucial in triggering anxiety. Different researchers have found a direct association between fear of pain and a dysfunctional way of coping [130, 131]. For example, often muscle hyper-reactivity causes postural problems with the intention of reducing pain.

Anger is also common in the lives of people with chronic pain; the greater the pain, the greater the anger. Anger begins at frustration generated by the persistence of pain, the unknown cause of pain and the search and failure of traditional or alternative treatments. Such anger is also transferred to employers, family members, and caregivers, who also become impatient, leading to a vicious circle of anxiety, depression, and anger.

Interestingly, while anxiety and anger, both negative aversive responses to pain, serve a protective function, motivating the person to escape actual or imminent threat has a counterpart called "positive affect," which are pleasant feeling states ranging from contentment to intense states of joy and bliss [132]. Positive affect has to be distinguished from both optimism, which is a cognitive style that is more stable and personality-driven than the moods and emotions typical of positive affect [133], and resilience, the maintenance or recovery of a healthly functioning during periods of physical, psychological, or social adversity [134].

Several studies support that positive affect attenuates both the perception of pain and the negative affective response to pain. In contrast, the absence of positive affect exposes vulnerable patients to poor pain-related outcomes (see [132]). Based on this fact, Finan and Garland [132] have proposed a spiral of positive affect, resilience, and pain self-management that includes mindfulness, broadened attention, positive stimuli, positive emotion and affect, positive reappraisal, and adaptive and prosocial coping.

Resilience-based positive affects have also become the focus of attention for the treatment of chronic pain. Thus, it has been shown that chronic pain patients with high self-reported perception of being able to recover or sustain function following adversity dampened pain catastrophizing levels by upregulating positive emotions [135]. Interestingly, this resilience-based effect appears not necessarily to alter measures of pain severity, but to contribute to chronic pain adaptation (see [136]). This type of analysis has led to the development of so-called positive activity interventions: "those that are primarily aimed at raising positive feelings, positive cognitions or positive behavior, as opposed to interventions aiming to reduce symptoms, problems or disorders" [137].

Finally, compassion also emerges as an additional component in pain modulation. Compassion is defined as "a sensitivity to the suffering of self and others, with deep commitment to alleviate it" [138]. Self-compassion in particular is receiving attention, as a strategy that may counteract some of the negative consequences of persistent pain, such as social discrediting interactions where patients may be ignored, embarrassed, or humiliated [139], or internal feelings such as fears of being disbelieved or considered unproductive or a burden [140]. All these situations lead to a reappraisal of the self, described as "self with pain" [140], where patients with chronic pain blame, condemn, and criticize themselves. In such context, self-compassion reappraises the difficulty through comforting/soothing internal dialogue, improving the affect regulation and promoting the development of adaptive coping strategies [131]. Importantly, self-compassion appears to associate with greater pain acceptance and positive affect and lower levels of depression, anxiety, stress, and catastrophizing [141, 142], without influencing the unpleasantness of intensity of pain perception [142].

## Cognition, Expectation, and the Perception of Chronic Pain

Following numerous observations in patients, today the predominant idea is that the way that people are able to deal with pain, the way they value it, can have a significant effect on their perception of pain and more importantly how they tolerate it.

As mentioned above, the private experience of pain can be modulated by internal states and emotions. This is also the case for expectations, which have been thoroughly addressed through analysis of three different situations: placebo analgesia, nocebo hyperalgesia, and stimulus expectancies [143]. The placebo effect, for example, that has been linked to the endogenous opioid system is understood as pain reduction due to expectation that a treatment will produce pain relief, even when the treatment in itself is inert [144]. Interestingly, not every person responds in the same manner (or even at all) to placebo, which has promoted the search for "biomarkers" (e.g., molecular, psychological) to identify placebo responders (see [143]).

Expectations not only result in behavioral effects but have also been shown to result in

neurobiological changes [143]. In fact, brain regions coding for pain intensity (insula, thalamus, and anterior cingulate) show reduced activity in patients enrolled in placebo effect experiments [145, 146]. Moreover, it appears that placebo analgesia already acts at the spinal cord level, modifying the ascent of painful information through modulation by descending input to the cord (see [147–149]).

What is interesting about placebo effects in pain modulation is that the activated areas such as insula, cingulate cortex, and thalamus are not necessarily specific to pain perception and can also be activated by interoception, conflict, and negative affect among others [150]. Conversely, placebo effects are only occasionally found in areas specific to pain such as the dorsal posterior insula and the secondary somatosensory cortex [151, 152] and also involve the dorsolateral prefrontal cortex and orbitofrontal cortex [145], areas associated with cognitive control and expected value computation [143].

Finally, pain is not only felt but also expressed. Therefore, pain is subject to social influences surrounding the person that experiences it. In fact, pain is modulated by the presence of others and their offering or withdrawal of assistance. It is here where pain is not any longer a private, subjective experience, but a social one[153]. On the other hand, pain cannot be understood as a single conscious sensorimotor "event" but as part of an ongoing, subjective, and complex experience [1]. In fact, it is this characteristic of pain that facilitates the conscious experience of pain and the advantage of letting other experiences and actions to modulate pain. In this way, the consciousness of pain allows for other conscious experiential interactions that are key to survival and success [154].

## Conclusions

As we, authors and readers, can now envisage, pain is more than a complex set of neurobiological processes. It is indeed an experience without which human life would not be complete. In this sense nothing has changed, to our knowledge, since human beings reached that stage in evolution. It is also an experience that, when transforming itself into a persistent ailment challenges us with suffering, an outcome far more complicated to understand and also to solve. Perhaps the best way to perceive the truthness of this statement is to go through narratives referring to the experience of pain and suffering as transmitted by two persons living in different times. We have chosen the case of Alphonse Daudet (1840–1897) and that of the recently deceased Henning Mankell (1948–2015).

Alphonse Daudet was a writer who died of syphilis in 1897. In the process of his disease, he wrote *In the Land of Pain* which has become an example of interesting notes on pain from underground. They include a narrative of his treatments (in which the author is hung in the air by the jaw and injected with a solution extracted from guinea pigs), ruminations on fear and fraud, and sharp observations of the healthy. But much of the book, and the book's force, lies in the patient's flailing search for a language to match his suffering. "Tonight, pain in the form of an impish little bird hopping hither and thither," he wrote: "The only part of me that's alive is my pain." It is appealing to recall the words of Julian Barnes, the translator of Daudet's book (2016) [155] when he states "How is it best to write about illness, and dying, and death? … pain is normally the enemy of descriptive powers. When it became his turn to suffer, Daudet discovered that pain, like passion, drives out language. Words come 'only when things have calmed down. They refer only to memory, and are either powerless or untruthful' [155]. The prospect of dying may, or may not, concentrate the mind and encourage a final truthness; may or may not include the useful *aide-mémoire* of your life passing before your eyes; but it is unlikely to make you a better writer. Modest or jaunty, wise or vainglorious, literary or journalistic, you will write no better, no worse. …" [155].

Daudet's text is organized with a certain perceptible plot progression, and it has the advantage of summarizing a decade of suffering in a few thoughtful pages. Painful as it is to read, this writing confronts people living in their own land of pain. However, in the end it

seems that it is impossible to describe pain; in Daudet's notes, pain is rendered in scribbles of desperation and despair.

Henning Mankell is the Swedish author best known for writing the *Wallander* crime novels, when he was 67 [156]. In January 2014, Mankell revealed that he had been diagnosed with cancer after going to see an orthopedic surgeon for what he assumed was a slipped disk [156]. However, tests revealed he had a tumor in his lungs and neck. "It was a catastrophe for me," he told US radio station NPR. "Everything that was normal to me up to that point was gone all of a sudden. No one had died of cancer in my family. I had always assumed I'd die of something else." All this process led Mankell to write *Quicksands*, a series of notes about his life, remembrances, and particular episodes. However, he started with his disease, where the message has to do with time, time running out. Perhaps single moments as that of his diagnosis, where life can take a sudden new direction [156].

In Mankell's Web page [156], he states, "It is now two months since I was diagnosed with cancer. I am already well into the second series of chemotherapy treatment. Thus far I have been spared any noticeable side-effects. The fact that a battle is taking place inside my body is more of a vague suspicion than a definite feeling. I have many reasons to be grateful. That is a thought that occurs to me every morning when I wake up. The efforts made by the staff at the Sahlgrenska Hospital in Gothenburg could hardly have been greater, quicker or more efficient. But of course nobody – neither I nor the doctors treating me – know what my state of health really is. How effective the cytotoxins really are. In a few weeks' time, various checks will reveal more about that. Until then, all I can do is to hope for the best … There are so many people who are desperately lonely with their cancer. Who have hardly anyone with whom they can share their torments, nobody to discuss their worries with, the angst, the panic that so often looms large during the nights … The loneliness that has been allowed to spread over the last 50 years and become almost the norm is casting us ever deeper into a society that is basically inhuman. One in which solidarity and brotherly love has become the exception … When all is said and done, the way we see others is always the way we see ourselves. No one should be alone with his or her cancer, their hopes and their fears." While the word pain is not mentioned a single time, the suffering caused by Mankell's condition is palpable, not at all dissimilar to what a patient undergoing chronic pain may tell us about nowadays.

Two different authors with exquisite capacities for vital narrative and more than a century apart; two different diseases, and in the end, the same difficulty to capture the right words to accurately describe pain and suffering, but with the same need for a more humane approach to the problem of chronic pain.

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# Self-Lie Detection: New Challenges for Moral Neuroenhancement

4

Luis E. Echarte

## An Overview on Lie Detection

According to the Oxford English Dictionary, lying is "to make a false statement with the intention to deceive" [1]. It is just one of the many ways of deception, because the act of deceiving may be not intentional [2]. This is the case of someone that unwillingly deceives other people by forgetting part of the information provided. A desert traveler may be deceived by a mirage too. However, it should be acknowledged that today there is not a general agreement about the distinction between lie and deception. For example, Timothy R. Levine defines deception as a term that refers to "intentionally, knowingly, and/or purposely misleading another person" [3]. In this paper, both terms will be used in its traditional sense, i.e., "a lie is a statement made by one who does not believe it with the intention that someone else shall be led to believe it" [4].

Then, what is a lie detector? Broadly speaking, it is a method or instrument that facilitates the objectification of lies. The most ancient and widespread precedents are those in which the liar was implicitly or explicitly forced to confess inner thoughts: from inflicting torture to intoxicating with liquors, some type of psychotropics – as LSD or sodium pentothal – or even with that captivating but partisan love of spy novels. Nevertheless, besides the ethical issues, it is well known that these indirect techniques are not totally reliable because they do not only strip or uninhibit but also alter the perception of reality or even liar's will. Confessions are there compromised by suspicion of false positives [5].

A better way to uncover the truth is using non-testimony-based methods: looking for bodily signals that reflect the presence of lies in a statement. Of course, this presence may be detected in different ways. For example, we can look for the inner tension that a lie causes in the liar.

One of the oldest documents talking about such signs is the *Mitákshara Shástra*, a 900 B.C. papyrus Vedas: "A person who gives poison may be recognized. He does not answer questions, or they are evasive answers; he speaks nonsense, rubs the great toe along the ground, and shivers; his face is discolored; he rubs the roots of the hair with his fingers" [6].

It was only far later that, besides external signs as sweat, tremor, or bizarre behavior, internal evidences began to be taken into account. In the eighteenth century, for example, irregular heartbeat was interpreted by many physicians as

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indicator of lies and under the assumption that pulse rate is connected with emotional distress, which in turn is linked to deliberate sustaining of falsehoods [7]. In the following century, thanks to the invention of plethysmograph by Angelo Mosso, the center of concern was moved to blood pressure which, as he demonstrated, was closely associated with the emotion of fear. Mosso is also considered the first physiologist who was able to create a neuroimaging technique: the first to link the mental activity with blood flow increases to the central nervous system and measure it [8].

However, brain approach to the study of lies was eclipsed, nearly the entire twentieth century by the polygraph: a device capable of recording and combining skin conductivity, pulse, and blood pressure during questioning. It was invented in 1921 by John Augustus Larson and later developed by Leonarde Keeler, both in Berkeley, California. Polygraph use among the law enforcement was almost immediate in USA and then the rest of the world, although always with controversy. The most important objection is again related to the contamination of the sample. For example, an interrogation may elicit in guiltless individuals' amplified body responses – i.e., because of the anxiety for a false detection or of the horror of crime for which he has been charged [9–11]. Conversely, for the reasons I will later explain in the next paragraph, some real criminals may not respond in an incriminating manner to the police queries. It is for this reason that, in our days, there is a high variability of polygraph's acceptance in courts.

In the past few years, and thanks to the new neuroimage analysis methods, like functional MRI-based lie detection, the government and public confidence in such devices' results was found to have increased: examples include national security, job recruitment procedures, and divorce disputes [12]. A unique feature of these new techniques is that we could theoretically use them to detect not only signs of psychological inner tension but also to notice the presence of neural functions in charge of producing and monitoring lies. In resume, nowadays Mosso's perspective about the study of mental activity has been rehabilitated and, what is most important, improved to provide us with the most conceivable direct method for the analysis of lies.

## Differences Between Voluntary and Conscious Lies

The cognitive approach of lying is based on the study of the mental process linked to liar's behavior. Two lie detection approaches are mainly considered among scholars. In the traditional one, it is assumed that lying is more cognitively demanding than truth telling [13, 14]. Lying "requires more complex, novel, or memory-dependent responding; deception imposes more concurrent cognitive tasks than truth telling; and deceivers monitor the behaviors of the self and others in a more vigilant fashion than truth-tellers" [15]. Police usually manage this hypothesis in criminal interrogations to distinguish credible and non-credible stories too.

In the second approach is defended that not necessarily all lie is associated with high levels of cognitive load. For example, according to Aldert Vrij, Ronald Fisher, Samantha Mann, and Sharon Leal's paper, six conditions determine the amount of loan. "First, formulating the lie itself may be cognitively taxing. Second, people are typically less likely to take their credibility for granted when they lie than when they tell the truth […] Third, because people do not take credibility for granted when they lie, they may monitor the interviewer's reactions more carefully in order to assess whether they are getting away with their lie […] Fourth, when people lie, they may be preoccupied by the task of reminding themselves to act and role-play, which requires extra cognitive effort. Fifth, people have to suppress the truth when they are lying and this is also cognitively demanding. Finally, whereas activating the truth often happens automatically, activating a lie is more intentional and deliberate, and thus requires mental effort" [16]. Therefore, there are circumstances in which truth telling may require more effort and resources. For example, when liars are not concerned about being believed, they are either motivated to monitor their own behavior or interviewer's reaction. The difficult

memory access to the truthful event would be another example of a lie with low cognitive load.

More radical defenders of the second approach are authors like Jeffrey John Walczyk or Steven Allen McCornack. According to them, on the first hand, lying and truth-telling would share the same processes: memory, problem-solving, and speech production, which could be triggered by different stimuli toward opposite goals. On the second hand, the most common lies have something of truth in it [17, 18].

Finally, but not less important, McCornack claims that some lies (namely, voluntary deceptions) are not preceded by a prior intention-to-deceive mental event (a mental plan or prior intention, in John Searle's words) but by information that acts here as the primary causal antecedent [19]. It is an old question, even though studied extensively by twentieth-century analytical philosophers. For example, for Ludwig Wittgenstein, "When I raise my arm I do not usually try to raise it" (Philosophical Investigations §622). And for the same reason, he writes: "One knows what one was going to say or wanted to say, and yet one does not read it off from some mental process which took place then and which one remembers" (Ibíd §637). In other words, people do not usually have a previous deliberation about what to do, before doing it. Voluntary behavior is not based necessarily in reflective thinking.

At this point, conceptual limits between lies and deceptions must be clarified. The voluntariness of a lie does not imply what is commonly understood as reflective thinking, that is to say, the existence of a previous well-laid plan in which liar have taken enough time to evaluate conscientiously the pros and cons as compared to alternatives. Indeed, some lies are not automatic – not consequence of automatic stereotypical responses – because they are based on cognitive process, i.e., tasks that involve abstraction, memory, inferences, associations, synthesis, etc. However, they may be generated on the fly, very quickly. It explains our tendency to confuse them with those routines over which the environment seems to have more control than do liars. The methods to differentiate both lies and deceptions, using Elizabeth Anscombe's perspective about what intentions are, consist in asking liars about the reasons of their behavior [20] (p. 9). If there is any reason, then lie is voluntary. For example, "I lied to start a war." Certainly, this will only work when the liar gives us a sincere answer. All the same, the point here is not how to detect a lie, but what the differences between lie and deception are.

## Teleological Brain Markers and Cognitive Load

Following last considerations about voluntary or intentional lies, well-planned lies, namely, lies triggered by a prior intention, would be those for which liars are fully conscious of their production, sustaining and monitoring. This sort of voluntary lies is also known as conscious or reflective lies.

One consistent working hypothesis is that conscious lies would require a specific type of cognitive processes: those aimed at analysis and comparison of alternative goals [21]. In other words, in mere *voluntary lies*, liars have some end in view, and all the calculation on the decision-making process is geared towards its achievement. For example: "I want the job. Should I lie?" By comparison, first deliberations around *conscious lies* are not about means but goals. For instance, "why do I want to get the job and at what cost?" Probably, this kind of higher-level cognitive process needs more time and the particular conscious attention of the liar. These would be also the lies that are labeled, in legal language, as done with premeditation and malice. Because conscious lies are attributed to responsible agents, their behaviors are punishable. Conversely, no evidence of planning is usually considered an attenuating circumstance.

Legal perspective introduces us in another controversy: to accept an attenuating factor is not to say that agent's behavior was necessarily irresponsible. It only means that, in that case, there are no evidences about responsibility. Why does agent not stop and think before telling a lie? Maybe, agent has cultivated since many years an

irresponsible lifestyle – what could have been originated by responsible decisions, at least in the beginning. Anyway, these questions remain beyond the reach of the courts and, probably, of lie detectors too.

What kind of or signs or brain markers are associated with conscious lies? First, it would be interesting to look for specific neural pathways involved in processes of goals. Conscious reflection – for example, "to lie or not to lie" – does not imply multiple tasks but about a singular human one: human ability to think about goals and replace natural ones for another new one. In my opinion, and for reasons mentioned above, this kind of specific markers would be more specific than the presence of high levels of cognitive load. For the same reasons, reaction time would not ensure the exclusion of false positives and false negatives either.

However, as Machiavelli wrote, the best is the enemy of the good. Scientists do not yet have the technology and the paradigms to adequately identify this particular neural activity, much less linked to lie production. At this time, we have to be content with the identification of high levels of cognitive load in the context of the six situations defined by Vrij and his team. The classic methodology described in the literature is to detect the increase in cognitive load through the measure of response times: the greater the cognitive load, the longer the response times. This may be reflected not only in the speed of the answers to questions but also in the decrease of the movements of the head, hands, and legs [22, 23].

Vrij's team proposes also an indirect but easier test: "additional cognitive demand is imposed on interviewees to enlarge the observable cognitive differences between lying and truth-telling […] This should result in more pronounced differences between lying and truth-telling in terms of displaying signs of cognitive load – e.g. more stutters and pauses, slower speech, slower response times, less quality details, inconsistencies, fewer movements – when these cognitively demanding interventions are introduced than when such interventions are not introduced" (Ídem). However I must insist, in particular if the hypothesis of teleological process is correct, that some lies could be linked to low levels of cognitive load. This statement would be especially true, as I will explain in the next paragraph, in the case of self-lies.

## Self-Lie Strategies

The phenomena of lying to oneself have received much less attention than the phenomena of lying to others. There are several reasons for this. Three of them are very practical: first, people usually prefer to know about lies than about self-lies. Second, some vitally relevant self-lie often go completely unnoticed to the holder. Unveiling the mystery could have serious and deep consequences. Third, standard lies are more transparent and comprehensible, hence, more easily accessible to lie devices. However, much remains to be done about these easier objects of study to waste time pursing more distant horizons. However, on the basis of the above arguments, this last statement could be called into question. Let us look at this briefly.

According to the traditional perspective, they are more cognitively complex and demanding process than some types of standard lies. The reason for this is because in the latter cases, liars only need to hide *in their mind* the attempt to deceive (the prior intention) and the truth. By contrast, in the context of self-lies, own mind ceases to be a complete refugee. So, these liars need alternative strategies. Some of them have to do with the splitting of the mind, which it may require implicit process and false memories [24]. However, from the fresh new McCornack's perspective, like the rest of lies, self-lies are not necessarily preceded by a reflective plan. They could be the result of a quick rational decision-making, i.e., a voluntary reaction in a situation in which to know the truth could present a disadvantage to individual's plans or to biological or social adaptation. More importantly, liar's reactions could imply the use of strategies in which there is no need to hide the harsh truth in anyway. William von Hippel and Robert Trivers identify five manners: (1) avoiding further information search, (2) making a selective

searching, (3) orienting attention to a certain aspect of the reality, (4) obscuring or biasing interpretation of unwelcome information, and (5) misremembering [25]. In neither of those cases is obligatory to hide a truth nor to create different canals for managing correct information.

Among all strategies on self-lies described just above, misremembering is particularly important. The main obstacle of mere voluntary self-lies has to do with the presence of the rational decision of biasing information. It is often a fast event, hardly noticed by the agent – barely conscious – and therefore it would be easily forgettable. However, it seems likely that some "forgetting" process helps in doing so. To find neural markers of such task may be a step forward in the design of reliable self-lie detectors.

Turning to conscious self-lies, it is clear that the forgetting process has also an important role. However, because reflective thinking involves many tasks and gives semantic and operational content to many plans, believes, and behavior, it is unlikely that only one specific neural function is responsible of erasing every trace of the lie-prior intention. Time has here a fundamental place. Unfortunate, it does not leave a clear footprint. Rationalization and other forms of convincing the self that a lie is a truth are more specific strategies for the construction of conscious self-lies. However, their markers would be also many and very complex to be identified by a machine at the present moment.

Another important strategy for creating self-lies has to do with psychological ability to repress perceptual inputs and representational contents that are very distressing to us. This mind's defense system protects individuals against emotions that they cannot cope. The notion of unconscious mind was founded in Sigmund Freud's postulation of such ability, which is still being studied in most of the present psychoanalytic and non-psychoanalytic psychotherapy schools. The clue here is to notice that such overwhelming events are not blocked or erased in the entire mind but only confined in a nonconscious part of it. In other words, mechanisms of repression, maybe others too, are involved in the division of human mind. But to say all this must not lead us to think that the unconscious is the small stronghold of the mind. It is the opposite, as Freud claims, "The unconscious is the larger circle which includes within itself the smaller circle of the conscious; everything conscious has its preliminary step in the unconscious, whereas the unconscious may stop with this step and still claim full value as a psychic activity. Properly speaking, the unconscious is the real psychic; its inner nature is just as unknown to us as the reality of the external world, and it is just as imperfectly reported to us through the data of consciousness as is the external world through the indications of our sensory organs" [26] (p. 436). In this quote, Freud also outlines a proposal about why a divided mind may be beneficial from the point of view of adapting. For Freud, unconscious is not an impassive pool of memories but a hub of activity where higher-level cognitive process takes place. There, strong emotions do no prevent or distort the effective calculus of the mind, the outcome of which may or may not emerge to the conscious mind one day. This Freudian interpretation of the deep nature of the unconscious mind is not only suggestive but also begins to be supported by neuroscientific evidences [27, 28].

Defense mechanisms, in the Freudian frame, are not controlled by the self (conscious mind) although they serve a purpose: to maintain one's self-schema, i.e., the web of belief about the world in which the subject is installed [29]. However, the external and internal senses are not the only gateways of the disturbing and sieving inputs: conscious mind – reflective thinking – has the power of generating great anxiety and unacceptable impulses. Thus, the bridge between conscious and unconscious mind acts in two directions. Besides, such inhibitory activity may be somehow controlled by the self – in psychology, it is usually called *suppression* [30]. Creating a lie and afterward hiding the intention of lying and the own truth in the unconscious mind would be a good example of this. While very promising for self-lie detection, this area of research is still at its beginning [31–33].

Finally, I want to mention a complementary self-lie strategy that could strengthen all the abovementioned ones: deception of others

intended to facilitate self-deception. According to von Hippel and Trivers, self-deception can facilitate the deception of others because it blocks other's capacity of detecting deception. It is easier to cheat others when the cheater gets first lying to oneself. "Self-deception can also facilitate the deception of others in a more general sense, in that it can help us convince others that we are better (e.g., more moral, stronger, smarter) than we really are. Thus, the benefits of self-deception go beyond convincing others of specific lies, as self-deception can also help us accrue the more general social advantages of self-inflation or self-enhancement" [25] (p. 4). Reversing the logic of this argument, it is also plausible that some truths about oneself may be directly harmful and not because of other's reaction. In this context, the adaptive behavior would use interpersonal reactions to a lie as a mean to strengthen liar's false beliefs. Returning to the subject, the challenge here is to learn to distinguish, through physical, chemical, electrical, or psychological markers, between these two sorts of self-lies: I will refer to as primary and secondary self-lies, respectively. To achieve this would imply to take a tangible step toward knowing the real goal of a lie, that is to say, the true intention of the liar.

## New Horizons in the Interpretation of Evidences

As we have seen, depending on the external context and physiological and psychological liar's starting conditions, telling a truth, a lie, or a self-lie may be equally cognitively demanding. Indeed, some sort of self-lies may be less effortful than truth-telling, that is to say, requires less concurrent cognitive and affective tasks. As the saying goes, some truths are harder to accept than white lies. In other words, the detection of high levels of cognitive load must not be accepted as sufficient evidence.

On the other hand, not all unreflecting – unconscious – lie is involuntary, and the same could be said for self-lies. Most importantly, some voluntary lies and self-lies may become a routine and, therefore, be later triggered and executed without a rational judgment. They would be difficult to discern from standard deceptions, unless this voluntary routines, as I have proposed in other work, drag some type of distinctive pointers – I will call it *teleological and conscious markers* – what would be useful to undo and redo habits [21]. This is another way of saying that human unconscious is, at least in part, the result of the conscious choices made by the individual and their ancestors.

But, is it possible that some apparently conscious lies were truly and merely voluntary or even involuntary and, thus, only deceptions? It would be the case, for example, with the rationalization of the origin of a lie or self-lie. Human beings like to consider themselves as responsible of their own actions, even those more onerous or cowards [34].

Another possibility is that, for some very dangerous truths, rational or irrational mind's defense system labels fraudulently the origin of some deceptive behavior with teleological and conscious markers in order to cheat rational or conscious motorization of the subsequent decision-making. A self-deception may be easier to keep in mind if agent feels that it makes sense or even if agent thinks that it has been chosen. The issue here is whether there are some specific neural or psychological areas or functions in charge of such hypothetical false marking and the possibility of reliably detection.

Finally, I want to drag up a last controversy on interpretation of data: the mistake of associating contradictory behaviors to self-lies or self-deceptions. It is not uncommon to observe that certain people show different value system or beliefs depending on the context. For instance, a despotic, selfish, and promiscuous boss may be a kind, generous, and chaste husband at home. In view of this situation, we tend to think that only one of the two lifestyles is real or authentic, while the second one is an imposture, a farce conscious sustained for darker purposes. Using the frame of false beliefs, we would say that, in the absence of illness, this double life is voluntary: no matter whether maintained by conscious judgments (prior intentions) or, at least, by rational ones. However, on the basis of some recent theories about the self, there is a third possibility. For example, for

neurologist Antonio Damasio, the self-referential concept is built from multiple representations of the relationship between subject and environment [35] (pp. 215–220). These representations converge progressively in different role structures: each of them comprises different meanings and rules about objects and circumstances – me acting as father, husband, friend, employee, etc. Philosopher Christine M. Korsgaard defines it as "practical identities" and uses them to explain why young identities are naturally more incoherent and incongruous than mature ones [36] (pp. 20–25). Over time, all this partial identities would begin to orbit around a single contextual center, the moral identity, in which norms and values express universal application. It is only there where it makes sense to assign hidden agendas and inauthentic behaviors.

Here we find another important challenge for self-lie detection researchers. How can we distinguish lies from immature statements? Perhaps it is possible to find some neural or psychological markers, but, in my opinion – and as I have defended in a previous paper – the key has to do with some specific phenomenological experiences of inauthenticity [37, 38]. Of course, this is an introspective method, which therefore requires the active collaboration of the supposed liar. It is not practicable in criminal investigations or civil proceedings. However, they are not the only uses we can give to self-lie detection. We have already talked about its advantages for psychotherapy. Besides, in the next paragraph, I will present some new applications on moral enhancement in which introspective analysis is workable.

## Ethical Reflections on Moral Enhancement

For the last 15 years, scientists and philosophers have been discussing possible ways of getting physical and psychological excellence through biotechnology. The goal of biomedical enhancement implies, as Thomas Douglas claims, "to alter the characteristics of already healthy persons" [39] (p. 228). It is also in this context where the notion of moral enhancement has been generated: "A person morally enhances herself if she alters herself in a way that may reasonably be expected to result in her having morally better future motives, taken in sum, than she would otherwise have had" [39] (p. 229). But, what does *alter* mean? Usually, it is understood as body modification. However, thinking about self-lie detection shows us a second form to use technology to be better moral people: favoring self-knowledge. The only difference is that, in this case, human body is not directly altered by technology but by the truths reached with it.

As we have seen, the human brain and mind constrain information flow and even induce involuntary false beliefs, i.e., deceptions. Besides, some voluntary fast decisions may have been forgotten and went to the unconscious side. It is also possible that some people have sunk consciously and deeply – through rationalization, misremembering, and other strategies–, into their own self-lies, unable of undoing the deceitfulness. The point here is that perhaps all these deceptions and lies were for "the best" time back but not necessarily right now. Moreover, not everybody shares the same value system. For example, evolutionary or adaptive values are not necessarily universal values. Furthermore, as Thomas Huxley writes "Social progress means a checking of the cosmic process at every step and the substitution for it of another, which may be called the ethical process. The end of which is not the survival of those who happen to be the fittest in respect of the whole of the conditions which exist, but of those who are ethically the best. As I have already urged, the practice of that which is ethically best–what we call goodness or virtue – involves a course of conduct which, in all respects, is opposed to that which leads to success in the cosmic struggle for existence" [40] (pp. 82–83). Self-lie detection devices may be an excellent support in escaping the evolutionary loop. The laws of evolution are blind, while human beings have the eyes of the reason. The same argument applies to transcendental – no naturalist – ethics. Even from idealistic Platonism, the famously said, "Know yourself," drags a bitter struggle against not only external appearances but also internal self-inflicted mirages.

Knowledge is power from almost all points of view: eudemonistic, deontologist, utilitarian, etc. This does not mean that the truth is considered always beneficial. It is the possibility or not of knowing what it is valued in all of them. Maybe, determinism is the only approach in which human freedom is unable to grow or diminish because it does not exist. In this context, philosopher Daniel Dennett writes: "You are not out of the loop, you are the loop. You are that large. You are not an extentionless point. What you do and what you are incorporates all these things that happen and is not something separate from them" [41] (p. 242). However, even under that assumption, the production of self-lie detection devices could be understood as a new evolutionary (deterministic) step toward more sophisticated mechanisms of adaptation. Indeed, this is how Dennett understand free will.

There may be a need for exceptions for the acquisition of knowledge. The most important is when truth results in a deterioration of free will. Bad news is difficult to embrace, yet a subject can choose to benefit from its position with clear mind and physical and mental forces. However, this would be the case, for instance, of some terminal patients: their precarious psychological state may prevent them from adequately facing and processing the problem, including their emotions [29]. Knowing about own death or about the recent death of a son or a daughter would only make things worse – induce them what I call the *oedipal madness*. This is the reason why physicians usually communicate fatal diagnosis when in its first stages, though not suddenly but progressively – being very mindful of the patient's reactions. Hopefully, patients will be able to make the right decisions and squeeze their last few days of life.

The case of terminal patients is interesting also because it offers us another perspective about the value of truth. In some philosophical and religious streams of thinking – classic Greeks, Buddhists, and Christians, among others – knowledge is not only valuable for its utility but also in itself. Behind this belief, there is a whole cosmological perspective about the blessings of nature and the *chain of being*, where everything has a place and role [42] (p. 3). Knowing the truth is, in this context, accepting and enjoying reality – including the real oneself. Self-lie detection devices would be, in this context, a tool for having a right conscience and a happier life. In short, to the value of freedom must be added the value of cosmic benevolence. It helps to know that, ultimately, everything is fine. This frame offers a bearable life, even having known the worst possible and irremediable news. But again, theory is one thing and practice is another. It takes courage to face, for example, that you do not like your job; love your wife or children; and believe – or do not believe – on Mohammed, democracy, communism, etc. Would it be easier for younger or order people? Perhaps it is easier for the youths to change their life expectations: they have not yet been fully committed to such goals and keep form and vitality. Perhaps it is easier for the elderly because they are wiser. Would it be easier in rich or poor countries, for physicians or politicians, scientists or philosophers, believers or atheists, etc.?

The last point I would like to bring is relative to our Western culture and, particularly, with the crisis of modernity and postmodernity. In previous writings I have studied the influence of culture in the development of moral identities and how strong current trends now prevent it or, what is worse, praise and promote the benefits of double-thinking, split minds, antagonistic emotions, and ambivalent values – in short, of practical identities [43–45]. The power of our cultural influence is so huge that it affects – both consciously and unconsciously – even those who try going against the main stream. Could self-lie detection devices be used as a *little magic mirror* to avoid a slave life, full of unauthentic emotions? What would be the price? These and other issues should be part of the new neuroscientific and bioethics agendas on moral enhancement.

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# 5 The Neuroscience of Psychiatric Disorders and the Metaphysics of Consciousness

Rocco J. Gennaro

In this chapter, I first review and assess evidence regarding brain damage or neural abnormalities associated with some psychopathologies and cognitive deficits, such as hemispatial neglect, agnosias, amnesia, somatoparaphrenia, alexithymia, and others. It becomes clear just how closely normal mental functioning and consciousness depends upon normal brain functioning as well as how some very specific mental changes occur when, and only when, very specific brain damage occurs. I then explore the metaphysical implications of these results with respect to the nature of mind and consciousness. In particular, I examine the plausibility of materialism, roughly the view that mental processes are brain processes, in light of the evidence discussed and in contrast to a dualist conception of the mind (whereby mental states are not physical in some sense). I also explore the prospects for a conscious afterlife based both on the brain damage evidence adduced and the metaphysical implications discussed. For example, even if conscious mentality merely depends upon proper neural function, does it then stand to reason that all of one's conscious mental activity ceases when all neural functioning ceases? One might suppose that an affirmative answer to this question is more reasonable than the negative answer, but it may be impossible to know with any degree of confidence.

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## Brain Damage, Cognitive Deficits, and Psychopathologies

In this section, I examine in some detail how closely normal mental functioning depends on normal brain function. This is important because it makes clear that specific mental changes occur when, and only when, brain damage occurs. It is true that such "correlation" is not the same as "identity" or "cause," but the best explanation for the neuropsychological evidence is arguably that all conscious mental activity *depends* for its existence upon brain activity. As we shall see, although many materialists typically hold the stronger thesis that mental states are *identical with* neural states, much of the skepticism with regard to an afterlife might remain even if one holds the weaker claim sometimes called the "dependence thesis" (DT):

**Dependence Thesis** Conscious mental processes depend upon brain activity.

The details to follow are exactly what one would expect if DT is true. An abundance of evidence from neuropsychological and neurophysiological studies in both humans and nonhuman



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animals strongly supports the DT. In humans, damage to particular brain regions, such as due to disease, trauma, or stroke, is associated with specific impairments of perception, memory, cognition, and emotion. There are of course many other disorders and psychopathologies which are not discussed below. Drugs also alter brain activity and produce clearly corresponding changes in one's conscious mental states.

Basic conscious perception seems to depend upon normal functioning in fairly well understood brain regions. Cortical blindness is a loss of vision resulting from damage to areas of visual cortex, whereas cortical deafness is a loss of hearing or the ability to recognize sounds, including speech, resulting from damage to regions of auditory cortex in the temporal lobes. Damage to no other brain areas results so clearly in such specific visual and auditory deficits.

There is a family of deficits known as the "agnosias" which most generally refers to higher-order deficits in which perception is normal, but recognition of objects, people, shapes, sounds, and odors is impaired. There is the loss of ability to recognize objects, persons, sounds, shapes, or smells, while the specific sense itself is not defective and there is no significant memory loss. More specifically, visual agnosia is the inability to comprehend the meaning of objects caused by lesions to the occipital or temporal lobes of the brain. There are actually two types of visual agnosia: *apperceptive* visual agnosia, cases where "recognition of an object fails because of an impairment in visual perception," and *associative* visual agnosia, cases "in which perception seems adequate to allow recognition, and yet recognition cannot take place" [1]. So, for example, a patient will be unable to name or recognize a whistle. Associative agnosics are not blind and do not have damage to the relevant areas of the visual cortex. In addition, associative agnosics have difficulty in naming tasks and with grouping objects together. Unlike in apperceptive agnosia, there seems to be intact basic visual perception, for example, patients can copy objects or drawings that they cannot recognize, albeit very slowly. Patients will also often see the details or parts of an object, but not the "whole" of the object at a glance. Yet a patient might easily identify a whistle by sound instead of sight.

Prosopagnosia is the inability to recognize familiar faces which is typically caused by damage to the occipitotemporal cortex (fusiform gyrus). Patients with prosopagnosia can sense that they see a face, yet they have no awareness of perceiving any information regarding whose face they may be viewing [2]. They do not have any sense of familiarity when looking at another's face but can sometimes make inferences via auditory or other visual cues (e.g., clothes, hair) to compensate. However, skin conductance responses show that there is some kind of residual emotional arousal when in the presence of a known person.

Simultanagnosia is the impaired ability to perceive parts of a visual scene as a whole (often associated with Balint's syndrome). It is typically associated with bilateral lesions of the dorsolateral parietal-occipital association cortex or with damage involving the medial occipitoparietal junction and the inferior intraparietal sulcus. Patients with simultanagnosia can perceive only one small portion of the visual field at a time and cannot integrate these parts to form a unified representation of the scene [3]. Simultanagnosia occurs when patients recognize objects in their visual field but only one at a time. Outside of a narrow area in the visual field, these patients say that they see nothing but an undifferentiated mess.

Other serious disorders include somatoparaphrenia which is a bizarre type of body delusion where one denies ownership of a limb or an entire side of one's body. It is sometimes called a "depersonalization disorder." Relatedly, anosognosia is a condition in which a person who suffers from a disability seems unaware of the existence of the abnormality. A person whose limbs are paralyzed will insist that his limbs are moving and will become furious when family and caregivers say that they are not. Somatoparaphrenia is usually caused by extensive right-hemisphere lesions. Lesions in the temporoparietal junction are common in somatoparaphrenia, but deep cortical regions (e.g., the posterior insula) and subcortical regions (such as the basal ganglia) are also sometimes implicated [4]. Patients with

somatoparaphrenia utter some rather stunning statements, such as "parts of my body feel as if they didn't belong to me" and "when a part of my body hurts, I feel so detached from the pain that it feels as if it were somebody else's pain" [5]. It is difficult to grasp what having these conscious thoughts and experiences are like. Patients with anosognosia are generally unable to acknowledge a deficit and often employ denial, projection, rationalization, and other defense mechanisms.

Akinetopsia is the inability to perceive motion in the visual field, while the ability to see stationary objects remains intact. It is associated with damage to higher-order visual cortical areas involved in motion processing (areas MT/V5). Akinetopsia is sometimes called "motion blindness." The visual world seems to come to a standstill or appears more like a sequence of frozen snapshots such that objects don't really move but appear to "jump" from one place to another. One's visual consciousness is distorted both with respect to temporal sequence and the unity of consciousness.

Hemispatial neglect (or hemineglect) is a neuropsychological syndrome resulting from damage to one hemisphere of the brain (usually involving the parietal cortex in the right hemisphere) which is characterized by a deficit in attention to one side of space (usually contralateral to the damaged hemisphere). Subjects not only show no conscious awareness of objects located in the space contralateral to the hemisphere of the brain lesion but also often show no awareness that they have a deficit. A patient loses all sense of one side of her body or sometimes one-half of everything spatial in one's experience.

There are two main types of amnesia corresponding to two kinds of memory failure: (1) *anterograde amnesia* is the inability to remember new facts and events following damage to limbic structures, including the hippocampus, within the medial temporal lobes, and (2) *retrograde amnesia* which is the impaired memory of events that occurred for a period of time before damage to limbic structures. Damage to regions of the prefrontal cortex lead to impairments in working or short-term memory, which is consistent with evidence from neuroimaging studies supporting the involvement of frontal brain structures in executive control functions, such as the maintenance of information in working memory [6]. Similar to anosognosia, subjects suffering from amnesia may deny their deficits and offer implausible rationalizations for their inability to remember. Interestingly, "skill" or "procedural" memory, such as the ability to type or play the piano, can remain intact and even be acquired in cases of severe (episodic) memory loss.

Perhaps most important for this chapter is that memory appears to be critical for creating and maintaining one's sense of self. Memory has long been considered essential to one's personal identity through time, especially since John Locke who influentially argued for the view that one's personal identity is closely tied to one's autobiographical (or "episodic") memories [7]. In the context of this chapter, it is worth pointing out that the Western conception of an afterlife takes it for granted that *you*, as a person, continue to exist beyond bodily death. It is supposed to be *personal* survival. After all, if it's not you, then why would you care about what might continue after bodily death?

Dramatic changes in personality can also be caused by frontal and temporal lobe damage. These changes are often characterized by an abrupt or argumentative manner and a loss of social inhibitions, consistent with damage to inhibitory centers of the brain [8]. A classic example of the effects of frontal lobe damage on personality is the case of Phineas Gage, a construction worker on the American railroads who suffered an accident in 1848 where a large iron bar was blown through the front of his head, damaging his frontal lobes. As a result of the damage, Gage became impulsive and rude which differed significantly from his personality prior to the accident. These personality changes were so dramatic that friends and acquaintances said that he was no longer Gage [9]. At least Gage could point to a pretty good excuse for the change in his behavior and personality! Related cases can be found today but instead often have more to do with the presence of a brain tumor or as a result of frequent concussions.

Disorders of language processing include "fluent aphasia" where there is impairment in speech

comprehension while speech production is intact. Fluent aphasia is typically caused by lesions to Wernicke's area which is located within the temporal lobe of the dominant (usually left) hemisphere. The inability to understand speech is a crippling problem for some patients.

Damage to brain areas involved in emotional regulation, including the limbic system and particularly the amygdala, commonly result in impaired processing of emotional stimuli [10]. For example, subjects with damage to the amygdala often exhibit an impaired perception of danger. They fail to show the typical emotional responses to stimuli that tend to cause fear in normal subjects. Damage to the orbital and cingulate cortices may also result in a disorder called "alexithymia," which is characterized by an inability to read emotions, including one's own. Damage to the insula may result in the inability to experience the emotion of disgust and impaired perception of disgust in others [11]. Alexithymia is a deficiency in understanding, processing, or describing emotions. It is common to many on the autism spectrum and can be difficult to distinguish from what is sometimes called "social-emotional" agnosia.

Along similar lines, a basic component of social cognition is the ability to attribute independent mental states to others or to predict other people's behavior based on their mental states. This is a capacity called "theory of mind" or "mindreading." Subjects with lesions of the dorsolateral prefrontal cortex show impairment in mindreading ability whereby they are unable to correctly infer the mental state of others [12].

Subjects with damage to ventromedial prefrontal cortex display impairments in moral judgment and lack of concern for moral rules. For example, these brain-damaged individuals are more inclined to judge moral violations, even attempted harms, including attempted murder, as morally acceptable relative to normal subjects. These results show the crucial role of the ventromedial prefrontal cortex in processing moral and emotional information which are essential for social cognition and the formation of moral judgments [13]. Other lesion studies indicate the involvement of several brain networks in processing the emotional and cognitive components of empathy [14]. This evidence is also consistent with findings suggesting that there are abnormalities in several brain structures, including the prefrontal cortex and amygdala, in criminal, violent, and psychopathic individuals [15]. Psychopathy is a mental disorder characterized by a lack of empathy and remorse, shallow emotions, egocentricity, and deceptiveness. These abnormalities include deficits of consciousness, such as the inability to show empathy to others or to experience some deep emotional connection to others. Psychopathy is sometimes accompanied by narcissistic personality disorder which results in a pattern of grandiosity, need for admiration, along with lack of empathy. Psychopaths are far less likely to feel distress when perceiving others in pain.

Finally, many neurological disorders and diseases, such as Alzheimer's and frontotemporal dementia, bipolar disorder, depression, schizophrenia, and autism, which are all characterized by profound changes in cognitive function, are associated with biochemical or neuroanatomical changes in the brain. While the specific causes and nature of some of these changes are still unclear and the subject of vigorous ongoing scientific investigation, what is not in dispute is that these mental disorders and diseases are direct consequences of aberrant brain function. It is also worth noting the importance of the role of neurochemistry in having various kinds of neurological disorders and conscious states [16]. There have been over 50 neurotransmitters that have been discovered thus far; for example, dopamine seems to contribute importantly to attention and working memory. Thus, it is not merely damage to specific brain *structures* that greatly affects consciousness.

Overall, therefore, there seems to be ample evidence that various cognitive abilities are altered or eliminated due to very specific lesions or abnormalities in the brain. It seems that DT is strongly supported by the evidence above. If so, we might wonder how one's conscious mind can continue on after all brain functioning ceases [17].

## The Metaphysical Issue

Before directly addressing the bearing of the above on the possibility of an afterlife, it will be useful to frame the issue against the backdrop of two broad traditional and competing metaphysical views concerning the so-called mind-body problem: dualism and materialism. While there are many versions of each, the former generally holds that consciousness is not physical in some sense. A *substance dualist*, for example, holds that a non-physical mind (i.e., mental substance) is associated in some way with each physical body. On the other hand, materialists typically hold that the mind is the brain or, more accurately, that conscious mental activity is identical with certain patterns of neural activity. This view is sometimes referred to as "identity theory." Adherence to DT, however, does not even require adherence to such strict identity since DT still says that conscious mental processes *depend* upon brain activity.

According to the so-called identity theorist, science is showing us that conscious mental states, such as visual perceptions, are identical with certain electrochemical processes occurring within specific regions of the brain (e.g., in the visual cortex). An identity theorist will liken these developments to the way that the science of chemistry taught us that water really *just is* H2O. The most obvious and natural conclusion to draw from contemporary neuroscience is that the mental activity in question *just is* the neural activity or at least that the former *depends* on the latter for its existence (as is stated in DT).

There is no doubt that some form of "materialism" is much more widely held today than in centuries past. Part of the reason has to do with the explosion in scientific knowledge about the brain and its intimate connection with consciousness including the link between brain damage and disorders of consciousness. Brain death is now the main criterion used to establish when someone has died and stimulation of specific areas of the brain results in modality-specific conscious experiences. It would also seem odd to say to a neuroscientist "you are not really studying the conscious mind *itself*" while she is examining the workings of the brain using electroencephalography (EEG), magnetoencephalography (MEG), or functional magnetic resonance imaging (fMRI). The fMRI, for example, measures changes in blood flow associated with neuronal activity within the brain, while the subject is engaged in various cognitive or perceptual tasks.

There are also important theoretical factors favoring materialism, such as the so-called principle of simplicity which says that if two theories can equally explain a given phenomenon, then we should accept the one which posits fewer types of objects or forces. Thus, we shouldn't posit the existence of additional entities unless the phenomenon to be explained requires us to do so. Materialists wonder why there is a *need* to believe in the existence of non-physical entities or properties which somehow causally interact with physical brains (as so-called dualists believe). At minimum, the burden of proof is on those who believe in the existence of such additional entities.

Moreover, in the aftermath of the Darwinian revolution and given the increased knowledge in comparative neurophysiology, it would seem that materialism, or at least DT, is on even stronger ground. It is now relatively uncontroversial that many animals are capable of having some conscious mental states (*contra* Descartes). And given the similarities between the more primitive parts of the human brain and the brains of other animals, it seems most natural to conclude that, through evolution, increased volume and complexity of brain areas correspond to increased mental abilities. For example, having a well-developed prefrontal cortex allows humans to reason and plan in ways not available to dogs and cats. We certainly don't find frogs and lizards, for example, capable of doing philosophy or advanced mathematics. It seems fairly uncontroversial that we should be materialists about the minds of other animals – few (if any) substance dualists would even hold a dualist view about dogs and pigs, not to mention the related belief in a dog or pig afterlife. It seems odd to hold that non-physical conscious minds or mental states suddenly appear on the scene with the emergence of humans. Yet if we are rightly led to believe that

the conscious states of animals, such as desires, fears, and olfactory sensations, depend upon their brains, then on what grounds can we deny this dependency when considering our somewhat similar conscious states?

There are, to be sure, several much discussed objections to materialism, but most of them question the notion that materialism can fully *explain* conscious experience. Even if they are successful, these objections still do not usually dispute the truth of DT. For example, Joe Levine coined the expression "the explanatory gap" to express a difficulty for any materialistic attempt to explain consciousness [18]. The basic problem is that it is, at least at present, very difficult for us to understand the precise link between brain properties and phenomenal properties in any explanatorily satisfying way, especially since it seems possible for one to be present without the other.

David Chalmers (1995) has articulated a similar worry via the catchy phrase "the hard problem of consciousness," which basically refers to the difficulty of explaining just *how* physical processes in the brain "give rise to" subjective conscious experiences [19]. Unlike Levine, however, Chalmers is much more inclined to draw anti-materialist metaphysical conclusions from these and other considerations. Chalmers usefully distinguishes the hard problem of consciousness from what he calls the (relatively) "easy problems" of consciousness, such as the ability to discriminate and categorize stimuli, the ability of a cognitive system to access its own internal states, and the difference between wakefulness and sleep.

There are many materialist responses to the above charges [20, 21], but it is worth emphasizing that Levine does not reject the metaphysics of materialism. Instead, he sees the explanatory gap primarily as an epistemological problem, that is, primarily as a problem having to do with knowledge or understanding. This concession is important at least to the extent that one is concerned with the truth of DT or the larger related metaphysical question of immortality. Perhaps most important for the identity theorist, however, is recognition of the fact that different *concepts* (one mental, one physical) can still pick out the same property or object in the world. Analogously, out in the world, there is only the one "stuff," which we can conceptualize either as "water" or as "$H_2O$." Two or more concepts, which have different meanings, can refer to the same property or object, much like "Venus" and "the morning star" [22].

It is also important to note that by "non-physical," dualists do not merely mean "not visible to the naked eye." Many physical things fit this description, such as the atoms which make up the air in a typical room. For something to be non-physical, it must literally be outside the realm of physics; that is, not in space at all and undetectable in principle by the instruments of physics. It is equally important to recognize that the category "physical" is broader than the category "material." Materialists are called such because there is the tendency to view the brain, a material thing, as the most likely physical candidate to identify with the mind. However, something might be physical but not material in this sense, such as an electromagnetic or energy field. As is widely held, matter is a form of energy. Thus, to say that the mind is non-physical is to say something much stronger than that it is nonmaterial. Substance dualists, for example, believe that conscious mental states or minds are radically different from anything in the physical world at all. The literature on various metaphysical views pertaining to the so-called mind-body problem is of course enormous [23, 24].

There are, to be sure, a number of understandable reasons why some version of dualism, including substance dualism, has been held throughout the centuries. For one thing, from the introspective or first-person perspective, our conscious mental states do not seem like physical things or processes. That is, when we reflect on our conscious perceptions, pains, and desires, they do not seem to be physical in any sense. Consciousness seems to be a unique aspect of the world not to be understood in any obviously physical way. Although materialists will urge that this way of thinking about consciousness completely ignores the more scientific third-person perspective on the nature of consciousness and mind, it continues to have force for many today.

Indeed, it is arguably the crucial underlying intuition behind historically significant "conceivability arguments" against materialism and for dualism. Such arguments typically reason from the premise that one can conceive of one's conscious states existing without one's body or, conversely, that one can imagine one's own physical duplicate without consciousness at all (what philosophers call a "zombie"). The metaphysical conclusion ultimately drawn is that consciousness cannot be identical with anything physical, partly because there is no essential conceptual connection between the mental and the physical. Arguments such as these go back to Descartes and continue to be used today in various ways [25, 26], but it is highly controversial as to whether they succeed in showing that materialism is false [27, 28]. And few, if any, contemporary thinkers in the philosophy of mind or cognitive science use such arguments to support substance dualism or to reject DT.

Historically, there is also a traditional link between dualism and a belief in immortality. Indeed, belief in dualism is sometimes explicitly theologically motivated. If the conscious mind is not physical, it seems more plausible to believe in the possibility of life after bodily death. On the other hand, if conscious mental activity is identical with brain activity, or at least dependent upon it, then it would seem that when all brain activity ceases, so does all conscious experience. Materialists will of course reply that such traditional religious beliefs simply ought to be rejected to the extent that they conflict with materialism or DT. In addition, the burden of proof ought to be on those who believe in non-physical minds and an afterlife, not on those who do not.

It is important to recognize that substance dualism is still the main form of dualism presupposed, or even explicitly endorsed, by many world religions (or, at least, Western Religions). More specifically, *interactionist dualism* or simply "interactionism" is the most common form of substance dualism, and its name derives from the widely accepted fact that mental states and bodily states causally interact with each other. For example, my desire to drink something cold causes my body to move to the refrigerator and get something to drink, and kicking me in the shin will cause me to feel pain and get angry. Due to Rene Descartes' influence, this is also sometimes referred to as "Cartesian dualism." Knowing little about just where such causal interaction could possibly take place, Descartes speculated that it was through the pineal gland, which of course is currently viewed as an almost humorous conjecture. But even a modern-day interactionist would certainly wish to treat various areas of the brain as locations for such interactions.

There are, however, several well-known and devastating objections to interactionism. Perhaps most common is simply the problem of just how such radically different substances could causally interact. How does anything non-physical interact with something physical, such as the brain? No such explanation is forthcoming or is perhaps even possible. Moreover, if causation involves a transfer of energy from cause to effect, then how is that possible if the mind is non-physical? If a non-physical mind can interact with a physical medium then, in principle, it could be experimentally detected. Indeed, we might, for example, expect to find neurons firing in the absence of any physical cause at all, which would most certainly be a news-making development. However, at least to date, no such evidence has been forthcoming.

But the main focus of this chapter is on the well-known fact that brain damage to specific areas of the brain causes very specific mental defects. Although the implications of this evidence have been appreciated for centuries, the level of detailed neuropsychological knowledge has increased dramatically in recent years. A dualist might respond that such phenomena do not absolutely refute her metaphysical position since it could be replied that damage to the brain simply *causes* corresponding damage to the non-physical mind. However, one might then wonder: Why not opt for the simpler explanation that brain damage causes mental damage simply because mental processes simply *are* brain processes? If a non-physical mind is damaged when brain damage occurs, how does that leave one's mind according to the dualist's conception of an afterlife? Will the severe amnesiac at the end of life on Earth retain such a deficit in the afterlife?

If proper mental functioning still *depends* on proper brain functioning (i.e., DT is true), then is dualism really in any better position to offer hope for immortality?

While a detailed survey of all varieties of dualism is beyond the scope of this chapter, it is worth noting here that the most popular form of dualism today is called *property dualism*. Due to the serious objections mentioned above, substance dualism has largely fallen out of favor at least in most philosophical circles, though there are some exceptions and it often continues to be tied to a theological world view [29]. Property dualism, on the other hand, is a more modest version of dualism which holds that there are mental *properties* (i.e., characteristics or aspects of things) that are neither identical with nor reducible to physical properties. The idea is that subjective and qualitative properties of conscious experiences (or "qualia") cannot be *explained* in purely physical terms and, thus, are not themselves to be identified with any brain state or process. Another version of dualism is called *epiphenomenalism*, according to which mental events are caused by brain events, but those mental events are mere "epiphenomena" which do not, in turn, cause anything physical at all, despite appearances to the contrary [30]. But it is crucial to emphasize that neither property dualism nor epiphenomenalism reject DT. According to these versions of dualism, conscious mental activity still depends entirely on proper brain functioning and thus the DT would still be true.

## An Afterlife?

Once again, then, it has long been known that brain damage has negative effects on one's mental states and alters (or even eliminates) one's ability to have certain conscious experiences, resulting in significant psychopathologies and cognitive deficits. Even centuries ago, a person would much prefer to suffer trauma to one's leg, for example, than to one's head. It seems particularly clear from all the recent empirical evidence above that human conscious mental processes are dependent upon the functioning of individual brains. Having a functioning brain is, at minimum, necessary for having conscious experience. That is, the evidence for DT seems overwhelming when one considers the detailed evidence from brain damage. It thus seems to stand to reason that when *all* of one's brain activity ceases upon death, consciousness is no longer possible. As Richard Carrier puts it, "…nothing mental happens without something physical happening…if destroying parts of a brain destroys parts of a mind, then destroying all the parts of a brain will destroy the whole mind, destroying *you*" [31].

Although it is likely impossible empirically to conclusively rule out an afterlife or "prove" that there isn't one, it might also be that some repeatedly demonstrated empirical results can strongly suggest or point to one metaphysical view over another. In addition, we should be careful not to shift the burden of proof from the believer to a non-believer. In any case, there seems to be strong empirical evidence against the idea that oneself, *as a person* with one's memories, desires, beliefs, and so on, continues to exist after brain activity ceases. The dominant Western conception of immortality involves the view that not only some "mind" or "soul" continues into the afterlife but that it is *my* consciousness, *my* memories, and so on. Moreover, we might wonder, what kind of horrible afterlife would it be if all mental damage were to be carried over to the afterlife? This is certainly not what believers have in mind, especially if one has in mind an eternally blissful or heavenly existence. (It is worth noting that many Eastern Religions do not share this conception of an afterlife.)

On the other hand and somewhat related to this issue, the existence of near-death experiences (NDEs) is sometimes used as evidence for dualism and an afterlife. Some patients, often in cardiac arrest at a hospital, experience a peaceful moving through a tunnel-like structure to a light and are often able to see doctors working on their bodies while hovering over them in an emergency room (sometimes akin to what is called an "out-of-body experience" or an OBE). These are often very moving emotional experiences which have a profound effect on those who experience them.

In some cases, the patient sees other deceased relatives and exhibits little or no electroencephalograph (EEG) activity. In response, materialists will point out that such experiences can be artificially induced in various experimental situations and that starving the brain of oxygen is known to cause hallucinations. This "dying brain hypothesis" is also bolstered by the notion that the release of endorphins during times of stress and fear can explain the feelings of peacefulness and pleasure. Interestingly, air force pilots can have at least somewhat similar experiences and often pass out when testing their ability to handle centrifugal force while training in a centrifuge which whips pilots around in a circle at high speeds. We must also remember that NDEs are supposed to be "near death" not "after death," and thus some brain activity is presumably still present during the time of the NDE (even if not always detected by the EEG which measures every surface brain activity). Of course, if it could ever be shown that one is having a conscious experience *at the time* there is absolutely *no* brain activity, then this would indeed be strong evidence for dualism (but I am not aware of this scenario actually occurring). Part of the problem of course is the methodological difficulty of performing controlled and repeatable experiments. Some mystical and religious experiences can often share some of the features of NDEs, but others also result from temporal lobe epilepsy. It of course remains highly controversial as to whether NDEs show a glimpse of a genuine afterlife [32, 33].

There is, however, at least one reason to think that the DT (or even materialism) does not automatically rule out an afterlife. This involves the notion that the afterlife is achieved via the resurrection of bodies, which can even be found in some theistic (Christian) traditions. The most popular materialist option here (following John Hick) is the "re-creation" theory, according to which, at some time soon after a person's death, God re-creates the person by creating a body with the identical characteristics of the body that perished [34]. One worry here is just how such a re-creation can really preserve the necessary personal identity relation. If you are "re-created," the "you" that comes into existence would arguably not really be you but rather an exactly similar physical duplicate. Further, if God could create one body that is exactly similar to the body that died, why not two or more? This would seem to have very odd consequences. Another option is van Inwagen's proposal for a materialist resurrection: "Perhaps at the moment of each man's death, God removes his corpse and replaces it with a simulacrum which is what is burned or rots. Or perhaps God is not quite so wholesale as this: perhaps He removes for "safekeeping" only the "core person" – the brain and central nervous system – or even some special part of it. These are details" [35].

This may avoid the response to Hick's proposal, but of course both views presuppose the existence of a God in the first place which raises numerous difficult metaphysical questions in its own right. At the least, the existence of God (and the right kind of God to do what is described) is a major presupposition. Perhaps we cannot know with certainty that some kind of bodily resurrection doesn't happen, but just because a scenario is "possible" in some sense, it doesn't follow that it is probable or that there is good evidence for it.

## Two Objections and Replies

It is worth addressing two potential objections to the line of argument in this chapter. (1) One might ask: "even if the mind is (or depends on the) physical, what about the soul?" Maybe it's the soul (or "spirit"), not the mind, which is non-physical. One might be told something like this within many religious traditions.

While it is true that the term "soul" (or "spirit") is often used instead of "mind" in religious contexts, the problem is that it is very unclear just how the soul or spirit is supposed to differ from the mind. The terms are used interchangeably in many historical texts and by many philosophers because it is unclear what else the soul could be other than "the mental substance." It is difficult to describe the soul in any way that doesn't make it sound like what we mean by "the mind." After all, what many believe goes on after bodily death is conscious mental activity. The term "soul"

may carry a more theological connotation, but it doesn't follow from this that the words "soul" and "mind" refer to entirely different things. And introducing the "soul" into the discussion just raises anew the objection raised earlier regarding substance dualism (i.e., the mysterious causal interaction between the body and mind), except now the question is pushed back to the soul's relation to the body. Further, and once again, if your soul is supposed to be *you*, then it must contain those essential features of your personal identity, such as memories, beliefs, and other mental states which guarantee mental continuity.

We might of course still concede that none of the aforementioned neuropsychological evidence can definitively rule out the existence of *something* called a "soul" that can survive the death of the brain. The evidence does suggest, however, that if disembodied souls do exist, then they must do so without any mental capacities normally associated with a conscious person. Without a properly functioning brain, the soul cannot see, hear, recognize, understand, remember, think, or decide; it has no capacity for moral judgment, empathy, experiencing pleasure, emotions, or desires; nor does it possess any distinctive personality traits. Thus, at the very least, the evidence from brain damage indicates that a soul that persists after death would have none of the features and capacities that souls are thought to have.

In light of this, one might opt for a different sort of "dualism" and hold that a nonmaterial energy field of consciousness is created or caused by brain activity and it survives bodily death (perhaps even based on the conservation of energy principle). The problem with this view is simply that there is no evidence for the existence of a separable "energy field" of consciousness, either during life on Earth or continuing on after bodily death. In addition, even if there were such an energy field, there would still be little reason to suppose that mental activity could continue on independently of the workings of the brain. Finally, even if there were some brain or mental energy "conserved" after bodily death, there would be little reason to suppose that you, as a continuous person, continue to exist, as opposed to, say, as the dissipation of that energy back into the universe. The burden of proof, one might again insist, surely lies with those who speculate about the existence of such energy fields or "life forces."

(2) A common reply to the brain damage argument, sometimes called "the instrument theory," can be put as follows: Brain injury and damage does not really affect the entirely independent mind at all but simply cuts off the ability of the mind to express itself through the body or just cuts off information from the body from being sent to the mind. The mind can exist independently of the brain, just as television signals can exist independently of the television sets that receive them. Damaging the brain is like damaging a television set – you interrupt, perhaps even destroy, the instrument which processes the signal. But the signal continues to exist because the television set does not generate the signal but simply processes it. In the analogy, the mind is to the brain as the signal is to the television set, and "behavior" is represented by the picture on the television screen [36].

The most obvious response is that if the instrument theory were true, interfering with brain processes should not then affect mental processes at all, for brain processes and mental processes would be independent of each other. Damaging the brain would have no effect on the mind itself, just as interfering with the television's internal parts does not affect the (independent) signal. But introspection reveals that altering brain states alters mental states themselves, rather than merely disabling an independent mind from communicating with or controlling its bodily vehicle. Someone with brain damage due to, say, a stroke clearly suffers real mental problems, such as an inability to think or understand properly. Thus, imagine saying to an Alzheimer's victim, an amnesiac, or one with a serious learning disability: "your mind *itself* is not really affected, it is merely your brain corrupting signals to and from your unaffected mind." This does not seem right even from the first-person point of view of such patients.

The instrument theory reply is also extremely puzzling for the following reason: It runs directly counter to the dualist emphasis placed on the first-person or introspective point of view from Descartes to today. For the dualist, first-person

subjective experience is what counts most with respect to consciousness. The mind at least *seems* to be non-physical from the first-person point of view. To be told by a dualist that we must adopt such a radically third-person perspective on the "real" mind in order to avoid the argument from brain damage is rather odd. Even those dualists who no longer believe, with Descartes, in the infallibility of introspection will find it difficult, if not impossible, to explain how one's own mind can merely appear to be badly damaged and dramatically affect one's everyday activities without being "really" damaged at all.

### Conclusion

It seems clear from the extensive empirical evidence drawn from brain damage studies that the very existence of human conscious states is dependent upon functioning individual brains. There is strong evidence in favor of DT which, we must recall, is an even weaker claim than a materialist identity theory. Having a functioning brain is, at minimum, necessary for having human conscious experience, and thus it would seem that conscious experience ends when the brain ceases to function although it is perhaps impossible to rule out with any kind of certainty. One might suppose that various metaphysical views or supernatural entities, such as an immortal non-physical mind or soul, are by definition outside of nature and thus cannot be "proven" or "disproven" by the methods of natural sciences. This might indeed be true, strictly speaking, but we still may try to assess the *likelihood* of such entities or views based on empirical findings and inductive reasoning, especially given what appears to be a very strong case for DT.

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# 6 The Double Challenge to Naturalistic Conceptions of the Mind

Juan F. Franck

Each facet in the human being is connected to and reverberates in all others. This makes human studies a fundamentally multidisciplinary and ultimately interminable task. If philosophy is the relentless effort not to leave aside anything true from our worldview, then an essential commitment of philosophers is to see that nothing relevant is forgotten in our self-understanding. Philosophical contributions may have many forms and may even occur outside the strict domain of philosophical discussion. Whenever science recognizes that a particular phenomenon cannot be rightly understood without incorporating further elements, principles, or theories, it is adopting a truly philosophical stance. In fact, reason itself urges us to expand our horizons continuously, and philosophy is to a large extent the unremitting habit of trying to see things under an ever-broader light.

We may see an example of this in the distinction between the first- and third-person perspectives. Whereas brains, neurons, and synapses are terms belonging to a third-person perspective – i.e., to external and objective observation – motivation, feelings, and intentions are first-person phenomena, disclosed by taking a view from the subject himself. The distinction between the two perspectives reveals an "explanatory gap," which can be described saying that we have no satisfactory explanation of how or why a given physical or organic process generates or corresponds to a given experience or phenomenal feeling. Probably no better metaphor has been found for this than "interior experience," and this contribution is dedicated to highlighting further aspects of this experience, but my point now is a different one.

Overly stressing the distinction may create a false dichotomy: knowledge is either of the sub-personal or of the individual self. But we are daily reminded of something else. Human behavior, although also externally observable, is indeed meaningless without reference to a subjective core. But if all knowledge of subjectivity were restricted to our own, we would never be able to recognize the reality of other persons, as we constantly and effortlessly do. Thus, beyond these two perspectives, there is second-person knowledge, which, rather than being a combination of the other two, is a distinctive experience. It is good news that an increasing body of recent literature is drawing attention to the specificity and relevance of the second-person perspective in neuroscience [1], ethics [2], and even moral theology [3]. The moral is that the deeper we go and the closer we look into the human being, the more urgent the need to widen our notions becomes.

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The goal of this contribution is to suggest a deeper understanding of the human mind from the first-person perspective. My claim is that naturalist attempts to bridge the explanatory gap face an even greater difficulty than explaining subjective experience from physical, biological, or neural processes. This may be enough to keep the gap open, but the intellective nature of the human mind poses an additional challenge, because reason presupposes or implies the existence of certain principles, which we may call ideal and for which any natural explanation is insufficient. These principles cannot be explained by any power of the mind either; on the contrary, it is the principles that ground the powers. There is no need to appeal to any form of dualistic ontology or metaphysics, but the challenge for naturalism is that a complete account of experience would also have to explain the existence of those principles, whose nature is such that neither the natural world nor subjectivity can account for them.

## The Explanatory Gap and the Concept of Emergence

In early modern times, Descartes and Leibniz, among others, insisted on the epistemological and presumably also ontological gap between the physical and the mental. Descartes famously divided created reality in two independently subsisting realms, intrinsically united in the human person but nonetheless still really separable: the res extensa and the res cogitans. Leibniz stressed so much the distance between the mind and bodily things that he stated the impossibility of causation from the one to the other – something that Descartes had still vigorously defended – explaining seemingly direct influences as the result of a harmony pre-established by God between a person's mental states and events in the physical world.

This long-standing discussion has received new impulse in the past decades. Few of those who now claim that there is an explanatory gap pretend to draw ontological conclusions from that. When Joseph Levine coined the expression, he was precisely trying to weaken Saul Kripke's argument against identity theories, by turning a metaphysical claim into an epistemological one. According to Kripke identity statements using rigid designators are true if both terms are identical in all possible worlds. Kripke argued that the physical and the mental appear to be different realities and there does not seem to be anything in one concept that refers necessarily to the other [4]. So, if no rigid designator for something physical is also a rigid designator for something mental, then the physical and the mental cannot be identical. While acknowledging the force of the argument against materialism, Levine claimed that the gap is in our conception of nature, not in nature itself. The firing of C-fibers may have a causal role in our feeling of pain, but that kind of functionalist account does not explain why pain feels the way it does [5, 6]. Nor did Thomas Nagel endorse dualism in his famed article, where he rightly argues for the inaccessible character of a bat's experience to us. We cannot know what it is like to be a bat simply because we do not feel like one. However, he claimed, "we also have some reason to believe that sensations are physical processes, without being in a position to understand how" [7].

Many philosophers, however, believe that the gap is either an illusion or is exclusively epistemological and can be bridged [8–11]. Others like Colin McGinn [12] think that even if in principle there exists an explanation, consciousness will always remain a mystery for us, because our conceptual tools will never be able to solve the issue. Owen Flanagan, who dubbed this rather pessimistic position *mysterianism* [13], opposes eliminativistic standpoints, like Dennett's quining of qualia [14], but remains quite optimistic and proposes a constructive form of naturalism, in which three compatible perspectives (neurologic, psychological, and phenomenological) act reciprocally as *constraints* in the explanation of mental phenomena. To these we may add cultural and sociological constraints [15].

John Searle is one of the most renowned philosophers of mind. His position however is a bit puzzling. On the one hand, he supports a "first-person ontology" on the grounds that subjective experience requires categories irreducible to the

ones employed in natural sciences, which are based on an objective or third-person perspective. But on the other hand, he argues that the ontological irreducibility of consciousness is compatible with its causal reducibility to neurobiological processes. Its irreducibility follows just from the fact that to reduce means to define a property in terms of another one, whose appearance it would be. But it happens to be the case that the very reality of consciousness consists in being an appearance. So, physicalist or biologistic worldviews would require no modification, simply because the concept of "reduction of consciousness" does not fit into our definitional practices. If we take Searle's reasoning at face value, one needs to wonder what his conception of ontology might be. What he calls a first-person ontology remains at the level of descriptions and falls perfectly well within an epistemological conception of the gap [16].

Perhaps the concept of emergence is causing the trouble. For Searle, consciousness would be a "surface feature of certain physical systems" [17], from which it would emerge. Now, emergence is probably one of the least precise concepts in the philosophy of science. In general terms, a property is said to be emergent when it manifests as a result from other properties – accordingly called base properties – without however being reducible to these [18]. Emergent properties are also thought to have proper and irreducible causal powers. Jaegwon Kim has sharply criticized emergentism as a form of non-reductionist materialism, which he also rejects as a compromise between physicalism and dualism [19]. Kim finds untenable that emergent properties would have their own causal power over a system (top-down or downward causation), while resulting, or emerging, from the base properties of the same system (bottom-up causation). If that were the case, "how could these higher-level properties causally influence and alter the conditions from which they arise?" [20]. This circularity would make the simultaneous possession of base and emergent properties something contradictory. Moreover, what happens in the base can be explained by events and processes going on in the base, so attributing any form of causality to emergent properties would imply overdetermination, i.e., assigning to an effect more causes than it needs. Since the whole causal power of emergent properties would belong to properties at the base, they would turn out to be "otiose and dispensable" [21]. Kim's proposal is to maintain downward causation but as a level of description, i.e., as a higher level conceptual interpretation, thus depriving emergence of any ontological density.

Despite his endorsement of materialism, Galen Strawson takes notice of the metaphysical implications of the explanatory gap, and like Nagel [22] and McGinn, he mistrusts the recourse to theories of emergence as an explanation of the coming to be of a conscious state as a result of the complex organization of matter. He holds that emergence cannot be brute. The fact that an emergent property cannot be understood in terms of the properties of that *from which* it emerges does not imply that the latter may have nothing that accounts for that property. Otherwise, emergentism would violate the *ex nihilo nihil fit* principle, appealing to a kind of magic or miracle. For this reason, Strawson thinks that panpsychism is in a better position than physicalism, because it admits certain at least proto-psychic properties in matter, not just those purely physical. Raw physicalism cannot explain consciousness, so we have to expand our view of the foundations of reality and include new principles and properties [23]. Recently, Nagel has also pleaded for an expansion of the ontological basis of naturalist theories, this time without questioning the concept of emergence [24].

The least one can say is that the gap remains unbridged [25] and that the explanation of consciousness from neural events still looks like the appearance of the genie when Aladdin rubbed his lamp [26].

## The Human Mind and the Double Challenge to Naturalism

Optimism about achieving a naturalistic science of consciousness pervades several current research programs, such as quantum brain biology [27, 28], the enactive approach [29–31], and the naturalization of phenomenology [32, 33].

Common to all of them is the search of a conception that does not take recourse to "supernatural" entities, such as God, an immaterial soul, or principles like Bergson's *élan vital*. However, unless one is adopting a physicalist stance from the start, such attempts should at least clarify the demarcation criteria between the natural and the supernatural, because even though we may pacifically exclude God from scientific explanations, we may ask why an immaterial soul or even something like the *élan vital* would not also be part of nature. Besides, why could there not be something in our own experience, broadly taken, that suggests an explanation beyond science and naturalism?

Although the explanatory gap concerns every form of consciousness, discussions focus primarily on phenomenal consciousness. Now, human consciousness is naturally best suited for our study, and it presents some peculiar features, which we may not extend validly to other living beings gifted with perception and feelings, presumably similar to ours. Insofar our mind is intellective – i.e., capable of understanding that something is in a certain way, not just of perceiving it – it presupposes and requires an at least implicit understanding of the unconditioned validity of some objective principles and notions, which we can also turn into object of our consideration.

Let's illustrate this with an example. On August 21, 2017, a total solar eclipse could be observed in the United States. Totality crossed from West to East through the whole country and was indeed a unique astronomical event. Millions of persons saw the daylight become fainter and fainter due to the Moon's passing between the Sun and the Earth. But it is one thing to experience an eclipse and another one to know what stars, planets, and moons are, how they formed, which laws explain their orbits, and how to calculate the next eclipse. Moreover, the science obtained through the centuries following certain rules does not properly speaking consist in observations, but is a body of knowledge that can be expressed objectively in order to be transmitted. An observation, on the contrary, cannot be transmitted, because it is always and necessarily individual. If nobody had watched the eclipse and no camera had recorded it, astronomical science would not have perished for that reason, because it has an ideal and universal nature.

Besides, some principles must be true not only as warrants of science but also in order to guarantee the perception of those things of which we have knowledge and even the reality of such things. If mathematics held no longer, then not only astronomy would be overturned but also planets would not follow their orbits any more. However abstract it may seem, the validity of the renowned principle of contradiction is not restricted to the realm of logic telling us when we are not reasoning correctly, but extends also to everything that is: to things themselves, our perception of them, and the science we have of things. So, just as a gap separates the physical from the mental, a still bigger gap opens between the physical and the mental, on the one hand, and the mind's objective contents, on the other hand.

The awareness of this difference was present in phenomenology as a philosophical school since its beginnings. Many developments of phenomenology have proven productive in the discussion with the cognitive sciences: the analysis of embodiment, of our experience of time, of our agentive character, and of intersubjectivity [34]. However, the initial inspiration of phenomenology was the overcoming of psychologism, i.e., the attempt to explain psychical acts, their objects and the laws they follow, as natural events, or explainable in such terms. In particular, Husserl vehemently rejected the idea that consciousness could be studied with the methods of the natural sciences. The recent project of naturalization of phenomenology tries to turn around precisely that anti-naturalistic inspiration making use of present-day resources of mathematics and science, which Husserl would not have known.

Commenting on the nature of the ideal, Husserl says: "Numbers, propositions, truths, proofs, theories, form in their ideal objectivity a self-contained realm of objects – not things, not realities such as stones or horses, but objects nonetheless" [35]. The ideal, or the eidetic, even without being a subsisting reality, is a true object of the mind. Not only does it exist in its own way,

but one must also acknowledge that its properties are immutable. Of course, if by Platonism we understand the claim that ideas subsist like real things, only in another world or sphere, not just Husserl would reject it, but even Plato himself. But it follows from the simple consideration of these entities that they possess their own laws and are also distinct from the mind, subject, or person that knows and thinks them, as well as from the acts of consciousness in which they are revealed. Moreover, their realm is properly the realm of truth, of what is unchangeable. Once a proposition is found to be true, even about temporal facts, it becomes meaningless to say that its truth-value is temporary or could be changed. This is how Husserl expresses it in the *Logical Investigations*: "truth itself rises above all temporality, i.e. it is meaningless to ascribe temporality, generation or corruption to truth" [36].

The importance of this observation for the problem of the nature of the human mind should stand clearly out. The a-temporal validity of these objects is essential to the intellective mind, because without them we could not perform any rational act. Then, to be successful a naturalistic explanation of human consciousness would have to provide an equally naturalistic explanation of them. But which naturalistic explanation could be given of what undergoes neither generation nor corruption, of what would continue to be what it is even if the world did not exist and even if no human mind considered it?

This last feature reveals what special characteristics the ideal has. Obviously, the existence of the universe does not logically derive from those principles, but if they were not unconditionally in force, reality itself would vanish. When thinking, the mind touches something properly immutable. We certainly understand this, and together with it we also understand that those principles do not depend from our consideration of them, because their truth is independent from our thought. We also understand that our own mind, just as anything else in the world, could cease to exist, without them losing their validity for that reason. Far from diminishing the value of the human mind, this consideration upraises its ontological category, since it has such principles as objects.

What we call the ideal, or the eidetic, turns out to be the biggest obstacle for a naturalistic program. The recognition of its existence strengthens indeed the need to admit something completely independent of matter and which at the same time is not the result of a mental act, but its very condition. This fundamental structure of all intelligibility underlies even the specific physical, chemical, and biological regularities we take to underlie the whole universe. These might be completely different, but some basic principles – logical, mathematical, ontological, and, why not, also ethical – remain the same. One cannot reproach this strongly Platonic claim that it presupposes the existence of anything immaterial, because the validity of such principles reveals itself directly to our understanding, without further assumptions. Even naturalism presupposes these principles, but the question is whether it is able to account for something that transcends the whole of nature.

Among contemporary naturalists, Thomas Nagel has recently touched upon this point, which is one reason for his disappointment with current naturalistic theories. Nagel categorically calls truth timeless and objective. Sentience – including perception, emotions, and feelings – may find an explanation in its evolutionary utility, but we don't trust reason on the same evolutionary principles. Reason is justified by itself because it connects with truth directly: by reason we can have "immediate contact with the rational order of the world, or at least with the basic elements of that order." On the contrary, perception involves highly complex mechanisms, physical and neural, and is always perspectival. According to Nagel, "[r]eason (…) has completely general validity, rather than merely local utility." There are even "eternal and necessary truths of logic and mathematics" [37], and both science and ethics are built on timeless norms of thought too. The validity of systematic reasons can be grounded neither in biology nor in culture [38].

One may recall that Plato called the ideas "the divine" (*to theion*) [39], because, on the one hand, what is eternally identical to itself and immutable deserves that qualification and, on the other hand, it would be an excess to deify an

idea. However, if nothing within the range of our knowledge can sufficiently account for the ideal, it seems reasonable to admit the possibility that an infinite intelligence is ultimately responsible for it. Plato did not explicitly draw that conclusion, but one may count among Nagel's merits that he explicitly acknowledges how close his Platonic position about cognition and the mind is to a religious stance, mentioning an understandable "fear of religion" in this respect [40].

This further explanatory gap is significant because it reveals the mind-independent character of truth, whereas sensory qualities are not completely independent from the bodily constitution of the perceiving subject. When we grasp objective truth, we attain something that is not relative to us, but imperishable and timeless. Therefore, the intellective power of the mind is not at the same level as sensory faculties.

## Conclusive Remarks

Consciousness in all its manifestations continues to be the main obstacle for any naturalistic project. Independently of the many forms of "consciousness," attempts to naturalize it would sooner or later have to provide an explanation of human consciousness as well. The explanatory gap becomes even more unbridgeable for human intellectual or rational consciousness, including the naturalist's when he tries to naturalize consciousness. If by naturalism we understand materialism or physicalism per default, as Block suggests [41], the attempt is desperate, even more so because, to put it in Ulises Moulines' words, "materialism is a confused doctrine," since "nobody knows today most certainly what matter is" [42]. Nonetheless, the main allure of naturalism lies arguably in its materialistic stance, and dropping materialism may turn naturalism into a trivial and uninteresting position [43].

The admission of this further explanatory gap suggests that the study of the mind may overturn naturalistic explanations from within, i.e., natural observation discovers in the operations of the human mind something that escapes a naturalistic explanation. It can thus reveal some deficiencies of naturalism and open up a more comprehensive understanding of what it means to be human.

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# What Is Understood by "Neural Correlate" in Mind-Brain Relations

7

Consuelo Martínez Priego

## Introduction

When William James wrote, "What is emotion?" [1], he clearly distinguished between bodily affections, especially neural ones, ideas, and the awareness of those affections. In this way, he justifies that ideas devoid of bodily change are cold ideas. Bodily affection follows, directly, the perception of stimuli, and the awareness of the response to that perception, while it is produced, is an emotion. This differentiation, the neural/somatic and the mental – the ideas – as well as the awareness of somatic changes, delineates the framework of dialogue in which we want to situate ourselves: the relationships between the mental and the cerebral. In any case, as the problem is addressed, emotion becomes one of the keys to show the extent to which the two extremes have been, in some way, integrated.

The question we pose runs through these channels: the somatic (the body or the brain), the mind (or soul, according to traditions), or the consciousness (which only to a certain extent identifies with the soul but definitely does identify with the mind). The ordinary thing is to present these terms in a problematic form, such as "mind-brain" or "body-soul," sometimes falling into an identification of both problems, which supposes for many a "package error" [2, p. 158]. We will establish proximity in the approach to the problem, since in the contemporary discussion, "mind-brain" contains the whole problem, and we will distinguish with greater rigor in the attempts toward discussion and openness to other solutions. However, when it is positively accepted that there are mental – or "psychic" – and bodily or neural events, it is common to resort to the term "correlation" to show the link between one and other events.

Thus, given the repeated occurrence of the term "correlation," in areas where the mind-brain distinction appears, since "mental states (or events) have neural correlates" [3, p. 16], we will pay attention to that question. In particular, it seems appropriate to ask if it is the most apt term to use for the interaction, relationship, or coexistence of the physical and the mental. For that reason, it will be necessary to clarify what the use of that term implies, as well as if there is another approach – and expression. This will lead us to question the link between the mode and the terms of the questions, and the scope of the answers, when the "mind-brain" problem is investigated.

Obviously, to address the questions posed, it is necessary to show briefly both what the term "correlation" means and what it contributes, both in general and in this epistemological field. Likewise, it is necessary to discuss the meaning of the term "consciousness," in which the

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problem of the mental is usually condensed – and to a certain extent that which refers to the soul. It could not be otherwise; the relationship between the psychic and the physical has already been approached by historically consolidated traditions. From these, we will try to take a somewhat different approach, in order to shed light on the scope of the expression "neural correlate" and other, similar expressions. In the final discussion, there will be a brief detour into a question which is always at play: the understanding of the "personal reality" of each human being.

## Clarification of Terms: Consciousness and Correlate

Research into the mind-brain problem has regained strength especially in the field of the analytic tradition, mainly for three reasons: (A) subjectivity and consciousness are inescapable realities; (B) it is not clear that current science is capable of offering sufficient explanation of how the activity of the brain generates conscious activity or, simply, of how both realities are related, and (C) ultimately, it is believed that it is possible to provide a truly scientific approach to solving the problem [4].

In this framework, the term "mind" – the thinking subject or *res cogitans* – is not understood as a simple cognitive capacity of a subject in the sense used by contemporary cognitive science [5]. Rather, it is understood as "consciousness," that is, human knowledge that possesses a peculiar quality. For this reason, before starting the description of the thesis and arguments about correlation, it is necessary to clarify in the first place what we understand, in general, by "consciousness." The term "alludes to the self-transparent dimension of psychic life, by virtue of which the thinking subject becomes an active spectator of himself, which gives him the opportunity to see himself as the protagonist and the one responsible for his own actions" [6, p. 19].

The subjet is spectator, protagonist and responsible; that is, on the one hand, being able to objectify the activity itself and look at it from the outside, as if one were a third. On the other, the knowledge of oneself that accompanies one's actions, including thinking. Finally, responsibility, which emphasizes that the ultimate origin of the action is simply a "free self". This self-transparent dimension belongs, according to Descartes, to "thinking" as an activity of the *res cogitans*, so that "by means of the word to think I understand everything that happens in us, in such a way that we immediately perceive it; thus, not only understand, want, imagine, but also *feel* is considered the same as thinking" [7, p. 9].

The "immediate apperception" is, of course, the aforementioned self-transparency; the knowledge of oneself as cognizant that one is knowing, concomitant to every cognitive act: one's way of being, one's way of being in the world, the intention of one's actions; etc., that is, psychological contents or a certain "meta-knowledge." Seen in this way, we could detect degrees or levels of consciousness: from the bodily "self" to the conscious self – which implies moral responsibility. If there is also sensible consciousness, common to animals, and a strictly human, personal, hierarchically superior consciousness, we must affirm that the cognitive act is not always the same, but allows a greater and a lesser, as we will have occasion to study. Although it is true that this point would require more argumentation, this is beyond the scope of the present work [8].

As for the term "correlation," first, it should be considered that, by itself, it does not mean more than the existence of two elements with a certain relationship but without attributing an intrinsic or extrinsic character to the link between them. For this reason, "correlation" does not necessarily imply causality – although it does not exclude it – but it does not mean anything other than the mere verification of the existence of a certain association between two variables [9]. It establishes that there are two changing sets in which modifications occur with some type of regularity. Indeed, "correlation can be thought as a linear measure of the association between two variables. Note that correlation does not imply causation. Correlation between a variable at a certain time instant and itself at other time instances is known as self-correlation, while the correlation between two variables is known as cross-correlation…" [10, p. 890].

To say that there is a "correlation" between the neural and the psychic does not in any way signify what the nature of the link is, nor whether it really exists or whether it is just an established relationship born of "logical attribution" [11]. It is convenient, therefore, to address some answers given to the question of the articulation between the psychic and the somatic.

In a broad sense, we are facing two extremes:

- Cartesian dualism [12], which marked a before and an after in anthropology and psychology. It clearly distinguishes two substances whose mutual influence must be explained. This problem is solved with the existence of a causal relationship – of an efficient character, through the pineal gland – between one substance and another. A privileged place for the consideration of this "relationship," as we pointed out above, is the topic of emotions. For Descartes, emotions are "dark and confused ideas" of the mind with bodily origin; they are the fruit of connections established in childhood, not originated by the will, but by the body, but controllable from the will [13]. His approach, "was, as later history attests, the object of fruitful controversy" [14, p. 225].
- At the other extreme would be the materialist monism that, at present, is substantiated in the proposal of the "naturalization" of consciousness. In general terms, we can say that it consists of the "thorough and complete explanation of a certain object (in this case the mind) by means of physical-chemical laws based on observations and testable experiments" [6, p. 111].

This would be the position, for example, of the "eliminationist materialism" of the philosophers Patricia and Paul Churchland (1998) "[which] collects and assumes a broad sector of positions" [14, p. 227]. On the other hand, in simple terms, monism – materialism or naturalization of consciousness – states that "the mind is simply and definitely what the brain does" [15, p. 56]. This is meant to express that everything is reduced to the reality of the matter-energy brain.

## Proposals for Articulation

Trying to show all stances or attempts to understand the articulation between the psychic, or mental, and the somatic, the brain, from the contemporary approach is completely impossible, although there have been important attempts [6]. In the psychosomatic medical perspective, the demand for articulation arises immediately [16], and the reason is clear: it arises from the immediate antecedent of the critique of the causal relationship between the physical and the psychic [17]. Rof Carballo, father of psychosomatic medicine in Spain and very knowledgeable about its origins, synthetically categorizes three routes or proposals [18]:

1. Interactionism. The soul and body interact with each other like the electric current in a machine. In this case, vitality comes from the soul, and the machine has a marked passive character. The machine is resistance – but also possibility – against electricity. So far, the term "correlation" has a certain space. Now, since the cerebral reality can be described in physical, chemical, and therefore material terms, the current would be the acts of that same brain, that is, the living brain. This perspective, however, can lead to a kind of monism.
2. Psychophysical parallelism or pseudo-parallelism. These are two processes that run parallel to each other. To each physical process corresponds another psychic process. Between them, there is a relationship of causal type – having efficiency as its model – or a temporary connection. Libet's experiments [19, 20], for example, underlining the temporary nonconnection, or more properly, the priority of neural reactions with respect to consciousness, were interpreted as a denial of the real existence of the free and therefore of the mental [21]. In this proposal, the term "correlation" may be appropriate.
3. Organismic solution. This states that there are two aspects of the same reality, such as two sides of a coin, or two conceptual systems – a point that is also present in the analytic

tradition [4]. An event can be spoken of in biological or psychological (or psychiatric) terms.

Although the organismic solution could satisfy some of a non-monistic or dualistic vision, it does not clarify the link or the foundation of this double conceptual system [18]. Now, what can be proposed as an alternative?

Understanding the complex as a "sum of parts" is always a solution, albeit one of commitment. However, in psyche-soma relationships the sum is not possible. Rather, Carballo – in the wake of Zubiri – prefers to speak of "everything" [18], understood as the "unitary compound," the one that precedes or "is" in the multiple. In classical logic, there was already the distinction between the "whole of order" and the "integral whole" [22]. The highlight of the distinction is that in the integral whole, the unit formed has a substantive character, so that the whole is superior to the sum of the parts. The perfect example is the living being. If an integral whole (living being) is modified in its organicity and heterogeneity of parts to turn it into a whole of order, it would cease to be what it is. In a whole of order, the juxtaposition of elements does not allow everything to be a living being [17]. That is to say, the living being is not simply the sum of the chemical elements that compose it; rather, it requires a concrete way of being linked or integrated.

In the integral whole, because of the "type of order and relationship of the parties," we can affirm that this whole is more than the mere sum of the elements that make it up. Life is alive when it is not a conglomerate of parts, but an organism. In the pluricellular living being, the logic is the same: "the type of vitality of these separated cells is inferior to the one they have within the organism" [23, p. 25]. That is, "every member [of an integral whole] is at the service of the whole, within which it plays a specific role. Its mission is determined by the future of the whole; that is, it has a prospective tendency" [18, p. 9]. In this sense, the type of structure, in particular, organicity, is a condition of life and therefore of operability, which is what is proper to living.

The scientific search for the soul [24], or the overcoming of the error of Descartes [25], researches into how the brain created man, the ego [26], the attempts of Eccles and Popper to solve the problem of articulation "I-brain" [27], or the philosophical materialism of Pérez Álvarez [15], following Gustavo Bueno, which are other paths that seek solutions to the problem, although none of them seems fully satisfactory.

Considering the monistic or naturalization position of consciousness, where correlates have no place, the dualism and the emergentisms insofar as they "consider ideas as 'segregated' from brain activity" [23, p. 40], where correlation has a clear space, it is now necessary to introduce another perspective: "duality."

Now, is the integral whole, the "structure" in the Zubirian tradition [28] followed by Rof Carballo, enough to show a dual reality? Certainly, the living is clearly differentiated from the inert, but it does not seem clear how operation – activities proper to the living being – can be initiated by the integral whole. The duality required to sustain the existence of the "soma" and its peculiar organization and operability is not explained. Neither is "consciousness" explained.

## Another Perspective: Beings with a Psyche

Delving into other levels of analysis, without starting from the assumption of the Cartesian thesis of the existence of two "substances" that are connected – and that correlate – it seems possible to understand reality as being "composed" but not by two types of substances. It is rather (A) the actual composition "act-power" in everything that exists, and more specifically, in living things, and (B) the reality of causality – its different senses – in general and in living beings in a particular way. This perspective, from Aristotelian tradition [29], can shed light on the articulation we have been studying and on the term "correlation."

We will now focus our attention on a distinction prior to that which exists between consciousness and the body. It has to do with the difference between "being alive" and "being inert." If between the two modes of existence there was no intrinsic, constitutive difference,

that is, if there were not something intrinsic in the living that is not present in the inert, it would be necessary to conclude that all matter would be alive or all matter would be inert [30]. Four characteristics, at least, appear in the living that are completely absent in the inert: self-motion, the living being is the principle of its movements, not only of the transport; organicity, the living being consists of diverse, heterogeneous elements but in perfect reciprocal coupling; and unity so that the living is "a" being and not a conglomeration of beings, in fact, what possesses more vital intensity is more unitary, more individual [31]. Likewise, immanence – *manere in* – is highly relevant. This means that in the living, the purpose and the end of the operations begun by the subject are in himself. Possibly the most valued classical affirmation, at least since Aristotle, is *vita in motu*. Thus, from what we have established, the living being has movement with specific features: "life is movement, but this vital movement is self-regulated movement and this self-regulation is intrinsic" [23, p. 23].

If this is the key to the difference between the living and the inert, it is necessary to ask the reason for that difference, what is intrinsically different between the living and the inert. In other words, what are the causes of this fact? We point out that reality – and living reality especially – "is" composed, but not of two substances, rather, that two "components" make up the substance – among other types of reality. All substance is and can be; therefore, it is act and power. The elements of this composition are to be called "causes," not simply as a principle of movement, or efficiency, but as constitutive elements on which the being and mode of being of the real depend: "formal cause" (act) and "material cause" (power). The "formal cause" is the antecedent principle on which the "way of being" of the real depends, its particular configuration or structure, and therefore whether it is a living or inert being. The intrinsic difference between the living and the inert is in the different "formal cause," that is, in the different configuration. It may be useful to think about the structural distinction between the organic and the inorganic. Thus, the formal cause of living beings, responsible for the organic configuration of the living being, can be called "psyche." "The soul is not the essence and definition of a body of this type, but of a natural body of such quality that it possesses in itself the principle of movement and repose" ([32], p. 169 [412b 16–17]).

The "psyche" – formal cause of the living – configures matter in such a way that the living being can act from itself (self-motion). Not only does it form the subject, but its active character allows "operations" to be started. In some cases, these can be called "actions" and in others, "acts." Therefore, we can say that the psyche is a special formal cause, which not only configures the material but also makes it possible to act. In precise terms, Polo explains this circumstance by pointing out that:

> … if we admit that a form does not exhaust itself in informing its organ, then we have the necessary elements to understand that this form informs the organ and also has an immanent activity. That means that in a certain sense that form is immaterial. It is not that it is immaterial because it is separated from the organ, but that it is immaterial because it has a surplus, a formal surplus, on the organ. [23, p. 121]

At this point, we can approach the problem posed: matter and form are not two independent realities, but the form exists "informing" the material, so that it cannot be said that the body and the soul are two substances but that the body lives due to concausality, at least, of matter and form. The brain itself is matter-form concausality, the living being having a surplus (formal surplus) when it has configured the matter. Thus, the immaterial dimension in all living things is clear, without it being necessary to appeal to two independent substantial realities. The first, the act, in this case understood as a form, is the cause of existence of the living being. By virtue of the matter, which is potential, change is possible.

Matter and form are two concauses, not two substances. It is precisely bi-causality that allows one to speak of substance. Indeed, by the form (act) the matter becomes "something organized and capable of self-movement," since "matter" only says that it is space-time as pure power – *partes extra partes* – capable of being organized. Now, in living beings, not only the "disten-

sion" that comes from matter and the configuration that comes by form but also the concrete "self-regulated intrinsic movement" must be explained. Taking place in the living substance, nature is another cause called "efficient cause," principle of the movements of the living being [33]. Usually, this is the primary sense to which causality refers in the field of natural science. But something else must be added: every self-regulated movement has a meaning and an end, which is primarily the subject itself – that is why it is capable of growth. This is so because the causality of which we speak demands the presence of the "final cause." In this way, the living being, and also man, is not composed of substances, but it exists and is as it is by the concurrence of causes, taking into account that "the causes are divided into four" ([29], p. 19 [983a 27]). In other words:

> First, that life was always unitary, that there were as many degrees of life as there were degrees of vital unity. Second, that life was always real and even radically real, as substance. Third, that life was a self-exercise and a self-possession, that is, that it had immanent value from the point of view of efficiency, of triggering movement, and from the point of view of the end of the movement, that is, of efficiency and the purpose. [23, p. 47]

This is, synthetically, the proposed thesis: there is a level of analysis, the causal one, which forces one to consider living reality as a composite, but not as a substance. Following the reasoning initiated, it is even clearer that the distinction between matter and form is not identified with that of mind-brain or with the soul-body distinction. In fact, the body – or the brain – is at least "matter-form," not just matter. If it were only matter, we could not say what it is, and of course, it would not be alive; it could neither perform operations from itself nor would these have any meaning. On the other hand, the term "psyche" appropriately designates the vital principle of the living being – also of man. The psyche speaks of organicity, and it remains after informing the organs (formal surplus), of levels of operability, but it is not identified with the operations. Even less can be identified with a very special dimension of cognitive operations: consciousness or the transparency of thinking before the subject [6].

In this context, it does not seem entirely appropriate to speak of soul-body "correlation", since the living body is for the soul and as soon as the soul configures the matter. Two concurrent causes allow us to speak of the living body: the soul is one of them. Moreover, being the psyche the act that, by being surplus, is the principle of the operations (faculties) that man organizes organically, it is obvious that the priority is of the psyche (act), not of the matter (power). In the living body, what is relevant is not matter, but the psyche (form, not matter).

## On the Types of Analyses: The Question and the Answer

If in the context of applied science, the first thing in the investigation is not the facts – "science does not begin with facts, but with questions; and the questions depend on the theoretical framework from which they are formulated " [34, p. 13] – in the theoretical field, the conceptual frames come from observations, not by deduction, rather thanks to "epagoge" (inductive reasoning). However, certain metaphysical principles govern the future of research, the formation of questions, and the real theoretical scope of the answers. Bear in mind that, if the origin of the questions is known and the scope of the answers, they may not be incompatible but complementary in certain cases. In our presentation, we will cite three of those perspectives that have a certain historical trajectory, referring now to the questions that arise in the context of the mind-brain problem (consciousness-neural activity).

1. One may inquire about the condition that makes something possible. In terms of Kantian origin, we ask about "conditions of possibility" of experience in general or that something is known and the known is given [35]. Without reaching the strict Kantian sense, in the field of consciousness, the question of the conditions of possibility refers to the organic dimension of the subject. Now, being a possible condition of something does not mean being the "cause" of something, nor having explained "what is" that something. From this

perspective, when asking about conditions of possibility, the possibility – linked to the power without fully identifying with it – becomes explicative of the act, but not necessarily constitutive of it. That is, correlation is the appropriate term that, without specifying and not referring to the real relation, marks a dependence of logical order. The condition of possibility becomes a "sign" of the act, being alive, consciousness being a way of being alive, although it is clear that this statement would require detailed arguments for which we do not have enough space. All this seems consistent with the mode of explanation of natural science: "If such or such conditions are given, then there is such a probability that this or that thing will happen" [6, p. 132]. In short, we have explained what is required for something to "probably" happen. With this, we have neither explained what that something "is" nor does it seem logical to reduce it to its conditions.

2. One may also look for the reason why something is. In this case, we stand before the classical term (Leibniz) of "sufficient reason" [36]. From this point of view, to the same extent that something is possible – noncontradictory, primarily – it is affirmed that it exists. It is affirmed with this that the act is a consequence of possibility, more than of potentiality. Here the naturalist, monistic perspective would be situated: the totality of possibility is existence [37]. Consciousness, the mind, is nothing other than neural activity. If neural activity is a sufficient reason for consciousness, there is no real distinction – but only of reason – between one and the other; the explanation for consciousness is found in its sufficient reason: neural activity.
3. The third option we propose is to look for the "cause" and, therefore, the antecedent principle – or the principles, not in a temporal sense – with dependence on the being of the effect or reality in question. In other words, the constitutive elements – the causes – are antecedent elements on which the being and the mode of being of reality depend. You look at the real and the act and not its possibility. The cause is real, and the possibilities are not saturated until the event becomes "real." The causes make the event – or the being – exist and exist in that way. It would be necessary to describe the causes by which the living being is and is as it is – man being a case in point. These are real principles called material, formal, efficient, and final cause, as explained above. With this, we explain the living and operationality and the psyche, which is not matter but structure and allows the operation as "surplus." It remains to establish, in this context, what is consciousness – it is possible to assume the definition of consciousness provided at the beginning of these pages – and what link it has to the living being.

Perhaps the most revealing of what has been said so far is that the living has a dimension – a cause – that is not matter and that makes it exist and exist as such and as a living being. That cause – the psyche – remains after configuring the matter (the faculty) and can thus carry out operations. If this were the case, consciousness as self-transparency would be an essential feature of certain cognitive operations. They have an immaterial origin and they are immaterial. They come from an act and are acts of different kinds. Not all operations – even the cognitive ones – are of the same hierarchical level, as we saw. In this sense, we could say that some operations have a greater dependence on the organic and that it is possible that others do not. If this is so, it could be said that consciousness (self-transparency) that is act is explained and understood from another act as a principle (formal surplus), that it has as a condition that subject is living, and that the organic activity of the living being is a forerunner of consciousness, but not its immediate principle [8].

The terms "condition of possibility" and "correlate" in the light of this description could be applied to the organic with respect to consciousness, indicating that there is a priority – not ontological but procedural – in the organic, the organ of the faculty. However, it neither explains what consciousness is nor does it intend to explain it. It would be appropriate to assume that power or possibility cannot explain the self-transparent act,

whose origin and principle are another act. The term "correlation" that links neural activity and consciousness in this context seems appropriate in a precise sense and if, whenever it is explained, it is not designated a causal relationship – consciousness is not an effect and even less a product of neural activity. Otherwise, it could happen that the real link is not between the organic (with a potential dimension) and consciousness, but between the faculty (formal surplus) and the self-transparent cognitive act.

## Discussion and Pursuance

We have spoken of two critical places, as we indicated in the introduction: the psychosomatic articulation and the problem of the mind-brain "correlation." The first has been made explicit especially with the study of the "living-inert" difference and the causal analysis of living reality, the dualities act-power and matter-form (psyche) as overcoming dualism. In this context, the "correlation" does not seem to have a real space. On the other hand, the term "correlation" has appeared as more or less appropriate and of greater or lesser scope in introducing the concept of "condition of possibility." This term here – the most proper place – indicates only the possibility that must occur for the mental event to occur, but it does not indicate that it is a cause not that it explains the nature of consciousness. The need to explain consciousness (act) and not only its conditions of possibility (logical side of potentiality) has led us to describe the elements that, after the causal analysis of the living being, allow us to open a possible explanation: consciousness (act) has begun by the formal surplus, that is, by another act.

The essential feature of consciousness – "realizing *qua* realizing," the "self-transparency," or the "immediate noticing" that Descartes talked about – requires some further clarification: the relationship between "consciousness" and "who thinks," that is, the person. Identifying both realities is extremely problematic. On the one hand, consciousness is discontinuous in time, so that its identification with the person would make it impossible to sustain the continuity of the personal character – it is the aporia of the sleeping man [38]. Identifying the person with consciousness, on the other hand, would lead one to think that the person begins to exist very late, as the "Great Ape Project" defends [39]. Finally, identifying the person with consciousness, and the latter with neural processes, forgets that the person – the "I" that thinks, wants, and acts – is the one who is always new in each cognitive act. The one who thinks is not the thought. And if I think about myself, I turn the subject into an object, and then I take away its active reality, put more precisely: "the thought-me does not think" [40, p. 174].

From the above, it seems that the study of "consciousness" from the conditions of possibility, typical of neuroscience, always leaves hidden the thinking subject – the Kantian *noumenon*. It is quite appropriate to realize this, that is, the scope of the conclusions themselves and the need to ask more questions and other theoretical horizons. Indeed, the consideration that an act comes from another act – and is not the product of an organic process, nor does it emerge from potency nor is it explained from conditions of possibility – seems to open the opportunity to approach human knowledge, and the person, opening the way to other dimensions that, in this case, would be nonorganic.

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# 8

# Techne and Episteme: Challenges for a Fruitful Translation Between Neuroscience and Psychiatry

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## Introduction

Psychiatric disorders are a heavy burden on the individuals who suffer from them and on society at large. They are leading causes of disability and are related to high morbidity and mortality [1]. However, despite all the funding directed to psychiatric research (which is nevertheless low compared to other health problems), improvement in the number and quality of existing therapies has been limited, and the same can be said for knowledge of the biomarkers that could aid diagnosis or prognosis prediction.

The ultimate goal of psychiatric research is to improve the life of those with mental problems, and this can be carried out through a variety strategies that focus on prevention of mental disorders, the reduction of stigma, the empowerment of service providers, the refinement of diagnostic criteria, the discovery of causal mechanisms, and the development of new and improved interventions [2]. Translational approaches that connect neuroscience with psychiatry are considered to be the cornerstone of these last three foci—diagnosis, explanation, and intervention—and will be the focus of our discussion in this chapter.

For most of the past half-century, psychiatric diagnosis has been based in descriptions of the patient's signs and symptoms and hence rooted in the subjective perspective of the individual (or individuals, as both patient and psychiatrist judge psychiatric manifestations). Standard diagnostic criteria are described by the *Diagnostic and Statistical Manual of Mental Disorders* (abbreviated DSM), which has undergone four revisions since its creation in the 1940s (the current version is DSM-5). In the late 1970s, a substantial revision (DSM-III) combined this descriptive approach with classification systems that grouped signs and symptoms into diagnostic clusters that, for the most part, were defined independently of etiology. These classifications were considered an important advance in the objectivity of diagnostic

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criteria, and by the end of the twentieth century, it was expected that rapid progress in neuroscience advances would bring further objective clarity to the practice of psychiatry. Considerable research was carried out toward this end [3], as seen in the steady growth of publications indexed in MedLine with the term "biological psychiatry" (see Fig. 8.1), which increased at a constant rate until the 1990s and then reached a plateau of constant production that has continued until today.

In short, as indicated by this publication trend, recent decades have witnessed a surge of confidence in the benefits of applying methods of neuroscience to psychiatric research. However, the expected benefits for psychiatric practice have not materialized. In 2013 (shortly before the publication of DSM-5), Thomas Insel blamed this lack of progress on the existing classification system and presented the Research Domain Criteria (RDoC) [4] as an alternative framework designed to align classifications of mental disorders with observable behavior and biological features [5].

The main tenets of the RDoC proposal, which underlie many of the current translational approaches between neuroscience and psychiatry, are as follows: (1) a conceptualization of mental disorders as dysfunctions of neural circuits that, from a phylogenetic perspective, are adapted to certain functions; (2) the theory that these circuits or systems are the basic units of behavior and function dimensionally in a continuum from normal to abnormal across the population; (3) the expectation that these systems and their characteristic dysfunctions can be detected across many different levels, including genes and molecules, cells, circuits, physiology, neuroanatomy, behavior, and self-reports [5].

Accordingly, translational psychiatry looks to a wide range of modern fields and techniques to fulfill its promise of a precise and objective set of diagnostic criteria: genetics (and more specifically GWAS—genome-wide association studies); functional and structural magnetic resonance imaging (fMRI and MRI, respectively); systems biology, -omics and other computational approaches; and, more generally, the field of Big Data analysis [6]. It is important to note that all of these fields are still in their infancy, insofar as they have all evolved hand-in-hand with the recent explosion of computational power. Likewise, RDoC can be seen as new diagnostic strategy that seeks to take advantage of the enormous mushrooming of data that has resulted from

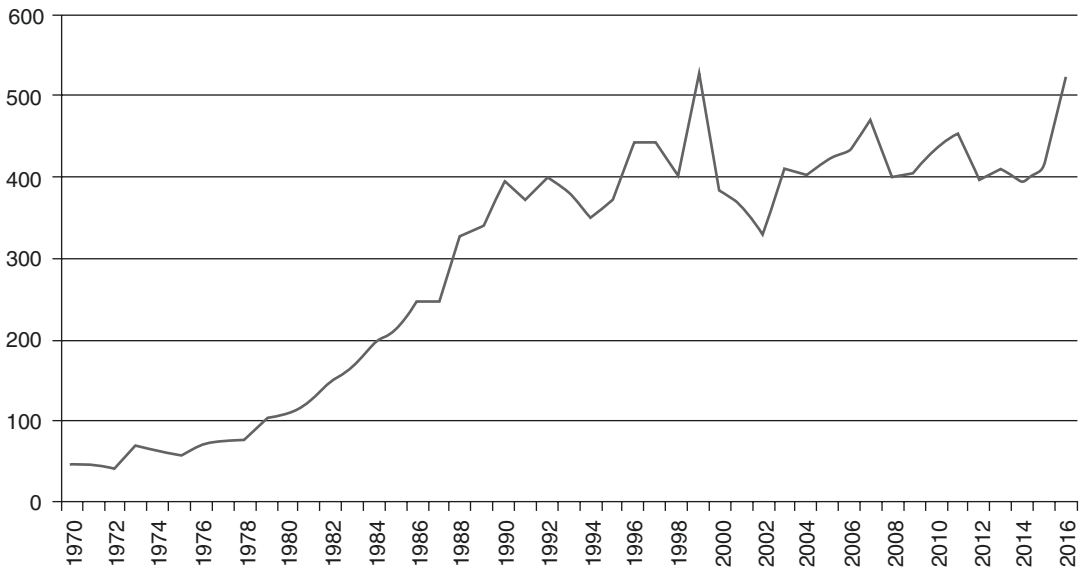


**Fig. 8.1** Number of articles in PubMed with the text "biological psychiatry" from 1970 to present. Number of articles increased until the 1990s and then reached a plateau

combining new measurement technologies (e.g., fMRI) with this newfound computational power.

It is difficult to foresee the impact that such technological advances will have on the classification and diagnosis of mental disorders, let alone the field of psychiatry as a whole. No one doubts the overall, long-term value of access to vast reams of neuroscientific data. The question is how best to use these data, as data, by themselves, are not likely to tell us what we want to know. Indeed, early empirical results indicate that future progress will be less straightforward than anticipated and that expectations for the field of biological psychiatry may have to be adjusted or pared down. Relevant findings in genetics and neuroimaging are particularly illuminating in this regard.

In genetics, the initial excitement regarding the possibility of locating the genetic causes of mental disorders has been deflated in recent years. GWAS studies showed that the increase in risk due to common alleles is tiny so that huge samples are required to find this type of association between psychiatric disorders and genetic variants. The problem of sample size is being circumvented by the Psychiatric Genomics Consortium, an international collaboration that pools together the genetic profiles of thousands of patients with ten different psychiatric disorders. However, while its data base now includes almost one million samples and it has helped to discover more than a hundred genetic associations, its findings have been mainly confined to schizophrenia and will not impact diagnosis or therapeutics in the near future [7, 8]. In the face of such challenges, it is hoped that endophenotypes—defined as internal, measurable phenotypes—will be more amenable to current research methodologies for the characterization of mental disorders in association with genetic variants [9]. However, the largest analysis of the genetics of psychophysiological endophenotypes (including almost 5000 participants) has so far yielded no major results, and many proposed candidate endophenotypes have not been replicated. Indeed, authors of the study concluded that the investigation of endophenotypes is not likely to simplify the genetics of psychiatric disorders [10].

Another booming area of research in translational psychiatry is neuroimaging, which can be roughly divided into structural and functional studies. Similarly to what has just been recounted in the case of genetic studies, the actual findings of neuroimaging have so far fallen well short of expectations. Take, for example, the case of autism spectrum disorder. Contrary to previous studies, which found numerous neuroanatomical abnormalities, extensive scientific collaboration on the neuroimaging of autism has not been able to find consistent differences that characterize the brains of autistic individuals [11, 12]. Perhaps even more striking are the results of a meta-analysis that examines over 500 fMRI studies of psychiatric patients (totaling about 20,000 participants): when only results at the whole brain level are taken into account (likely the most unbiased perspective), the analysis failed to find any differential brain activations corresponding to either specific disorders as defined by the DSM or the RDoC domains. The inclusion of all articles does yield some differential subcortical activations related to the RDoC domains, but no such correlation can be found to support DSM criteria. In conclusion, the authors caution "against attributing undue specificity to brain functional changes when forming explanatory models of psychiatric disorders" [13]. Finally, it is worth noting that the entire field of neuroimaging has been shaken by a recent announcement that the rate of false positives in functional imaging could be much higher than expected due to inadequate statistical control [14]. In fact, similar findings were published in relation to volumetric studies back in 2011 [15], but few seemed to notice at the time.

What do these findings tell us about the project of translational psychiatry? What lies behind its apparent lack of progress? How can it be improved? Some believe that current research strategies only need to be tweaked or expanded, for instance, by combining with a brute-force approximation of increasing sample sizes in empirical studies. We do not agree with this position and, in what follows, we indicate that more substantial reforms are needed.

To be sure, the question of how to improve diagnostic criteria in psychiatry is very complex:

regardless of the path taken, progress will not be easy. There is a rich tradition of debate within psychiatry about the reliability and validity of psychiatric diagnosis [16, 17]. Although the introduction of diagnostic manuals with operational diagnostic criteria led to an increase in the reliability of psychiatric diagnoses, the discussions over the validity of such diagnoses have been endless. In the 1970s and 1980s, validation of psychiatric constructs using the Robins and Guze standards was supposed to follow from the improved reliability of DSM-III, but this proved to be a far more arduous task than was expected [18]. Notwithstanding the interest and relevance of this issue, our purpose here is not to delve into the reliability and validity of psychiatric diagnosis per se. Rather, our main purpose is to examine the epistemological validity of neuroscience research in relation to psychiatry and, related to this, to examine certain flaws in how this research is implemented. To frame these questions more clearly, we find it helpful to consider the Aristotelian concepts of *techne* and *episteme*.

Aristotle distinguished five virtues of thought: *technê*, *epistêmê*, *phronêsis*, *sophia*, and *nous*. *Episteme* is typically translated as knowledge, that is, as the acquisition of truths that are established with certainty. By contrast, *techne* is translated as art or craft: it aims to create something, and its value lies in its product. Thus, in *episteme* and *techne,* we have the well-known Aristotelian division between theoretical and practical spheres of thought. However, Aristotle himself noted that the study of nature would never be purely theoretical or result in knowledge that is completely certain, and the reason is that in the study of nature, *episteme* and *techne* are frequently mixed together. For instance, medical science involves *episteme* insofar as it seeks the facts of human health, but it is also a *techne* insofar as it pursues health as its goal, its product [19].

From this angle, modern science can be seen as a form of *episteme* that is based in a wide variety of experimental and statistical methods, all of which are forms of *techne*—means of acquiring knowledge driven by particular aims and purposes. This is a simple point, but it is often lost in popular images of science, especially those that exalt the unique epistemic status of professional science by downplaying the role of *techne* in the production of scientific knowledge. Drawing attention to *techne* reminds us of two important ways in which such images of science need to be corrected: first, that scientific knowledge consists not just in abstract representations of nature but also in practical knowledge that cannot be divorced from our interests, aims, and purposes; and second, that scientific knowledge depends on the development of highly specialized practices through which the objects of science are prepared and studied.

In the case of translational neuropsychiatry, this perspective helps to clarify two key points that will be elaborated further below. First, it clarifies that the overall aim of neuropsychiatry is to discover the physical underpinnings of mental disorders in service of clinical practice, that is, with the ultimate aim of improving the life of people with mental illness. Second, it clarifies that the authority of neuroscience as *episteme* depends on the cultivation of forms of *techne*, or specialized craft, namely, the skillful and ethical use of neuroscientific tools and measures. Whereas the widespread public fascination with neuroimaging has encouraged neuroscientists to present their knowledge as if it were simply "read off" the brain, the concept of science as *techne* encourages scientists to present their knowledge as a highly refined product whose meaning is not self-evident and whose objectivity should not be taken for granted. For those engaged in neuropsychiatry, it urges the following questions: As (translational) neuroscientists, have we been master craftsmen (i.e., *technites*)? Have we carefully and deliberately refined our *techne* with its goals and purposes in mind? Have we demonstrated the relevance of our *techne* for the *episteme* of psychiatry? In the remainder of this chapter, we explore various issues related to these questions, and we conclude that many of the challenges faced by translational psychiatry can be traced to simplistic views of science, the brain and the mind that gloss over the dimension of *techne* and its critical importance for establishing the *episteme* of science.

## Techne

In a widely read 2005 article, John Ioannidis of Stanford University declared that most published scientific findings are false [20]. His thesis is that research biases, combined with the low statistical power of results, habitually lead to unreliable results [21]. Viewed more than 1.5 million times since its publication, Ioannidis's article has sent shock waves through the scientific community, and in the last decade, many others have concurred that there is indeed a problem in the way that we do science. We suggest that this problematic unreliability of scientific knowledge can be traced to problems of scientific practice—*techne*—problems that are endemic in the domain of translational neuroscience. For neuroscience to generate high-quality *episteme*, it is necessary to cultivate the proper virtues of *techne*, which seem to have been neglected in recent years. Many scientists lament that fierce competition for funding high-profile publications and the recognition of colleagues have undermined the values of scientific practice, as research is rewarded for flash rather than substance. A 2013 editorial by Cambridge University psychiatrist Paul Fletcher and UC Santa Barbara psychologist Scott Grafton summarizes the situation as follows:

> It is an embarrassing, though by no means unique, failing in the neuroimaging field that the quest for the new and exciting has frequently over-shadowed the more humdrum side of science—the need to replicate and re-evaluate. This failing is particularly indefensible in clinical research where a key part of the goal must surely be to translate the insights generated by initial experiments into credible, practically useful advances in patient management. [22]

The warnings of Fletcher and Grafton have been echoed by many other leading experts in neuroimaging. It is now clear that a high proportion of current neuroimaging experiments are in need of substantial qualification [23], similar to problems of replicability encountered in other areas of science [24]. In this section we highlight specific problems of *techne* that plague fMRI studies. These studies are especially relevant to the present discussion because of their high impact on translational psychiatry and also because they exemplify critical issues of scientific practice that extend much further than the MRI field. The problematic lack of rigor of many fMRI studies, as described in a recent manifesto [23], includes a number of interrelated problems, which can be broken down as follows.

*Degrees of researcher freedom*: the analysis of fMRI data is complex and involves numerous steps and decisions on the part of the researcher. Each of these decision points constitutes an additional "degree of researcher freedom," which, ideally, should be determined a priori. Instead, these degrees of freedom are often exploited (consciously or unconsciously) by researchers to obtain a desired result. Results are often presented as if they were the outcome of a single, predetermined strategy for the production of data—a single "pipeline"—and thus indicate a region of activation that is uniquely correlated with the experimental setup. However, when the tens of thousands of possible alternative strategies are followed for a single experiment, it is possible to obtain activations throughout the brain [25]. Similar problems can be found in most scientific fields [26].

*Low statistical power* refers to the relation between the number of individuals actually included in a study and the number that would be needed to find a result of a given strength. Neuroscience studies are difficult and expensive, and costs go up steeply when imaging is included. As a result, typical sample sizes of fMRI studies fall way under those needed to reliably detect the small activations that the scanners produce, even in the case of "powerful" tasks such as motor paradigms [23]. Such difficulties call into question the methodology of psychiatric studies that compare activations between patients and controls in a task by measuring activity correlated with very subtle mental constructs, and then at the group level try to correlate those activations with clinical ratings obtained through questionnaires or similar measures. In fact, translational psychiatry that does not rely on fMRI has better statistical power, although it is still low and has not improved over time [27].

*Significance chasing* may be the root cause of many bad practices in science. It is characterized by the adoption of search strategies that maximize the probability of (spuriously) obtaining a result below a conventional statistical threshold (i.e., lower p values). In fMRI, significance chasing is most commonly manifested as the incorrect use of regions of interest (ROIs) in the measurement of activity responses. When searching for correlations, ROIs can be defined in a way that is not strictly independent from what is to be measured, leading to inflated statistics and effect sizes. Similarly, a researcher can decide to limit the search for activations to a ROI that he or she has already been determined to be a site of activation. These types of voodoo correlations occur frequently in fMRI studies but are indicative of a more widespread problem in science [28]. Strategies of significance chasing in psychotherapy trials, albeit superficially different, involve similar mechanisms. For a highly critical (but ironical) description of such strategies, see [29].

Finally, regarding *incorrect or over-lenient statistical methods*, we have already mentioned the work of Eklund et al. which was widely reported in the media [14]. This article shows that certain common statistical parameters are strongly related to false-positive results (which is a likely reason for their popularity).

It must be clarified that these problems do not invalidate the use of modern imaging technologies that now dominate the domain of translational psychiatry—rather they indicate problems in the use of these technologies. Nevertheless, bad practices are so widespread that they have severely eroded confidence in published results of imaging studies. From an Aristotelian perspective that emphasizes the importance of *techne*, we could say that the tools for the acquisition of knowledge are not necessarily flawed in themselves, but the skill with which they are used needs to be improved.

Why are these bad practices so common [30]? The likely reason is that researchers do not believe that the biases introduced by flawed methodologies are strong enough to impact the conclusions of their studies. However, the evidence indicates otherwise. The naïve belief that high-quality knowledge can be produced without due diligence in the production of scientific data is a major hurdle for the successful translation between neuroscience and psychiatry. But it is not the only one.

## Epistemological Considerations in Psychiatry

One of the most common criticisms of the RDoC program and of translational approaches in biological psychiatry more generally is that the view of the relationship between the brain and mental symptoms tends to be overly reductive. Translational psychiatry is thus considered by many a neurocentric approach that assumes a direct equivalence between certain aspects of mental life and brain configuration and functioning [31]. However, most psychiatric symptoms can only be understood as such in reference to the perspective of a self-conscious individual. Each person interprets the meaning of their own mental experience in a particular way, and this meaning is as important to diagnosis as any detectable dysfunction of underlying brain circuitry [31]. Furthermore, given that human minds are social entities, psychopathology occurs within a specific social and relational context. These subjective and intersubjective perspectives are registered by the DSM-ICD approach insofar as any symptom can only be considered as such if it leads to suffering, distress, or impairment to the subject or his or her peers. Nevertheless, they have been pushed to the margins of the RDoC framework. The implicit assumption is that in definitions of abnormal behavior, biological data trumps any other kind of reality or influence [32].

The limits of current conceptualizations of psychiatric disorders have been explored in detail over the last 30 years by Germán E. Berrios and his colleagues at the University of Cambridge [33]. Since his retirement he has endeavored to synthesize this past work into a coherent theory of mental symptoms [34]. In this section we use the perspective of Berrios and his colleagues as a guide to highlight a key epistemological challenge for translation between neuroscience and psychiatry.

Current neuroscience of psychiatry, whether based on the DSM-ICD or in the newest RDoC, takes as its starting point the assumption that its objects of inquiry are stable, natural objects whose identity is determined independently of our conceptualizations, much like the objects of natural science [35]. This assumption leads directly to the belief that empirical neuroscientific data is more important than theoretical interpretation and analysis concerning the objects, categories, or concepts of psychiatry. Accordingly, the adequacy of a conceptualization of psychiatric disorder is judged primarily by how well it helps neuroscience research to obtain the objective data that will ultimately determine the true nature of mental problems. There is little room in this line of thought for contextual influences or personal differences in how individuals experience or live a similar event. In this sense, RDoC represents an even more extreme approach than previous approaches, as it disregards the phenomenological perspective and uses its dimensions of psychiatric analysis primarily as probable cognitive domains whose purpose is to guide data acquisition in service of the objective classification of mental disorders [35].

However, *"the findings of the natural sciences (i.e. the inscriptions of the configurations in the brain) do not and cannot by themselves produce definitions of mental disorders"* [36]. Behavioral and mental abnormality is defined or at least heavily influenced by socially constructed expectations and norms; empirical research into the causes of mental disorders is carried out only when an abnormality has been identified as such within a particular social context. In turn, this empirical research can influence the collective semantic space and change the way we see these abnormalities, most likely moving them from a concept of deviation toward redefinition as pathological [36]. In short, the intrinsic characteristics of the basic objects of psychiatric study are such that a purely biological approach cannot suffice. These objects are mental symptoms, defined by the Cambridge group (and many others) as hybrid objects: they have a physical kernel, but the significance of this kernel is determined by a semantic envelope that is subjectively and intersubjectively defined [34]. This characterization of the object of psychiatric inquiry draws a line between medicine and psychiatry. Whereas in medicine signs and symptoms function primarily as pointers toward bodily pathology, in psychiatry, "mental symptoms and signs constitute both the diagnostic tools as well as the diagnostic products" of psychiatry [35]. Hence, psychiatry needs its own epistemology, one that accounts for the peculiarly compound nature of its objects of study [34].

So, given this complexity, what can we say about the relationship between brain structure and mental symptoms? According to Markova and Berrios, while all mental symptoms are somehow represented in the brain, it is important to distinguish two very different types of brain inscription. Primary brain inscriptions are those in which the relationships between neuroanatomy and mental states are mostly direct. In secondary brain inscriptions, however, the semantic aspect of the psychiatric symptom is the decisive factor. Accordingly, secondary brain inscriptions are more complex, as the neurobiological perspective provides only a non-specific substrate that, by itself, does suffice to define any symptom [35–37]. Neuroimaging research may help to pinpoint the neural location of both types of inscription, but in the case of secondary inscriptions, it cannot determine the interpretation of the mental symptom. Thus, biological data plays a very different explanatory role in cases of primary and secondary inscription; in the latter case this role is very limited. Similar limitations may apply when trying to explain mental symptoms in terms of genetics or basic neuroscience.

To summarize, current translational neuroscience assumes that the typical relation between the brain and symptomatology is of the primary type [37]: all psychiatric disorders are thought to consist primarily in disruptions of biological systems, and, as such, when their neural substrates are understood, they can be explained satisfactorily. However, as indicated by cases of secondary inscription, many mental symptoms require more complex conceptualizations of mental symptoms that include the semantic dimension. Certainly it would be easier if all symp-

toms could be traced to primary inscriptions, but to base the entire enterprise of translational psychiatry on such a simplistic epistemological model of mental symptoms can only hinder its progress in the long run.

## Epistemological Considerations in Neuroscience

In the previous section, we discussed epistemological limitations within psychiatry, especially with regard to the definition and understanding of symptoms. In this section we turn to consider similar issues within neuroscience. In particular, we wish to call attention to signs that the dominant scientific conceptualization of the brain is due for careful reconsideration. During the last decades, the brain has been conceptually operationalized as a computational machine. However, as we learn more about the complex dynamics of the brain and their relation to mental processes, the differences between computers and the brain have become clearer [38]. It is too soon to announce that computational theory is defunct, but there is a clear need to gain critical distance on computational and informational concepts that have until recently been widely taken for granted in cognitive neuroscience.

Computational theory belongs to a long history of technological metaphors for the brain and its functions [39]. Yet many scientists and philosophers have insisted that the image of the brain as a computer is *not* a metaphor (see [40] cited in [39, 41], cited in [42]; see also [43]), even while they admit that the brain is not like any of the computers that we build and use. On closer examination, it is difficult to pinpoint exactly how the brain has been demonstrated by neuroscience to be like a computer, as the most precise accounts of the brain's computational nature tend to be theoretical accounts proposed by philosophers without any clear empirical support [e.g. see, 44]. Accordingly, it seems more accurate to say that the alleged computational nature of the brain is not an established empirical fact so much as a very influential theoretical framework—a Kuhnian paradigm—that has served for many years to orient investigation and interpret data about brain architecture and function. When scientists insist on the brain's computational nature, therefore, perhaps what they are defending is a kind of theoretical foundation which they believe is necessary for any coherent understanding of the available data—similar to the way in which evolutionary theory is necessary for understanding data about form and function in living systems. However, its widespread influence in neuroscience and psychology notwithstanding computational theory clearly does *not* have the kind of undisputed status in these fields that is enjoyed by evolutionary theory in biology. And if one traces its trajectory over the last 60 years or so, it becomes evident why this status is lacking. It is critical, therefore, to gain historical perspective on the current prevalence of computational vocabulary and imagery in neuroscience.

The "cognitive revolution" of the 1950s that established cognitive science as a field was driven by the computational theory of mind and its view of the mind as an information processor [45]. During the period in which the computational paradigm gradually came to prominence (1950–1970s), neuroscience was not well developed, and so, for the most part, the computational theory of mind developed independently of biological data. This division was reinforced by the influential position of "functionalism" [46], which established a separation of the mind and brain so that computational functions of the mind could be investigated independently of their biological instantiation. Moreover, insofar as neuroscience had something to say, early and influential work (e.g., [47, 48]) seemed to indicate that neurons could be understood as computational mechanisms. In the 1970s and 1980s, the functionalist separation of computational theory of mind from neuroscience gradually began to be replaced by a more integrated approach. Influential accounts of the integration of computational theory with neuroscience such as David Marr's three-level approach [49], together with some version of functional modularity [50], defined the explanatory agenda for the emerging field of cognitive neuroscience for decades to come (see also [51, 52]).

There are indications that the influence of the computational paradigm is now in decline. It never enjoyed unanimous support—see criticisms by neuroscientists [53, 54], psychologists [55, 56], and philosophers [57]. But especially since the early 1990s, the emergence of alternative research programs in robotics/AI [58, 59], cognitive science [60], and neuroscience [61] has changed the landscape of cognitive theory. Within neuroscience, an emerging family of "neurodynamic" approaches that regard transient, large-scale patterns of rhythmically coordinated neural activity as the main vehicles of cognition/emotion [54, 62–66] presents a rather different picture of the neural embodiment of cognitive functions. The upshot of this potentially radical change of perspective is that the precise functions of neural structures at nearly all scales are not fixed; rather, functional roles of structures can change in relation to the context of neural activity [67, 68].

While it is too soon to say exactly how this new and still emerging picture of the neural basis of cognition will affect the translation of neuroscience to psychiatry, at the very least, one can say that the need to be critically aware of how computational concepts of the brain guide this translation is now greater than ever. Whether or not neuroscientists deliberately adopt computational models of cognitive functions, computational *vocabulary* (e.g., "information processing") and *imagery* (e.g., diagrams of boxes and arrows) still pervade the field of neuroscience and influence the way in which its results are interpreted and translated to other fields. Moreover, this dominance of computational concepts, together with advances in neuroimaging techniques, has supported an explanatory agenda that remains largely focused on the precise localization of cognitive functions [69], which, in turn, supports the expectation that mental symptoms can be similarly pinpointed. The reason is that the discrete, rule-based nature of computational operations, whether executed in parallel or sequentially, strongly supports—if not requires—the assumption that mental functions are realized by neural processes in a consistent manner. In other words, a basic premise of computational theory is that cognition functions can be analyzed as highly complex but relatively stable systems of component operations, each of which is realized by a specific pattern of neural activity.

However, as indicated by neurodynamic perspectives, it may be that cognitive functions are assembled "on the fly" by transient patterns of coordinated activity and that contexts of activity alter the functional contribution of component structures and processes. If so, the relations between neural structures and functions are many-to-many, and the agenda of functional localization is misdirected. All this is to suggest that we are arriving at a critical juncture, perhaps even the beginnings of a "paradigm shift," with respect to our understanding of functional specialization and localization. Accordingly, we believe that psychiatrists would do well to anticipate this shift and consider how the neural basis of mental symptoms might be conceived differently.

## Relationship Between These Difficulties

We have proposed that lack of depth in the way that we do science, conceptualize mental symptoms, or understand the brain is partly responsible for the lack of success in building bridges between neuroscience and clinical psychiatry. These three hurdles might seem independent, but we suggest that they are united by a common ideal regarding the kinds of causal explanations that are supposed to be produced when science is successful. This ideal is the highly influential model of scientific explanation by Cartesian reduction, whereby a complex system is analyzed into its simplest functional constituents. The extent to which modern science has actually pursued this ideal is by no means clear; probably its influence has been felt more strongly in some fields of science than others [70]. What is clear is the fact that in the last several decades, an increasing number of scientists in a variety of fields from physics to sociology have explicitly called this ideal into question [71].

In the case of neuroscience and psychiatry, the influence of this Cartesian ideal can be seen

wherever research agendas are oriented toward the production of "essentialist," i.e., context-independent, kinds of causal explanation. In other words, we see this ideal at work whenever neuroscientists seek a one-to-one correspondence between functions and neural structures (at any level of analysis) and, likewise, when psychiatrists seek a one-to-one correspondence between mental symptoms and neural causes (functional or structural). On the one hand, we do not wish to exaggerate the degree to which these fields are driven by this expectation: no doubt many neuroscientists and psychiatrists are well aware that the mind/brain may be too complex to yield simple, causal accounts of mental functions and illnesses. On the other hand, the attractiveness of this ideal, both for scientific understanding and for clinical diagnosis, is such that its influence is likely to be felt even when it is not explicitly adopted as an explanatory goal. Take, for example, the difficulties of diagnosing, explaining, and treating cases of autism spectrum disorder: how much easier would it be to identify and treat such cases if they could be easily pinpointed as the manifestation of a readily detectable neuroanatomical anomaly, cognitive deficit, or genetic mutation? But it seems that such features can only be associated with autism with more or less frequency so that psychiatry cannot dispense with more complex diagnostic criteria.

As indicated briefly in the previous section, the computational paradigm has reinforced the expectation that the brain works like a machine and that neuroimaging research will reveal explanations of cognitive function that have the form of one-to-one correspondences between functions and structures, circuits, or patterns of activity. The reason, as we pointed out, is that the idea of computation as a rule-based process requires that cognition ultimately consists in operations that are always executed the same way and are thus indifferent to context. It would certainly be much easier for neuroscience, and for the translation of neuroscience to psychiatry, if the brain did work this way. But if, in fact, the brain does *not* work this way, translational psychiatry may have to revise its goals and expectations considerably.

We wish to clarify that the problem with such explanatory models is not just that they oversimplify, although that may be the case. Science depends everywhere on the construction of simplified models of reality, and in this respect the simplifications of the computational paradigm of cognition or biological models of mental symptoms are not problematic in themselves. Instead, problems arise from the temptation to accept simplified models as if they were complete descriptions and the tendency to treat standard models as if their mode of simplification is the only one possible. In either case the fact that scientists must choose among alternative simplifications is denied. Here again we see the importance of keeping the *techne* of science in mind: given that science is driven by particular aims and purposes— in the case of translational psychiatry, the ultimate goal is the improvement of clinical practice—it is crucial that scientists are critically aware of how their choices about simplification contribute to these aims and purposes. Even if it is true that science cannot dispense with simplification, scientists must constantly be on guard that their preferred simplifications are not taken for granted. It is possible to have a sophisticated and subtle understanding of how a simplified model functions to direct inquiry and produce knowledge, and this understanding is at the heart of *techne*.

At the same time, it must be acknowledged that the role of simplification in science has been called into question in recent decades. This question is at the heart of the development of "complexity science," a collection of research programs in multiple disciplines that seeks a unified approach to the study of complex systems [71]. We cannot enter into the details of ongoing debates about the nature of complexity science and its promise of a "new kind of science." Let it suffice to point out that the peculiar complexity of the brain (both structural and dynamic), and questions about the kinds of models that are appropriate to this complexity, are at the center of this controversy. Some argue that human brain dynamics is precisely the kind of complex phenomenon that calls for a radically new set of scientific methods and explanatory standards,

although exactly what that means for neuroscience and its translation is not yet clear.

## Future Directions

We have indicated various reasons why scientists—especially in the increasingly high-profile field of neuroscience—are tempted to neglect *techne*, for instance, by downplaying the importance of methodological choices on the production of data and the conclusions drawn therefrom. This problematic attitude toward neuroscientific data has a bidirectional effect, as the production of inconclusive results leads more readily to incomplete or even erroneous models of the brain and mind [72]. In contrast, a research community that is critically aware of its responsibility for the maintenance of good *techne* is more likely to produce results that are both substantive and useful. In this final section, we discuss possible ways in which a culture of *techne* might be revived so as to support a more productive relationship between neuroscience and psychiatry.

Scientific pursuit is a human endeavor, and as such it is heavily influenced by cultural practices. For instance, neuroscience will always be impacted by contemporary technology in its conceptualization of the brain, as well as by popular images of the special authority and status of science. Neuroscience is also affected by the special incentives and constraints of academia (the pressures of peer review, the constant hunt for funding, tenure evaluations, etc.). In this context, novelty and "flashiness" are often prioritized over robustness of data. To combat this trend, we have argued for renewed attention to the importance of *techne* for the successful pursuit of translational neuroscience. In particular, scientists must hold each other to higher standards of scientific "craft," prizing the quality of experimental design as much as, if not more than, the noteworthiness of results: they have to "publish houses of brick, not mansions of straw" [73]. Replication should be upheld as an important part of science, interpretation should be as clear and unambiguous as possible, and robustness of data should be paramount. Goals and priorities may also need to be shifted: for instance, scientists may need to be less ambitious regarding the novelty of their theories and more meticulous regarding the rigor of their methods.

Toward this end, the specific measures that have been recently proposed include the improvement of methodological training, the protection of researchers from their own cognitive biases through blinding and preregistration of the analysis of experiments, and the encouragement of more collaboration between centers, groups, and disciplines [24]. Such measures can contribute to the refinement of any scientific discipline, but they are especially relevant to the improvement of translational neuropsychiatry. Methodological training is paramount for clinical researchers, while basic statistical knowledge is also lacking in many neuroscience researchers. As explained above, there is an urgent need to minimize the effects of the many degrees of researcher freedom involved in neuroimaging studies and the problems derived from using small sample sizes. Finally, collaboration between centers and groups could help to reduce research costs and improve statistical power, while collaboration between disciplines could raise critical awareness about the limitations of standard methods and theories. As we have emphasized repeatedly, the *techne* of neuropsychiatry calls for greater awareness of the limitations and pitfalls of measurement tools, such as measurement error [9]. The need for increased attention to measurement error applies equally to behavioral paradigms and imaging techniques.

At the same time, outside of scientific practice, there is growing need to address the external incentives that have played such a key role in maintaining problematic approaches to translational psychiatry—for instance, the way in which the pressure to publish in high-impact journals undermines the fundamental need for replication studies. Any thoroughgoing attempt to improve scientific *techne* must address the political structures of academia and inquire how their reform might ease the transition to a different kind of research culture and environment.

On the other hand, the primary limitation of biological measures is epistemological. As we

have shown, the problem with these measures is that, even when robustly determined, they are insufficient for the explanation of most psychiatric illness. No one should question the relevance of biological data to psychiatry; at the very least, they can serve as the basis for cross-disciplinary validating techniques in combination with subjective reports, which, in turn, must be used to validate biological measures [74]. The critical point is to guard against exaggerating or overemphasizing the explanatory power of biological measures [9], relegating non-biological sources of information to a secondary position. The nature of mental illness is such that subjectively defined symptoms and intersubjectively defined socio-personal impairments must always play a major role in the study of psychiatric disorders. As discussed above, this is because mental illnesses are partly socially and historically constructed, and this nonphysical component cannot be forgotten or set aside. On the other hand, to say that mental symptoms are ineluctably subjective does not mean that psychiatry should not aspire to appropriately rigorous standards of objectivity. To stabilize our understanding of mental symptoms, Berrios argues that psychiatry should include conceptual analysis and historical studies within its methodology [35]. The former seeks to understand the semantic relationships between concepts and clarify their usage and reference within a particular domain [75] and can be applied to the domain of mental psychopathology to better understand mental disorders and symptoms. The latter aims to identify changes in the definition and understanding of a psychiatric concept over time and can serve to complement and contextualize conceptual analysis. For instance, we have recently carried out a historical analysis of the evolving understanding of identity disorders in different versions of the ICD and DSM manuals and related this trajectory to various philosophical positions [76]. Any methodology that places contemporary biological measures into a broader historical or theoretical context could help to bridge the gap between neuroscience and psychiatry.

Finally, it is important to consider how attempts to improve the *techne* of translational psychiatry can be aided by competition within the relevant disciplines. As we have seen, competition in science can be a two-edged sword. On the one hand, it is essential for separating out good science from bad science and encouraging scientists to be more diligent in the acquisition of data and presentation of results. On the other hand, competition can also work the other way, tempting scientists to cut corners so as to produce more attention-grabbing results. We have just discussed how the bad effects of competition might be mitigated by shifting the "value system" of professional science toward the virtues of *techne*. However, because all scientific disciplines must make do with methods that are far from perfect, even when scientists are attentive to *techne*, it can be difficult to know where to draw the line between standard and substandard science. This is especially true for scientific fields where measurement presents special challenges, as is arguably the case in neuroscience. So, for instance, in reply to criticisms of the low statistical power of imaging studies, neuroscientists can always say that they are well aware of these problems, but they are doing the best they can, and low statistical power is better than nothing. Thus it seems that the best way to raise standards is to promote a substantial diversity of theoretical approaches that are competing with one another in their use of the same measurement techniques.

As discussed above, most of the brain imaging studies that have come to dominate so much of current neuroscience—and, in turn, so much of translational psychiatry—are likely to have been oriented in their search for data by a single theoretical paradigm, the computational theory of the mind. While precise formulations of computational theory are hard to come by, in vague outline, it leads to certain expectations about the functional specialization of structures and networks and thus to certain expectations about the localization of brain function. Thus it is highly plausible, although by no means certain, that these widely shared expectations have a lot to do with the lack of statistical rigor that has plagued neuroimaging studies in recent years. It may be readily admitted that the correspondence between localized brain activity and a given cognitive task

has not been established with sufficient statistical power, but such limitations are much easier to tolerate when no one doubts that the establishment of *some such correlation* is the ultimate goal of neuroscience research. If, on the other hand, the fundamental assumption of functional localization is explicitly challenged by an alternative theoretical paradigm [69], then the statistical problems of neuroimaging research suddenly appear in a very different light.

Thus one of the most promising future directions of translation psychiatry would be the development of a robust alternative paradigm that can challenge the assumptions of mainstream translational research. And in fact it seems as if such a paradigm is emerging from the branch of cognitive science known as enactive theory [77–79]. We cannot enter into the details of enactive theory, and in any case our purpose here is not to advocate for the adoption of enactive theory as an alternative paradigm for translational psychiatry. Rather we simply wish to point out that enactive theory is a well-established and increasingly influential non-computational theory of cognition that has connections with complementary views of brain function [62] and has begun to yield new theoretical perspectives in the field of psychiatry (see especially works of Thomas Fuchs https://www.klinikum.uni-heidelberg.de/Publications.6067.0.html?&L=1). Perhaps in the years to come, translational psychiatry will be invigorated by internal competition between "traditional" computational approaches and newer approaches such as enactive theory. In a best case scenario, this competition would propel the refinement of *techne*, which in turn would help to improve the diagnosis, understanding, and treatment of mental illness. Let us hope for the best.

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# Part II

## From Basic Neurosciences to Human Brain

# 9 Vascular Alterations in Mental Disorders: Focus in Angiotensin II Role

Leticia Ester Delgado-Marín, Osvaldo Martin Basmadjian, Victoria Belén Occhieppo, Natalia Andrea Marchese, Claudia Bregonzio, and Gustavo Carlos Baiardi

## Vascular Function: A Coordinate Response with Brain Activity

The continuous metabolic demand of all tissues in the body is sustained by oxygen and nutrient supply and waste product removal through the vascular system [1]. This exchange mainly occurs in a large interface area provided by a fine microvessel network. The brain is the most metabolic active tissue in the body. Its activity demands 17% of the heart blood flow and consumes 20% of the available energy during the resting state, despite it comprises only 2% of the body's mass [2, 3]. Furthermore, it is known there is a close relationship between the metabolic demand and the vascular function, where the blood vessels can coordinate the cerebral blood flow (CBF) with the neuronal activity, a process called functional hyperemia. Thus, the local increase of brain activity is accompanied by regional increased CBF; meanwhile, its cessation or reduction leads to time-dependent decrease in membrane electrical activity, neuron viability, and tissue integrity [4–6]. Moreover, it is generally accepted that hemodynamic responses are accompanied by changes in capillaries shape [7]. In this sense, the microvessels have highly dynamic architecture, since their growth adapts to the changing metabolic demands of central nervous system (CNS), process called angiogenesis. In an early stage, known as sprouting phase, the primary capillary plexus is formed, where multiple and successive sprouts, produced from preexisting microvessels, proliferate into the extracellular matrix in response to released factors by hypoxic cells [8]. Later, in a second stage named intussusception, simultaneous scattered pillar are generated to split primary vessels into new thinner capillaries. Along this process, capillary plexus is expanded to form a hierarchical vascular tree, providing a larger surface area for the exchange of oxygen, carbon dioxide, and nutrients [8].

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## Microvasculature: Formation and Growth

Microvessels represent the major percentage of the about $10^7$ m length of humans' blood vessels [9]. While main blood vessel structure is genetically determined, the number, length, and geometrical configuration of the microvasculature emerge as the adaptation to tissue necessities and stimulus [9]. From the abovementioned, it is clear that microvessels' genesis and growth are highly plastic processes that begin in the embryo and continue during the lifetime, two processes known as vasculogenesis and angiogenesis, respectively.

Capillaries are constituted by a monolayer of quiescent endothelial cells (EC) sheathed by pericytes with a common basement membrane. At resting conditions pericytes release angiopoietin 1 (ANG-1), vascular endothelial growth factor (VEGF), and fibroblast growth factors (FGFs) which stimulate EC survival and contribute to maintain the resting state, mural coverage, and basement membrane deposition [10]. In brain microvasculature, excluding choroid plexus and circumventricular organs, tight junctions produced by molecules such as VE-cadherin, claudins, and occludins are present between adjacent EC. The presence of tight junctions, the absence of fenestrations, the few pinocytotic vesicles, and the astrocyte function conform the blood-brain barrier (BBB), which protects the neural tissue from toxins and maintains ionic homeostasis [8]. In addition, VE-cadherin promotes vessel stabilization through the inhibition of VEGF receptor-2 (VEGFR-2) and activation of transforming growth factor (TGF) pathways [10].

## Vasculogenesis

In the developing mammalian embryo, vasculogenesis promotes angioblasts to differentiate into endothelial cells, producing de novo vessels, which afterward are assembled into a vascular labyrinth [10]. However, during repair of healthy vessels or expansion of pathological vessels in the adult, bone marrow-derived cells and/or endothelial progenitor cells may be recruited to the vascular wall, although this phenomenon is currently in debate [10].

## Sprouting Angiogenesis

The expansion of primary plexuses, in both embryonic and postnatal life, is produced by migration and proliferation of a sprout through the basement membrane of the vessel wall, spreading and anchoring into the surrounding tissue. This is a relatively sluggish process that takes a minimum of 3–5 days to generate perfused vessels [8].

Tissue hypoxia is a potent microvascular growth signal, triggering sprouting angiogenesis by the activation of proline hydroxylase, hypoxia-inducible factor (HIF) system, releasing HIF-1. This transcriptional factor induces the activation of genes directly involved in angiogenesis, including the VEGF genes, ANG-1 and ANG-2, and the inducible form of nitric oxide synthase (iNOS) [11]. In the CNS, the initiation of vessel branching is mainly driven by VEGF-A secreted by astrocytes and neurons which stimulates VEGFR-2 [1, 10]. In addition to the paracrine signaling of VEGF for angiogenesis, EC themselves are an important source of VEGF. Moreover, angiogenesis is promoted by neuropilin-1 (NRP-1) and neuropilin-2 (NRP-2), which, at the same time, are VEGF co-receptors and enhance its signaling [1, 10]. Furthermore, angiogenesis is also stimulated by the action of the FGFs family over its receptors on EC and other cells [12].

When the angiogenic signals arrive, the vessel is dilated, and an EC is selected as a tip cell, which loses its cell junctions and releases matrix metalloproteinases (MMPs). These enzymes degrade extracellular matrix, allowing the cell migration across the basement membrane in response to guidance signals from semaphorins and ephirins. Also, the tip cell releases ANG-2 promoting pericyte detachment through the antagonism over ANG-1. Delta-like canonical Notch ligand

4 (DLL4), released by the tip cell, increases the expression of VEGFR-1 in surrounding EC and promotes vessel lumen formation through their proliferation and elongation. At the same time, the proliferating EC release platelet-derived growth factor-B (PDGF-B) that attracts pericytes toward the basement membrane to stabilize the nascent vessel [10].

## Intussusceptive Angiogenesis

Intussusceptive process begins with the protrusion of opposite capillary walls into the vessel lumen, until they reach inter-endothelial contact. This process is a relatively new concept of blood vessel formation, described for the first time in 1986 by Caduff and coworkers. This could be explained by the small size of the pillars, their complex spatial structure, and the need of three-dimensional analysis for their visualization [8, 13].

In contrast to sprouting, intussusception implies redistribution of the preexisting cell volume by cytoplasmic thinning and spreading without massive cell proliferation or extensive basement membrane degradation. These characteristics make intussusception a more energetic and metabolically economical process than sprouting, requiring few hours for completion. So, once the primary capillary plexuses are formed, the vessels' growth continues mostly by intussusception [8].

Hemodynamic changes are a potent signal of intussusceptive angiogenesis. For example, when one of the dichotomous branches of an artery in the chick chorioallantoic membrane (CAM) microvasculature is clamped, the increase in blood flow in the other vessel triggers a swift branching [14]. The shear stress produced by the increase in blood flow can be sensed by endothelial cells, which synthetize angiogenesis-related proteins, such as nitric oxide synthase, adhesion molecules, and angiogenic factors [15]. Several mediators of sprouting seem to be also involved in intussusceptive angiogenesis. In this sense, exogenous PDGF-B leads to abundant large pre- and postcapillary microvessels but not to the expansion of capillary meshes in developed CAMs [16]. Moreover, the overexpression of ANG-1 or ANG-2 concomitant with VEGF is associated with increased intussusception and Notch4 signaling that are shown to be involved in remodeling of the vascular system [17]. However, the precise molecular mechanisms involved in intussusception remain to be elucidated (Fig. 9.1).

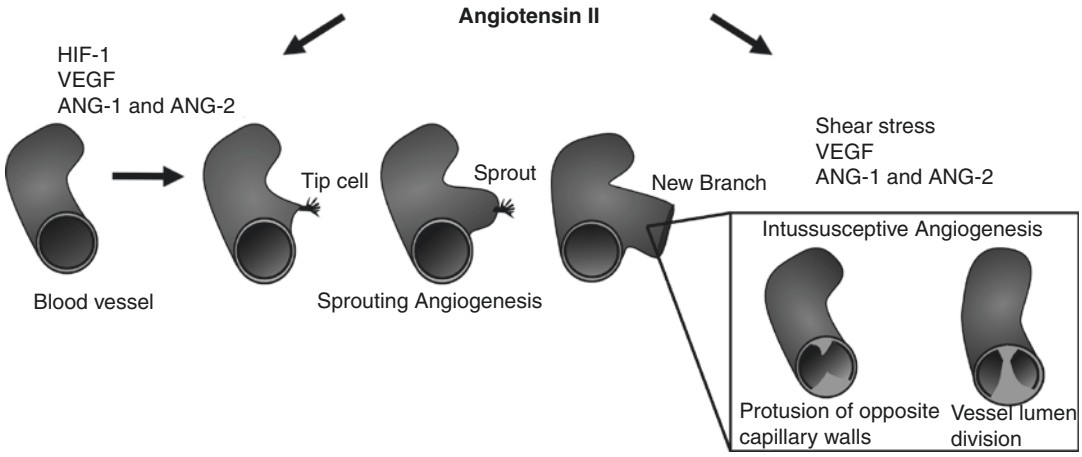


**Fig. 9.1** The schematic representation shows sprouting and intussusceptive angiogenesis processes and their main mediators. Angiotensin II modulates the expression of pro-angiogenic factors

## Microvascular Alterations in Mental Disorders

Despite their beneficial role in metabolic supply, tissue growth, and regeneration, blood vessels can be a source of reactive oxygen species and other pro-inflammatory factors. The expansion of the endothelial area may increase the release of these factors resulting in BBB permeability disruption and neuronal injury and contribute to the development of several CNS pathologies [18]. Moreover, angiogenic vessels are characterized by the presence of numerous fenestrae, widened inter-endothelial junctions, abnormal endothelial cell shapes, and basement membranes, which make them functional and structurally different from normal vessels [19]. Particularly, endothelial dysfunction and deviations from normal vessel growth have been implicated as a crucial event in the development of schizophrenia and Alzheimer's and Parkinson's disease [18]. Indeed, several well-defined markers of endothelial injury and molecular alterations of the cerebral microvasculature have been detected in these pathologies. In this sense, the plasmatic VEGF levels were lower in patients with schizophrenia, in comparison with healthy controls; meanwhile posttreatment patients showed significantly increased VEGF levels [20, 21]. Other markers of endothelial dysfunction, i.e., von Willebrand factor, have been correlated with the severity of clinical symptoms as psychotic events [18]. Postmortem studies in patients with schizophrenia indicated a positive association between VEGF and IL-6 mRNA levels in the prefrontal cortex (PFC), suggesting a close relation between angiogenesis, inflammation, and structural abnormalities [21, 22]. Indeed, the dysfunction of neocortical microvasculature has been observed as impaired vasodilation, lowered blood flow, and reduced metabolic rates, which might contribute to frontal hypo-activation reported in patients with schizophrenia [23, 24]. However, it has been observed that antipsychotic $D_2$ receptor antagonists modify the vasoconstriction-vasodilatation balance in the small vessels in frontal cortex, reducing the blood flow and metabolism and inducing structural microvascular changes. Moreover, in postmortem analyses of schizophrenic patients, structural changes were described, evidenced as capillary damage and atypically simplified angioarchitecture with abnormal arborization of vessels [23, 25]. All of these alterations in the neocortical microvasculature have been linked with the impairments of working memory, cognition deterioration, and presence of extrapyramidal symptoms [26].

Regarding Parkinson's disease (PD), the situation is diverse. On one hand, postmortem analyses of PD patients reported increased VEGF levels in the substantia nigra (SN) [27, 28]. In accordance with this evidence, in a monkey model of parkinsonism, it was found the overexpression of angiogenic factors together with an increased number of blood vessels and their volume occupying the substantia nigra [27, 29, 30]. Furthermore, in a rat model of parkinsonism, it has been found that treatment with L-DOPA induces angiogenesis [31]. On the other hand, in other animal model, it has been observed decreased blood vessel density and VEGF levels in SN, supporting the idea that these alterations could be implicated in the increased dopaminergic neurodegeneration [29, 32]. Microvascular proliferation has been associated with nigral degeneration since blood vessels contribute to neuroinflammation, by releasing pro-inflammatory and toxic factors, and fail to protect the cerebral parenchyma from peripheral immune cells due to BBB dysfunction [18, 27]. To this respect, angiogenesis has been associated with BBB dysfunction since immature vessels present numerous fenestrae, abnormal endothelial cell shape, and discontinuous or absent basement membrane [27, 28]. According with this, endothelial degeneration and capillary basement membrane thickening with collagen accumulation have been described in PD as well as in Alzheimer's disease (AD). These evidences support the theory that capillary dysfunction plays a critical role in the development of these two neurodegenerative diseases [18, 28, 30, 33–35].

It is known that AD is characterized by cerebrovascular hypoperfusion, pathologic microvascular remodeling, and BBB dysfunction [36–38]. Furthermore, it has been proposed that AD is mediated by pathological angiogenesis, given that there is a close relationship between brain microvessels and beta amyloid (Aβ) plaques [39–41]. Although the presence of angiogenic markers has been evaluated for this pathology, no concordant results have been found. Reduced VEGF expression might be associated with altered capillary function in this disease; thus high serum VEGF would decrease the risk to develop AD [42, 43]. On the other hand, analyses of intrathecal cerebrospinal fluid (CSF) reported that AD patients had higher VEGF levels than healthy controls [44]. Since VEGF was found to co-localize with Aβ plaques, it has been suggested that angiogenic activation of the brain endothelium could induce the Aβ plaque deposition and neurotoxic peptide secretion, such as thrombin [35, 40]. This peptide plays a major angiogenic role, inducing HIF-1α, ANG-2, and iNOS expression and a pro-inflammatory role by gliosis and inflammation-associated genes activations, such as tumor necrosis factor alpha (TNFα) and IL-6 [18, 39, 45–47]. Taking together these evidences, abnormal VEGF expression might be involved in neuronal survival, by the release of vascular-derived peptides and the cognitive impairment characteristic of this pathology [18, 47]. Interestingly, although hypoxia contributes to the ethiopathology of AD, it has been found that HIF-1 attenuates Aβ-induced neurotoxicity and prevents the apoptosis promoted by oxidative stress or hypoxia in cortical neurons [48–51]. Functional analysis determinates that cerebral hypoperfusion is a common feature in patients with AD and it has been directly associated with cognitive deterioration [43, 44, 52]. About this, it has been suggested that angiogenesis observed in AD may occur as a compensatory response to impaired CBF [53, 54]. However, in the hippocampus, the sustained angiogenesis results in increased vascular density concomitant with the Aβ plaque deposition. Moreover, it has been shown that this pathogenic angiogenesis is stimulated by the Aβ plaque deposition, creating a reverberant circle and resulting in BBB leakiness [19, 53]. In accordance, in animal models of AD, it has been observed increased vessel diameter, aberrant vessel branching, enhanced endothelial cell proliferation, and irregular basement membrane [19, 55].

Finally, it has been found that patients who develop depression during the course of AD show higher VEGF levels than those without depression, supporting the theory that depression is associated with changes in levels of VEGF [47, 56]. In this sense, depressive episodes might be accompanied by increased VEGF and FGF-2 expression. Indeed, patients with major depressive disorders (MDD) present higher serum VEGF levels. Interestingly, among these patients, those who had attempted suicide had a lower VEGF serum level compared to "not-suicide" patients [57, 58]. Moreover, it has been reported an increased HIF-1 mRNA expression in MDD and bipolar disorder patients [59]. However, it has not been reported significant differences in concentrations of others angiogenic factors, such as ANG-2 [57]. Hence, several authors reported angiogenic factor dysregulation as another possible facet of the endocrine and immunologic disturbances seen in MDD [57]. It has been proposed a vascular hypothesis for depression, where cerebrovascular disease disrupts principal brain circuits involved in mood regulation [60]. To this respect, it has been observed a decreased angiogenesis in MDD patients that might affect the neuronal replication and survival in elderly and is reversed by the treatment with selective serotonin reuptake inhibitors [61]. Studies performed in the acute phase of the illness showed that MDD patients have increased cortical and decreased subcortical CBF, compared with controls [62, 63].

Taken altogether, these evidences propose the cerebral microvasculature as a target for mental disorder treatment and stand out vascular modulators as new pharmacological tools (Fig. 9.2).

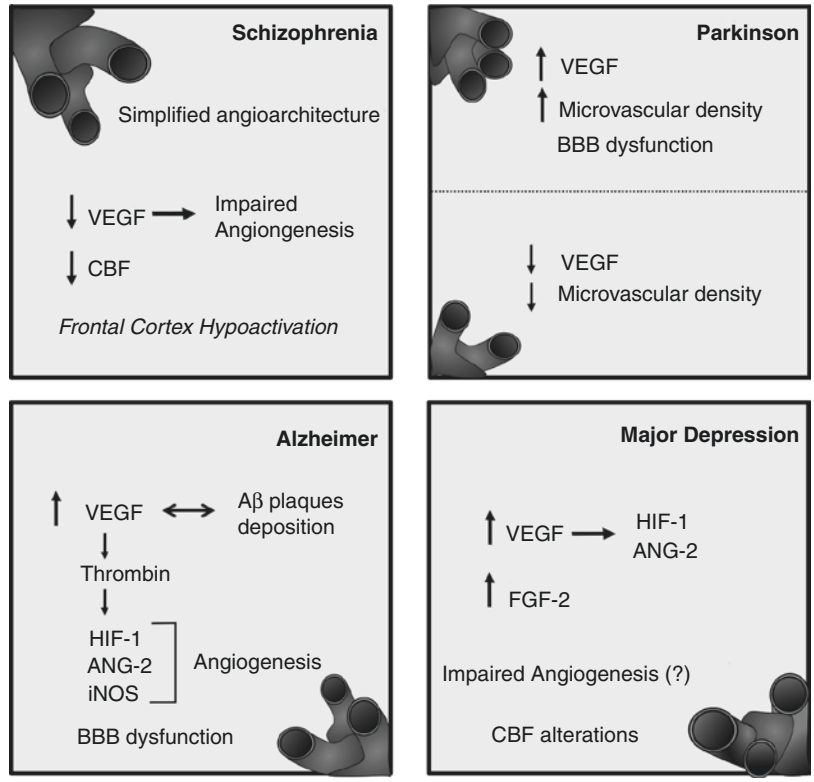


**Fig. 9.2** Microvascular alterations in mental disorders. Schematic review of the main angiogenic alterations observed in mental disorders

## The Central Renin-Angiotensin System

The renin-angiotensin system (RAS) was firstly described as a peripheral humoral system involved in blood pressure regulation and hydro-electrolyte balance [64]. Beyond the cardiovascular regulation, RAS has autocrine and paracrine properties; moreover the existence of local RAS has been described in a large number of tissues [65, 66]. In this sense, in several brain areas mainly at hippocampus, amygdala, thalamus, hypothalamus, basal ganglia, and nucleus of the solitary tract, a complete and independent local RAS has been identified [67–69]. Regarding it, the precursor synthesis (angiotensinogen) has been described in neurons and astrocytes, being this cell type the principal source [70–73]. Furthermore, at brain level it is known that renin and prorenin are secreted, while Angiotensin-converting enzyme (ACE) exists extracellularly as soluble and membrane-bound forms [74–76]. Alternative pathways of Ang II synthesis involve elastase, proteinase 3, cathepsin G, and tonin activity [75]. Cathepsins allow local angiotensinogen lysis to Ang I, instead of tonin, which directly synthetizes cytosolic Ang II from angiotensinogen [66].

$AT_1$ receptors ($AT_1$-R) mediate most of the principal effects known for Ang II. At CNS level, these receptors are localized in cortical areas: hippocampus, amygdala, hypothalamus, mesencephalon, and circumventricular organs [67, 74]. $AT_1$-R is a surface receptor with seven transmembrane domains that belong to the G protein-coupled receptor family, synthesized in neurons, microglia, astrocytes, and endothelial cells [67, 68, 77–81]. Its activation stimulates phospholipase C and produces the hydrolysis of $IP_3$ and diacylglycerol production, $Ca^{2+}$ release from intracellular compartments and protein kinase C stimulation [82–85]. Independent G-protein activation pathways involve later desensitization and internalization of the receptor by endocytosis mediated by β-arrestins [86]. Moreover, studies on endothelial cells demonstrated that shear stress, frictional force of blood flow on the vessel wall, activates

$AT_1$-R signaling independent of its ligand Ang II [87]. Among the main actions of $AT_1$-R are vasoconstriction, microcirculatory angiogenesis, cell growth and proliferation, trophic effects, oxidative stress activation, fibrosis, and thrombosis [88].

## RAS and Angiogenesis

$AT_1$-R activation induces the expression and release of several endogenous growth factors, such as VEGF, FGF, TGF-β1, PDGF, endothelin-1, and insulin growth factor (IGF) [89]. In this sense, Ang II enhances VEGF synthesis due to a potent angiotensin-dependent stabilization HIF-1α, through ROS production and indirectly through NO. Ang II stimulates NAD(P)H oxidase activation and augments NAD(P)H oxidase-mediated ROS production [90]. Moreover, in a model of cultured endothelial cells, it has been shown that Ang II increases the VEGF receptor expression [91, 92]. In addition, $AT_1$-R induces capillary proliferation by upregulation of VEGF and ANG-2 levels; meanwhile, since it is known that VEGF increases the expression of endothelial (eNOS) and iNOS in endothelial cells, this receptor promotes angiogenesis via VEGF/eNOS activation related pathway and inflammation [93, 94]. Moreover, Ang II may modulate new vessel formation by MMPs regulation in extracellular matrix remodeling [95]. Ang II vasculogenic and angiogenic properties were also observed in experiments with rabbit corneas [96]. $AT_1$-R signaling seems to be essential for postischemic recovery and reparative angiogenesis in peripheral ischemia [94]. In this sense, in experimental models, $AT_1$-R blockers (ARBs) or ACE inhibitors administration diminished VEGF protein expression and inhibited the angiogenesis induced by chronic electrical stimulation of skeletal muscles [97, 98]. However, it was found that ACE inhibitors and ARBs can induce angiogenesis, and long-term treatment increases capillary density possibly mediated by activation of bradykinin pathways generating VEGF and NO [93, 99]. Therefore, ARBs seem to display pro- or anti-angiogenic effects depending on the cell type and disease condition. ARBs enhanced pro-angiogenic state by increased cerebral levels of pro-angiogenic factors BDNF, ANG-1, and VEGF isoforms [100, 101]. In animal and cellular models of stroke, ARBs were associated with increased vascular density, reduction of cytotoxic mediator levels, and elevation of BDNF receptors [102–104]. It is important to highlight that angiogenesis induction after stroke could stimulate endogenous repairing mechanisms as neurogenesis, synaptogenesis, and neuroplasticity [102, 105]. In fact, ARBs' treatment limits ischemia, improves neurobehavioral outcome, and enhances angiogenesis, and these effects seem to involve BDNF expression increase [104, 106–108].

## Final Considerations

Pharmacological manipulation of the brain RAS may constitute an important and useful strategy to obtain effective and beneficial neuroprotective effects against brain disturbances like schizophrenia, depression, and Alzheimer's and Parkinson's disease [76, 109–112]. In this sense, Ang II $AT_1$-R blockade reduces stress-induced gastric ulcers, while antihypertensive therapy, with ACE inhibitors and $AT_1$-R antagonist, improves memory function suggesting the modulation of cognitive function by central RAS [113–117]. Moreover, in animal model of schizophrenia, it has been observed microvascular alterations in cortical areas, which were prevented by the $AT_1$-R blockade [118]. Ang II blockers are drugs relatively safe and besides their beneficial effects on cardiovascular disease, prove to be effective in reducing inflammation. Since cerebral small vessel disease is the major cause of dementia and considering the key role of RAS in microvasculature, it is possible to postulate this system as a new pharmacological target to treat these mental disorders [119].

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# 10 Heart Rate Variability: A Tool to Explore Autonomic Nervous System Activity in Health and Disease

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## Historical Perspective

Within the different rhythmic processes observed in physiology, the heart rate has been one of the first to be studied. The earliest references come from Egyptian papyri (1550 BC), where a dissertation on the heart and the veins in terms of measuring is found, probably with the meaning of "counting" the pulse, recognizing it as related to the heart. The first one who spoke of this calculation was Herophilus of Alexandria (third century BC) who used a clepsydra for this purpose. Subsequently, we find detailed descriptions of the pulse in the treatises of Galen (129–c.199) on the subject. In the Renaissance, Galileo used his pulse to evaluate the oscillations of the pendulum, although it was Santorio (1561–1636) who used the pendulum to measure the frequency and regularity of the pulse. John Floyer (1649–1734) published an essay in 1707 (*The Physician's pulse watch, or an essay to explain the old art of feeling the pulse and to improve it by the help of a pulse watch*), where he described the invention of a portable clock with a second piece that could stop the watch. Thus, he could register pulse and respiration under several conditions. In 1733, Stephen Hales (1677–1761) described for the first time the relationship between the respiratory cycle and heart rate (*Statical Essays, Vol. II Haemastatics*), while in 1847, Carl Ludwig (1816–1895) was the first who documented the respiratory sinus arrhythmia. The recording of the electrical activity of the heart using galvanometers due to Willem Einthoven (1860–1927) in the late nineteenth century and the further development by Jeff Holter (1914–1983) in early 1960s of portable devices capable of recording ambulatory ECG during long periods of time (24 h) allowed further research in the relation of heart rate variations with health and disease [1].

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## Sources of HRV

Heart rate is controlled by the periodic depolarization and repolarization of the cardiac pacemaker at the sinoatrial node, located on the posterior wall of the right atrium. Its steady intrinsic frequency range is 100–120 beats per minute. There are several neurohumoral factors that can modify this frequency, determining a lower or higher mean heart rate and beat-to-beat modifications of heartbeat duration. This latter phenomenon is known as "heart rate variability" (HRV) [2]. An intrinsic neural network within the cardiac fat pad provides local control of heart rate. This local network consists of sympathetic and parasympathetic neurons and interneuronal circuits. The spontaneous activity of these neurons even after cardiac denervation suggests an active role in the regulation of heart rate [3].

The origin of respiratory sinus arrhythmia (inspiratory tachycardia and expiratory bradycardia) is found in vagal modulation induced by the respiratory cycle on the heart. This mechanism determines that the duration of the heartbeat is modified following the respiratory rate, with cycles of 2.5–6.5 s in a healthy adult at rest, constituting HRV's high-frequency component (HF, 0.15–0.4 Hz). Two mechanisms could explain this phenomenon. On the one hand, there would be a central coupling of the respiratory oscillator with autonomic centers of the brain stem in the ambiguous nucleus and other related areas. On the other hand, this mechanism would be mediated via a cardiopulmonary reflex. A decrease in intrapleural pressure during inspiration reduces intravascular pressure within the thorax and increases venous return, leading to increased volume in the atrium and right ventricle. Atrial mechanoreceptors would be activated by conducting information through sympathetic and parasympathetic pathways that would result in an increase in heart rate. Only the parasympathetic component of the efferent pathway would be involved because the sympathetic effect on the heart is too slow to follow the respiratory rate. This reflex was first suggested by Francis Bainbridge (1874–1921) in 1915 after observing the increased heart rate in anesthetized dogs during volume infusions in the right atrium [4].

Spontaneous oscillations of blood pressure were first described by Siegmund Mayer (1842–1910) in 1875. The autonomic activity responsible for the genesis of these waves determines that the duration of heartbeats is modified with cycles of 2.5–25 s, constituting HRV low-frequency component (LF, 0.04–0.15 Hz). The main mechanism responsible for these oscillations is the baroreflex. An increase in blood volume distends the baroreceptors of the aortic arch and the carotid sinus, which through the X-pair and the IX-pair, respectively, send information reaching the nucleus of the solitary tract. This stimulates the ambiguous nucleus producing an inhibition of the sympathetic preganglionic chain and stimulation of the dorsal motor nucleus of the vagus. The combined effects result in a decrease in heart rate. In addition, it is believed that there would be a direct central participation by which sympathetic autonomic oscillators would determine hemodynamic oscillations in the absence of peripheral stimuli [5].

Thermoregulation and several hormonal processes are possibly involved in slower variations of heart rate, with cycles of 25 s to 5 min, constituting HRV very low-frequency component (VLF, 0.0033–0.04 Hz). Central processing of the central and peripheral information about temperature is done in the anterior hypothalamus. In this region, neurons whose activity is affected by the thermal stimulation of the preoptic area or the spinal cord have been identified. Thermoregulation exerts an indirect effect on the heart rate through the sympathetic activation triggered by cold. On the other hand, through a direct effect on the sinus node, cooling of the heart produces bradycardia, a mechanism used in cardiac surgery [6]. With regard to hormonal factors, the renin-angiotensin-aldosterone system is thought to influence VLF oscillations. Angiotensin and other factors such as aldosterone would directly or indirectly produce fluctuations in vasomotor tone. These fluctuations in turn would determine, mainly through parasympathetic outflow, fluctuations in the heartbeat [7].

Heart rate also exhibits a circadian rhythm, with ultralow frequency (ULF, <0.0033 Hz) oscillations. This rhythm is partially originated in the basal forebrain and is dependent on the sleep-wake state. This region exerts control of cardiovascular autonomic function through widespread projections to the paralimbic cortex, amygdala, hypothalamus, and brain stem autonomic nuclei [8]. In addition, the suprachiasmatic nuclei of the hypothalamus, considered the central pacemaker for circadian rhythms, regulate physiological functioning with cycles of about 24 h that are adjusted to 24 h mainly by the information of ambient light. These nuclei have projections to the paraventricular hypothalamic nucleus, which in turn modulate ANS activity by sending input to major sites of ANS regulation. HF, LF, VLF, and ULF regions in the power spectra of cardiotachograms (see below) can be described as a "harmonic" (sine wave frequencies) regulation of HRV.

Furthermore, HRV shows also "unharmonic" components within its power spectrum, which indicate a nonlinear dynamic behavior derived from the complex interaction of external influences, internal input, autonomic tone, and central organization. Indeed, nonlinear features are characteristic of complex systems, and the autonomic regulation of the heart can be described as one. As a complex system, it can be characterized by strange attractor's properties, fractal scaling, and the degree of entropy. Heartbeats may be seen as the projection on a line of one trajectory of a dynamical system that will converge to a limited region in space or attractor. Strange attractor's properties include a similar structure at different scales (fractality) and sensitive dependence on initial conditions for the trajectories on them (chaotic behavior). Fractals are geometric objects that have similar structure at different scales. In analogous form, nonlinear processes show a statistically similar dynamic pattern at different scales. In other words, the irregular fluctuations seen at multiple time scales resemble each other, and the pattern of variation across multiple scales of measurement characterizes complex systems. Entropy is a measure of disorder or randomness of a system. Systems tend to evolve from statistically ordered unlikely configurations to statistically disordered more probable configurations [9–12].

## Methods for Assessing HRV

The simplest way to assess HRV is provided by the time domain methods (Fig. 10.1). In these methods the intervals between successive normal QRS complexes are measured (RR interval). Among others, simple time domain variables that can be calculated include the mean RR interval (RRM, ms); the standard deviation of all RR intervals (SDNN, ms), which gives a coarse quantification of HRV; and the square root of the mean of the squared differences between adjacent RR intervals (RMSSD, ms), which quantifies high frequency variations of HRV (Table 10.1) [13].

Frequency domain methods or spectral analysis convert time domain information into frequency domain information (Fig. 10.2). Usually, the discrete Fourier transform is used for processing the signal, and the squared amplitude calculated for each frequency (the power spectral density) is obtained [13]. By integration within suited frequency limits, the absolute spectral power ($ms^2$) can be calculated for each band: HF($ms^2$, 0.15–0.4 Hz), LF ($ms^2$, 0.04–0.15 Hz),

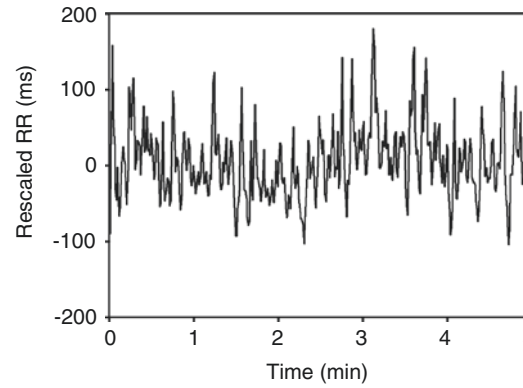


**Fig. 10.1** Time domain HRV. Five-minute section of a HRV recording of a young healthy subject. The mean RR interval was subtracted from the original data

**Table 10.1** Selected time domain HRV indexes

| Index | Definition | Interpretation |
|---|---|---|
| RRM (ms) | Mean duration of RR intervals | Reciprocal of mean heart rate |
| SDNN (ms) | Standard deviation of all RR intervals | Coarse quantification of HRV |
| RMSSD (ms) | Square root of the mean of the squared differences between adjacent RR intervals | High frequency variations of HRV of parasympathetic origin |

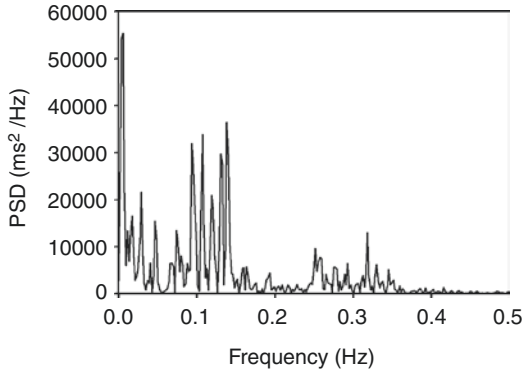


**Fig. 10.2** Frequency domain HRV. Spectral density of the same individual of Fig. 10.1 Peaks are observed around 0.3 Hz (high frequency), 0.1 Hz (low frequency), and <0.04 Hz (very low frequency)

VLF ($ms^2$, <0.04 Hz in short-term recordings or 0.0033–0.04 Hz in long-term recordings), and ULF ($ms^2$, <0.0033 Hz only in long-term recordings). Total power ($ms^2$, <0.4 Hz) is an index of overall variability. The LF/HF ratio and other normalized frequency bands indexes are also derived (Table 10.2). By means of the wavelet transform, it is possible to estimate the temporal progress of the frequency spectrum of the signal, providing optimal resolution both in time and frequency domain. Indeed, when time domain information is converted into frequency domain information, time-related information is lost, because Fourier transform provides the accumulated power of a given frequency along a period of time, rather than in a given point in time. Wavelet transform has been introduced to HRV analysis to overcome this problem [14].

The RR time series attractor can be observed by plotting each RR interval against the previous RR interval (Poincaré-plot, Fig. 10.3). An attractor is a unique region in the phase space toward a system which tends to evolve, departing for a large set of initial conditions. Once the attractor is constructed, several numerical methods can be applied to estimate its complexity. SD1 reflects

**Table 10.2** Selected frequency domain HRV indexes

| Index | Definition | Interpretation |
|---|---|---|
| TP ($ms^2$) | Total power (<0.4 Hz) | Coarse quantification of HRV |
| ULF ($ms^2$) | Power in the ultralow-frequency range (<0.0033 Hz). Only in long-term recordings | Circadian HRV variations |
| VLF ($ms^2$) | Power in the very low frequency range (<0.04 Hz in short-term recordings or 0.0033–0.04 Hz in long-term recordings) | Possibly originated in hormonal factors and peripheral thermoregulation. Depends mainly on parasympathetic outflow |
| LF ($ms^2$) | Power in the low frequency range (0.04–0.15 Hz) | Baroreflex. Depends on sympathetic and parasympathetic outflow |
| HF ($ms^2$) | Power in the high frequency range (0.15–0.4 Hz) | Cardiopulmonary reflex. Depends on parasympathetic outflow |
| ULF (%) | ULF power in percentage units ULF (%) = 100 × ULF/total power. Only in long-term recordings | Relative contribution of ULF HRV |
| VLF (%) | VLF power in percentage units VLF (%) = 100 × VLF/TP | Relative contribution of VLF HRV |
| LF (%) | LF power in percentage units LF (%) = 100 × LF/TP | Relative contribution of LF HRV |
| HF (%) | HF power in percentage units HF (%) = 100 × HF/TP | Relative contribution of HF HRV |
| LF (n.u.) | LF power in normalized units LF (n.u.) = 100 × LF/(LF + HF) | Relative contribution of LF HRV within LF + HF range |
| HF (n.u.) | HF power in normalized units HF (n.u.) = 100 × HF/(LF + HF) | Relative contribution of HF HRV within LF + HF range |
| LF/HF | Low frequency/high frequency ratio | Considered to reflect sympathetic – parasympathetic balance |

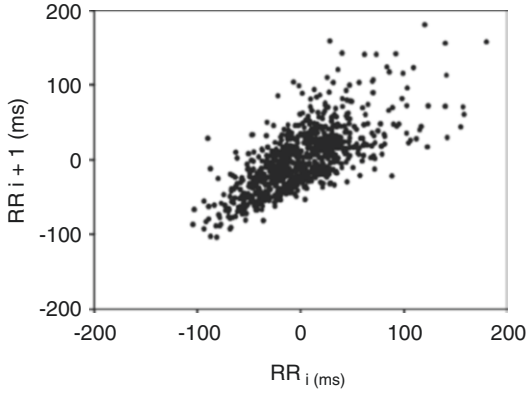


**Fig. 10.3** Poincaré Plot of the same individual of Fig. 10.1. RR intervals are depicted as a function of the previous RR intervals, composing the heart rate attractor

short-term HRV while SD2 reflects long-term HRV. Both indexes include linear and nonlinear HRV features [12]. The quantification of the statistical entropy features of the system can be performed by measures such as "ApEn" or "SampEn." Basically, they quantify the order of the RR interval time series by taking the logarithm of the probability that patterns being close to each other at the beginning will remain closer in subsequent observations. Regular sequences will result in lower ApEn values, whereas random behavior is associated with larger ApEn values. An increase of entropy values usually reflects parasympathetic predominance situations [12]. The detrended fluctuation analysis is a technique that characterizes the pattern of beat-to-beat variation across multiple scales of measurement, through the short- (α1) and long-term (α2) fractal correlation scaling exponent alpha. α1 correlates inversely with short-term HRV measurements, while α2 correlates inversely with long-term HRV measurements. Values of α close to 0.5 are associated with white noise (no correlation between values), whereas values close to 1.5 are associated with Brownian noise (strong correlation between values). Values near 1 are characteristic of fractal-like processes, associated with the dynamic behavior of time series generated by complex systems, such as the autonomic regulation of the sinus rhythm of a healthy subject (Table 10.3) [12].

**Table 10.3** Selected nonlinear HRV indexes

| Index | Definition | Interpretation |
|---|---|---|
| SD1, SD2 | Dispersion of the points around the minor (SD1) and major (SD2) axis of an ellipse fitted to the attractor | Set of numerical values toward which a system tends to evolve. SD1 reflects short-term HRV, while SD2 reflects long-term HRV. Both indexes include linear and nonlinear HRV features |
| ApEn, SampEn | Entropy measurement of heartbeat time series | Random behavior is associated with larger ApEn values. Usually reflects parasympathetic predominance |
| Short- (α1) and long-term (α2) scaling exponent alpha | Fractal correlation properties of heartbeat time series as calculated by detrended fluctuation analysis | Highly correlated heartbeat time series will result in higher scaling exponent alpha. α1 correlates inversely with short-term HRV measurements, while α2 correlates inversely with long-term HRV measurements. Values of α close to 0.5 are associated with white noise, whereas values close to 1.5 are associated with Brownian noise. Values near 1 are characteristic of the dynamic behavior of complex systems |

HRV indexes are correlated between them. An increase in heart rate is associated with a reduction in SDNN, RMSSD, HRV power at all frequency bands, entropy values, and attractor dimension and with an increase in scaling exponent α. However, these relations are not linear. The mathematical functions that describe them are different when considering sleep or waking states, which possibly reflect different configurations of ANS functioning [15]. In addition, it has been proposed that nonlinear HRV is a characteristic of the phase transition-like dynamics that a healthy human heart rate exhibits between the different behavioral states of the sleep-wake cycle [16, 17].

## Heart Rate Variability in Selected Physiological Situations

### Gender Related Changes of HRV

HRV measures change during the regular menstrual cycle. SampEn and HF HRV components decrease from the follicular phase to the luteal phase, whereas normalized LF components and LF/HF as well as resting heart rate increase. SampEn shows significant correlations with spectral indexes, free T4 concentrations, and the ratio of estradiol to progesterone concentrations. Thus, the hormonal fluctuations that occur during the luteal phase of the cycle are associated with a shift toward sympathetic prevalence [18]. During pregnancy, changes in HRV indexes are observed within the first 6 weeks after conception, showing a decrease in almost all HRV indexes. It was also found that VLF, LF, HF, and normalized HF were significantly decreased, and LF/HF significantly increased in pregnant subjects in the third trimester as compared to the first trimester. The results indicate that during gestation, sympathovagal balance shifts progressively from a higher vagal modulation toward a higher sympathetic modulation [19–21]. Finally, although HRV is not associated with vasomotor symptom frequency or intensity in perimenopausal and postmenopausal women, an increase in VLF component is described associated to hot flash periods, which may be involved in the regulatory mechanisms of hot flashes [22, 23].

### Aging

Aging is associated with alterations in the neural and endocrine mechanisms that regulate heart rate. Parasympathetic and sympathetic regulations become attenuated, renin and angiotensin levels are reduced, and circadian hormonal and temperature rhythms lose amplitude. Consequently, heart rate oscillations show decreased amplitude at all frequency levels with an overall reduction in HRV. Moreover, increasing age is related to alterations in fractal organization of heartbeat dynamics as well as to a loss of complex variability. These changes might lead to an impaired ability for stress adaptation and seem to be a common feature with many diseases [24–27].

### Cognitive Function

Several studies show that resting autonomic patterns can influence cognitive performance. Possibly, some amount of sympathetic activation reflected by intermediate HRV values would be necessary for optimal cognitive performance. In this regard, it was reported that subjects with higher HF (higher parasympathetic activity) perform better at executive function tasks, probably by concomitant lower anxiety [28]. On the other hand, lower resting baroreflex sensitivity, usually associated with a reciprocal reduction of parasympathetic activity and an increase of sympathetic activity, predicted higher values in all parameters of attentional capacity [29]. In addition, better performance in a decision-making task was associated with increased LF. The sympathetic prevalence may be necessary to adjust cardiovascular function to cope with increased mental demand [30]. Autonomic changes during meditation techniques deserve a separate comment. A prominent peak in absolute LF, not attributed to an increase in sympathetic activity, is usually found in meditation techniques derived from different traditions. Breathing patterns achieved during meditation are associated with a synchronization of respiratory and heart rate variations (i.e., cardiorespiratory coupling), which is reflected in this characteristic increase in the LF power [31–33].

### Physical Activity

During exercise, the resulting tachycardia is accompanied by a reduction of total HRV power. Thus, although LF absolute values seem unchanged, normalized LF and LF/HR ratio increases, reflecting the typical sympathetic activation associated with physical activity [13]. This pattern may vary within different subjects,

and a decrease in nonlinear indexes as SampEn may be robust for identifying brief physical activity episodes. On the other hand, long-term HRV indexes are relatively stable at various activity levels [34]. Of interest, extreme activation of the sympathetic nervous system underlying vigorous exercise leads to a marked reduction in global HRV power and increased nonlinear indexes as SampEn, a pattern also similar to situations with increased propensity to ventricular fibrillation [35]. Physical training is associated with higher HRV indexes reflecting vagal predominance which is considered a possible mechanism by which physical activity reduces coronary heart disease risk [36].

## Postprandial Changes of Heart Rate Variability

The regional distribution of ANS within the body makes plausible that the same stimulus triggers different responses in different physiological systems and specifically in cardiac and gastrointestinal activity. In this regard, typical postprandial parasympathetic prevalence within abdominal compartment was associated with a decrease of HF and LF around 30–60 min after a meal, with a concomitant increase in the LF/HF ratio, characteristic of sympathetic predominance [37]. The different autonomic configurations of body compartments make in turn plausible the hypothesis that the disruption of the sleep-wake cycle and other circadian rhythms leads to changes in the balance of the autonomic activity of the thoracic and muscular compartment (toward a predominance of the sympathetic branch) and the intra-abdominal compartment (toward a predominance of the parasympathetic branch) [38].

## Sleep-Wake Cycle

During wakefulness, reflex loops (respiratory sinus arrhythmia, baroreflex, and chemoreflexes) and central autonomic network areas (mid-cingulate cortex, insula, and amygdale) contribute to an increased heart rate, increased sympathetic activity (SNS), and decreased parasympathetic activity [39]. In addition, changes in HRV within wake states are associated or predict the operational levels of higher cortical functions, including alertness [40] and decision-making [30], suggesting a role of autonomic function in these processes.

Parasympathetic predominance during NREM sleep is characterized by slow EEG rhythms associated with decreased brain activity compared to wakefulness in subcortical (brain stem, thalamus, basal ganglia, basal forebrain) and cortical (prefrontal cortex, anterior cingulate cortex, precuneus) areas, suggesting a lower central command in cardiac autonomic control [39]. In this regard, it has been demonstrated that the degree of network connectivity and the strength of physiological interactions between different central and peripheral systems are minimal during slow sleep [41]. HRV studies during this sleep stage have revealed that there is a decrease in the LF component and an increase in the HF component relative to wakefulness [42–44]. The HF component is strongly associated with changes in the delta EEG band, preceding them in about 12 min [45]. As for the nonlinear components of HRV, slow-wave sleep is characterized as a stage with a higher degree of nonlinear variability in relation to wakefulness, manifested by a lower fractal correlation and a higher degree of entropy [16]. These findings are consistent with the parasympathetic prevalence characteristic of this stage and can be interpreted as associated with a decrease in non-reflex central influences [43].

During REM sleep, autonomic cardiac regulation is shared between central control in relation to amygdala activity and homeostatic control of the cardiovascular system by reflex arcs, leading to an increase in heart rate, with sympathetic predominance and decreased parasympathetic activity [39]. Consistently, the degree of network connectivity and the strength of physiological interactions between different central and peripheral systems are intermediate between NREM sleep and wakefulness [41]. This possibility is supported by the observation that the response of

peripheral centers to changes in blood pressure is modified and by the fact that the thermal or electrical stimulation of diencephalon structures is not accompanied by concomitant changes in certain autonomic functions [46]. During this stage, a pattern of increase in linear HRV is observed. Studies differ in their reported values for REM sleep, with maxima for the LF component and nulls for the HF component [42–44, 47, 48]. In comparison with wakefulness, no significant changes have been reported in the nonlinear dynamics of autonomic cardiac regulation [16, 49]. Variations in heart rate are particularly marked during the phasic stage of REM sleep and tend to coincide with ocular movements and with theta activity bursts of this stage [50]. Taken together, these findings would reflect a partial release of central modulation on peripheral autonomic activity.

Apart from variations in cardiac autonomic activity associated to sleep stages, an endogenous circadian rhythm has been demonstrated in heart rate and HRV, in the absence of sleep masking effects, general activity, postural changes, and light. The results suggest that circadian control of heart rate is not entirely mediated by the sleep-wake cycle and that autonomic modulations are influenced by the circadian regulation. Peak values of this rhythm are seen during late wakefulness for heart rate and during the latter part of the sleep period for HRV measurements. In addition, the administration of melatonin is capable of advancing the endogenous circadian rhythm phase of heart rate and SDNN, RMSSD, and HF [51].

## Heart Rate Variability in Selected Clinical Conditions

### Type 2 Diabetes Mellitus

The relationship between the presence of diabetes and alterations in cardiac autonomic regulation is well known. This extends to subjects with insulin resistance and to the offspring of type II diabetics patients with no history of diabetes or hypertension where the mean values of HRV are decreased. Low HRV in healthy people is associated with an increase of developing this disorder. In addition, low HRV in patients with diabetes increases the risk of complications and mortality compared with those with normal HRV values. Among other parameters, SampEn and HF HRV are better discriminants to detect autonomic dysfunction. From a circadian point of view, the amplitude of day-night variations in HRV is decreased in subjects with diabetes. These findings support the use of HRV as a risk indicator in type II diabetics [52–54].

### Obesity

Regarding the presence of obesity, a reduction of SDNN, RMSSD, and absolute and relative HF HRV is observed, pointing to a relative prevalence of sympathetic activity [55]. Circadian alterations of HRV are also described. The LF/HF ratio increases at certain points in the afternoon in association with high plasma insulin concentrations [56]. Interestingly, increases and decreases in the LF/HF ratio were respectively detected in response to gain and weight reduction achieved through an experimental design [57].

### Dyslipidemia

It has been reported an inverse association between short-term HRV and triglycerides in elderly people and between short-term HRV and the LDL/HDL ratio in elderly men but not women [58]. A further study demonstrated an inverse relationship between 24 h HRV indicators reflecting parasympathetic activity (RMSSD) and total cholesterol, LDL, and LDL/HDL, adjusted for various demographic and clinical factors including levels of noradrenaline [59].

### Hypertension

ANS disorder, clinically manifested as a hyperkinetic circulation characterized by elevations in heart rate, blood pressure, cardiac output, and plasma norepinephrine levels, has been systematically

demonstrated in hypertension. Increased sympathetic activity has been reported using spectral analysis of HRV [60]. Specifically, compared to control ones, subjects with primary hypertension have decreases in LF and HF components of HRV both during the day as well as the night. The day-night differences in HRV increase after 1 year of treatment with angiotensin-converting enzyme inhibitors [61]. In subjects with hypertension and left ventricular hypertrophy (but without coronary pathology), there is a decrease or absence of sleep-wake differences in heart rate, RMSSD, LF, and HF, thus evidencing alterations in the circadian rhythm of cardiac autonomic control [62]. In addition, flattening of the circadian rhythm of heart rate is independently associated with an increased risk of all-cause mortality [63].

## Ischemic Heart Disease

As described above, existing evidence support the notion that cardiovascular risk factors are associated with altered HRV patterns. Also, autonomic imbalance may provide a unifying framework within which to investigate the impact of those factors and other psychosocial determinants on cardiovascular disease [64]. When considering established cardiovascular disease, impaired HF oscillations of heart rate are the most prominent feature in patients with uncomplicated coronary artery disease. On the other hand, patients with prior myocardial infarction and impaired left ventricular function have a reduced overall heart rate variability and a specific spectral pattern with a reduced LF spectral component. In addition, patients with prior myocardial infarction have higher ApEn values and lower scaling exponent values, indicating that heart rate dynamics are more random. These measures have revealed to be strong predictors of fatal arrhythmias [65].

## Stroke

Autonomic imbalance has been identified prior to atrial fibrillation [66]. Global HRV, quantified by SDNN indicator, is a strong predictor for ischemic stroke development in apparently healthy subjects. The mechanism is unclear, but it is probably due to a decrease in parasympathetic activity that increases the risk of arrhythmias [67]. HF HRV is significantly reduced in patients with acute cerebral infarction [68], while elderly survivors of ischemic or hemorrhagic stroke show lower total HRV and LF HRV long after the event [69]. In the presence of a hemispheric or trunk stroke, changes similar to those described for coronary disease are observed, where all HRV components are similar during the day and at night, indicating the abolition of circadian rhythmicity of cardiac autonomic regulation [70]. HRV differences between hemorrhagic and ischemic stroke are not well established [71].

## Mild Cognitive Impairment/ Alzheimer's Disease

Several works have shown that central components of the ANS, mainly insular cortex and brain stem, are affected in early stages of Alzheimer's disease, manifesting itself as a parasympathetic dysfunction that contributes to the progression of the disease [72]. This pattern is maintained in later stages of the disease, where RMSSD and spectral components are lower in patients than in controls. In addition, HRV was found to be significantly correlated with the degree of cognitive impairment [73].

## Cancer

Autonomic activity may be an important marker in cancer due to its role in modulating inflammation and oxidative stress. HRV indexes have been used in several studies to assess autonomic profiles within this disease. Decreased heart rate variability (mainly reduced SDNN) is associated with shorter survival times in patients with several types of cancer, pointing out that higher vagal nerve activity might play a protective role in cancer [74]. Specifically, breast cancer survivors exhibit a decrease in overall variability (SDNN) and parasympathetic activity (RMSSD, HF HRV)

when compared to women without the disease [75]. Higher SDNN and RMSSD predict lower levels of carcinoembryonic antigen in colorectal cancer patients, supporting the hypothesized role of vagal activity in tumor modulation [76]. In prostate cancer patients, SDNN and RMSSD inversely predict PSA levels at 6 and 24 months, being particularly significant in metastatic prostate cancer, indicating stage moderation [77]. A study reported that SDNN univariately predicted poor survival in non-small cell lung cancer [78], while another one found that SDNN and RMSSD predict survival time independently of confounders but only in patients under 65 years old [77].

## Anxiety

Stressors, anxiety, and anxious personality traits are associated with increased cardiac frequency and lower values of parasympathetic HRV indexes during wakefulness, with the effects of stressors and concerns extending to the subsequent nighttime sleep period. These results are independent of other behavioral variables including sleep quality and may mediate the increased cardiovascular risk associated with stress due to the observed reduction in parasympathetic activity [79].

## Depression

Depression has been often reported to be associated with an overall reduction in total HRV, generally characterized by reduced HF HRV and reduced complexity. These are similar findings to those of aging. A reduced HRV characterizes decreased psychological flexibility, emotional dysregulation, and defective social engagement, which in turn are linked to hypoactivity of the prefrontal cortex [80]. Depression is also recognized as an independent adverse prognostic factor in patients recovering from an acute coronary episode [81, 82]. Subjects with major depressive disorder have a reduction in HRV in all frequency components both during the day and during the night. In addition, during the night they present a reduction in nonlinear HRV. Taken together, these findings point out a greater sympathetic activation throughout the whole day. It was observed that HRV indicators correlate with sleep quality, but not with depression scores, which shows that sleep disorders typical of depression play an important role in the alteration of autonomic regulation [83].

## Schizophrenia

Schizophrenia is characterized by abnormalities of cortical structures concerned with autonomic control, including prefrontal, cingulated, temporal areas and the hippocampus. Symptom development theories in schizophrenia have long incorporated the notion of autonomic dysfunction, including pupillary, vasomotor, sweating, heart rate, salivation, and temperature changes, most of them suggesting increased sympathetic prevalence as an important feature in the expression of psychosis. HRV pattern in acute schizophrenia is consistent with this notion, since RMSSD index is diminished [84]. In stable schizophrenia, subjects exhibit normal autonomic activity at rest and in response to mental stress, but they maintain HRV stress-related changes further than stimulus cessation, in the form of larger relative LF HRV component [85, 86].

## Social Determinants of Health

Extensive research has shown that adverse environmental and working conditions, such as shift work and excessive workload, are related to disease. Psychosocial workload and working time have been associated with low HF HRV [87]. In night shift work, typical patterns of autonomic predominance are inverted, with increased sympathetic activity during the night (wake period) and increased parasympathetic activity during the day (sleep period), making evident the strong dependence of the autonomic regulation on the sleep-wake cycle [88]. When these conditions are maintained for extended periods, sympathetic activity (LF HRV and LF/HF ratio) during sleep

in these professionals is greater than that of their colleagues in the morning shift [89]. Finally, the lack of exposure to natural light may result in the loss of the circadian rhythm of cardiac autonomic activity, as it was shown in prolonged confinement experiments [90, 91].

**Conclusion**

The analysis of the autonomic modulation of heart rate provides information about the state of the ANS in several physiological and clinical situations. It is now widely accepted that the interaction of several biological (genetic, biochemical, biophysical), psychological (personality, mood, behavior), social (family, work, society), and ecological (living environment) factors plays an important role in the preservation of quality of life and health. The ANS is structural and rhythmically interfaced between the forebrain and internal and external environments, to regulate energy, matter, and information exchanges. Its overall function is to maintain the body homeostasis and to react predictively or adaptatively to changes in the internal and external environment. All body systems are dependent and affected by the action of others and by external factors in a multilevel and dynamic organization. Thus, the biopsychosocial nature of the individual is expressed by the function of the ANS, which can be explored by the analysis of the variability of heart rate. In turn, autonomic imbalance, as evidenced by alterations in HRV, may configure a final common pathway to increased morbidity and mortality from a host of conditions and diseases [92–94].

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# 11 Pavlovian Blindsight and Masked Conditioning: A Neural Network Approach

José E. Burgos

## Introduction

Blindsight is the remarkable ability to appropriately respond to supraliminal or unmasked visual stimuli, despite cortical blindness due to extensive primary visual (V1) damage. Cortically blind humans, in particular, can locate, name, recognize, pick, and avoid objects when instructed, without any assistance or report of a specific visual awareness of the objects [1]. This phenomenon is often viewed as a paradigm example of visual control of behavior without visual consciousness. It thus has received much attention from theories about phenomenal consciousness [2–7].

However, two related phenomena have not yet been considered by such theories. One is blindsight in Pavlovian conditioning, or "Pavlovian blindsight" for short: the acquisition of a conditioned response (CR) to an initially neutral visual conditioned stimulus (CS), after pairing it with an unconditioned stimulus (US) that initially and demonstrably elicits a similar unconditioned response (UR). It has been observed in nonhuman primates and humans [8–10]. Typical responses in these studies are eyeblink, skin conductance, and startle responses. In humans, significant increases of such responses are observed without verbal reports of CS visual awareness (different from expectancy or contingency awareness as discussed by Lovibond and Shanks [11]).

The other phenomenon is Pavlovian masked conditioning, observed in humans with no V1 damage who receive a masked (e.g., very short) CS that is reported as unseen [12]. Strictly speaking this is not blindsight, as there is no V1 lesion. However, the phenomenon seems sufficiently similar to Pavlovian blindsight to suggest the possibility of a common underlying neural mechanism. I will propose such a mechanism, without denying the possibility of others, whether or not common.

Both phenomena are relevant to understanding phenomenal consciousness, especially from a connectionist perspective, because they suggest a role of learning. This role remains largely unexplored, theoretically and empirically. I shall propose a unified connectionist account of both phenomena. The account includes an interpretation of the two-stream hypothesis of organization of the human visual system [13, 14] in terms of an existing neural network model of conditioning. I focus on the neuroanatomical part of this hypothesis, as its functional aspect, especially the distinction between "vision for perception" and "vision for action," raises difficult conceptual issues that are beyond the scope of this paper [14].

Figure 11.1 shows a diagram of the hypothesis, with the aspects of interest here enclosed in a

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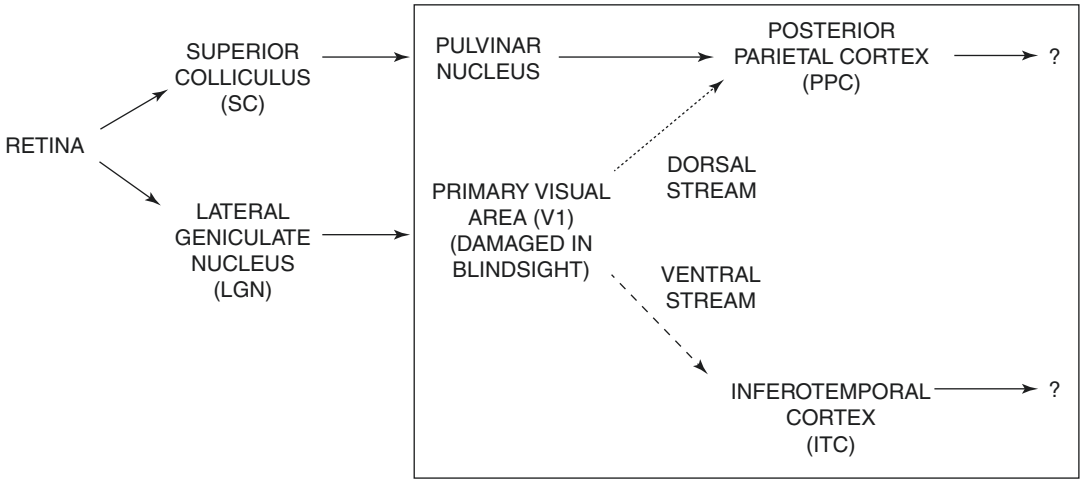


**Fig. 11.1** Diagram of the two-stream hypothesis of neuroanatomical organization of the human visual system

rectangle. Admittedly, the hypothesis is very simplified, and its accuracy has been questioned [15–18]. However, it still is widely used as a heuristic tool to guide experiment and theory [19–25]. Hence, I do not intend it as very accurate but only as a working theoretical hypothesis. Theorizing requires simplification if it is to allow for explanations and predictions [26, 27].

According to the hypothesis, the visual system consists of two discernible (albeit overlapping and interacting) neural pathways or streams, dorsal and ventral. Both originate in V1, which receives projections from the lateral geniculate nucleus (LGN) and projects to different polysensory (multimodal, sensory association) areas: the posterior parietal cortex (PPC) and the inferotemporal cortex (ITC). PPC also receives projections from the thalamic pulvinar nucleus, bypassing V1. The pulvinar receives projections from the superior colliculus (SC), which in turn receives projections from the retina. Of course, there are other structures and connections (e.g., V1 also projects to extrastriate areas such as V3, V4, and V5/MT complex), but they are ignored as a temporary strategic theoretical simplification.

The main implication of this hypothesis for my present purposes is that extensive damage (in some cases, total bilateral ablation) of V1 does not eliminate visual control of behavior. Except for certain kinds of reports of visual awareness that are impeded in cortically blind humans, substantial visual control of behavior survives the lesion. The two-stream hypothesis explains that such control occurs thanks to the activation of the pulvinar by the SC, and the PPC by the SC, which bypass V1. This explanation implies that reports of visual awareness depend heavily on V1 and structures in the ventral stream.

Figure 11.1 Diagram of the two-stream hypothesis of neuroanatomical organization of the human visual system (after [13]). On this hypothesis, such organization involves a dorsal (dotted arrow) and a ventral stream (dashed arrow). Both originate in the primary visual area (V1), which receives projections from the thalamic lateral geniculate nucleus (LGN, receiving projections from the retina), but project to different secondary sensory areas. The dorsal stream projects to the posterior parietal cortex (PPC). The ventral stream projects to the inferotemporal cortex (ITC). PPC also receives projections from the thalamic pulvinar nucleus, which receives projections from the superior colliculus (SC), which also receives projections from the retina. The square encloses the part that will be interpreted here in terms of a neural network model. The question marks depict a motor component that the hypothesis does not specify but such model can provide.

No theory of phenomenal consciousness thus far incorporates Pavlovian blindsight and masked conditioning in relation to the two-stream

hypothesis. In this paper, I propose such an account, using an existing neural network model of Pavlovian conditioning. I do not intend to emulate blindsight in all its behavioral or neural complexity. As any other modeling effort in science, neural network modeling included, the present will be very abstract and simplified. It will thus retain the toy character that is typical of neural network modeling. However, such character is the usual and proper beginning of theorizing about complex phenomena, especially in behavioral neuroscience [27]. The present study is thus intended only as a very short, suggestive, and tentative first step toward more realistic models and simulations of the phenomena of interest and their neural components.

The paper is organized as follows. In the next section, I summarize the model, focusing on its most relevant aspects for my present purposes. In section "Simulations", I describe two simulations (one for Pavlovian blindsight, the other for masked conditioning) with neural networks designed according to the model, inspired by the two-stream hypothesis as depicted in Fig. 11.1. I end the paper with a discussion about implications, limitations, and future directions.

## The Model

The model was originally proposed as a unified neural network account of Pavlovian and operant conditioning [28]. It is a relatively high-level, neural systems model that has been shown to simulate numerous Pavlovian conditioning phenomena, such as acquisition, extinction, faster reacquisition (savings), blocking, interstimulus interval (ISI) function (and its dependence on network size), generalization, discrimination, overshadowing, reinforcement revaluation, latent inhibition, autoshaping, automaintenance (positive and negative), simultaneous conditioning, context shift effects, misbehavior, and autoshaped choice [29–43]. I will show, however, that the model can be successfully applied to Pavlovian blindsight by making certain assumptions about network architecture, guided by the two-stream hypothesis.

### Computational Aspect (Neural Unit Level): Activation Rule

The activation rule consists of two modes of activation: innate and learned. Innate activation does not require any learning (weight change) and obtains when the activation of a certain input unit ($s^*$) at $t$ is larger than zero, and $j$ is either a $D$ or an $r^*$ unit (I describe these units in section "Network Aspect"). Otherwise, learned activation obtains. Learned activation requires learning (increases in connection weights) and has three possible mutually exclusive states: reactivation, decay, and inactivation. All these components relate mathematically as follows:

$$a_{j,t} = \begin{cases} a_{s*,t}, \text{if } a_{s*,t} > 0 \text{ and } j \text{ is either } D \text{ or } r^* \text{ (innate activation); otherwise,} \\ L\left(\text{exc}_{j,t}\right) + \tau_j L\left(\text{exc}_{j,t-1}\right)\left[1 - L\left(\text{exc}_{j,t}\right)\right] - L\left(\text{inh}_{j,t}\right), \\ \quad \text{if } L\left(\text{exc}_{j,t}\right) > L\left(\text{inh}_{j,t}\right) \text{and } L\left(\text{exc}_{j,t}\right) \geq \theta_{j,t} \text{ (reactivation)} \\ a_{j,t-1} - \kappa_j\, a_{j,t-1}\left(1 - a_{j,t-1}\right), \\ \quad \text{if } L\left(\text{exc}_{j,t}\right) > L\left(\text{inh}_{j,t}\right) \text{and } L\left(\text{exc}_{j,t}\right) < \theta_{j,t} \text{ (decay)} \\ 0, \text{if } L\left(\text{exc}_{j,t}\right) \leq L\left(\text{inh}_{j,t}\right) \text{(inactivation)} \end{cases} \tag{11.1}$$

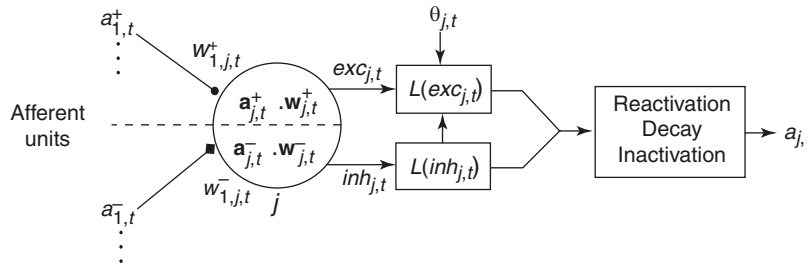


**Fig. 11.2** Shows the model's generic computational unit for learned activation, intended to simulate a relatively small neuronal group

where $t$ is an occasion, epoch or moment in time, or "timestep" of indefinite but relatively short duration (say, 500 ms, give or take, if the reader really needs a value, but no particular duration is presupposed for computational purposes) and $L(x) = \frac{1}{1+e^{\frac{-(x-\mu)}{\sigma}}}$ is the logistic function with constant mean $\mu = 0.5$, variable standard deviation $\sigma$ (a free parameter; typically, $\sigma = 0.1$, which allows for a spontaneous activation level of approximately 0.006 with initial connection weights of 0.01), and argument $x = \sum_{i=1}^{s} a_{i,t} w_{i,j,t}$, where $s$ denotes the total number of units connected to $j$. All activations are real numbers between 0 and 1.

Figure 11.2 shows the model's generic computational unit for learned activation, intended to simulate a relatively small neuronal group. It consists of one or more pre-connection units, which can be excitatory ($a^+_{i,t}$,…) or inhibitory ($a^-_{i,t}$,…) connected through variable weight connections to a post-connection process ($j$) that computes inner products of input activation and connection weight vectors at a certain moment $t$, separately for excitatory ($\text{exc}_{j,t}$) and inhibitory ($\text{inh}_{j,t}$) inputs and their respective connections. Each product is the argument of a logistic function ($L$). There are two thresholds to $L(exc_{j,t})$: a Gaussian threshold ($\theta_{j,t}$) and $L(\text{inh}_{j,t})$. The Gaussian threshold is a random number generated according to a Gaussian distribution with a mean of 0.2 and standard deviation of 0.15. $\theta_{j,t}$ is one source of randomness in the model (see section "Network Aspect" for another source). $\theta_{j,t}$ is also dynamical, as it is generated at every moment. Two other free parameters are temporal summation ($\tau_j$) and decay ($\kappa_j$), where $\tau_j = 0.1$ and $\kappa_j = 0.1$. These values have been used in all previous simulation with the model.

Figure 11.2. The model's generic neurocomputational unit ($j$) for learned activation. Line with circle end: variable excitatory connection. Line with diamond end: variable inhibitory connection. $a^-_{i,t}$: activation of excitatory pre-connection unit $i$ at $t$. $a^+_{i,t}$: activation of inhibitory pre-connection unit $i$ at $t$. $w^+_{i,j,t}$: weight at $t$ of a connection with an excitatory pre-connection ($i$) unit. $w^-_{i,j,t}$: weight at $t$ of a connection with an inhibitory pre-connection unit. $\mathbf{a}^+$, $\mathbf{a}^-$: pre-connection excitatory and inhibitory activation vectors. $\mathbf{w}^+$, $\mathbf{w}^-$: excitatory and inhibitory weight vectors. $\text{exc}_{j,t}$: inner product of $\mathbf{a}^+$ and $\mathbf{w}^+$. $\text{inh}_{j,t}$: inner product of $\mathbf{a}^-$ and $\mathbf{w}^-$, a threshold to $L(\text{exc}_{j,t})$. $L$: Logistic function. $\theta_{j,t}$: Gaussian threshold to $L(\text{exc}_{j,t})$. $a_{j,t}$: activation state of $j$ at $t$

## Computational Aspect (Connection Level): Learning Rule

A connection is intended to simulate a relatively small synaptic group and a weight to simulate the efficacy of a synaptic group to allow the activation of a postsynaptic by a presynaptic neuronal group. The learning rule describes changes in weights, as follows:

$$\Delta w_{i,j,t} = \begin{cases} \alpha_j a_{j,t} d_t p_{i,t} r_{j,t}, \text{if } d_t \geq 0.05 \\ -\beta_j w_{i,j,t-1} a_{i,t} a_{j,t}, \text{otherwise} \end{cases} \quad (11.2)$$

where $\alpha$ (rate of weight increment) and $\beta$ (the rate of weight decrement) denote the two free param-

eters of the rule (typically, $\alpha = 0.5$ and $\beta = 0.1$). The other terms of the rule are:

$a_{i,t}$: activation of presynaptic unit ($i$)
$a_{j,t}$: activation of postsynaptic unit ($j$)
$d_t = d_{H,t} = |a_{H,t} - a_{H,t-1}| + d_{D,t}(1 - d_{H,t-1})$, if $j$ is an $s''$ or $H$ unit; $d_t = d_{D,t} = a_{D,t} - a_{D,t-1}$, if $j$ is an $m''$, $D$, or $r*$ unit (see section "Network Aspect" for the different types of units)

$$p_{i,t} = \frac{a_{i,t} w_{i,j,t-1}}{N},$$

where

$N = \text{exc}_{j,t}$ if $i$ is excitatory
$N = \text{inh}_{j,t}$ if $i$ is inhibitory

$$r_{j,t} = 1 - \sum_{i=1}^{s} w_{i,j,t}.$$

Like some other models, the rule is strongly Hebbian and akin to (but also different in some respects from) unsupervised, reinforcement rules. The key factor is $d_t$, a signal that modulates changes of *all* weights, inspired by the roles of hippocampal (e.g., CA1) and dopaminergic (e.g., ventral tegmental area) systems in conditioning. In this sense, $d_t$ is a *diffuse* signal. It also is a *discrepancy* signal in that it is defined as a temporal difference between the activations of certain units (see section "Network Aspect") in pairs of successive moments (in early simulations, the $d_t$ threshold was 0 but was increased to 0.001 to simulate latent inhibition; see [32]). After this, it was further increased to 0.05 to simulate other phenomena. The $p_{i,t}$ and $r_{j,t}$ factors introduce a "rich get richer, poor get poorer" sort of competition among connections for a limited amount of weight on any postsynaptic unit.

The rule applies to all variable connections. Like activations, all weights are real numbers between 0 and 1 and can thus be interpreted as the proportion of transmitter receptors on $j$ that are controlled by $i$. Initial connection weights are typically set to near-zero values (between 0.01 and 0.2, depending on the connections; see section "Network Aspect"). The rule makes no distinction between Pavlovian and operant learning. This distinction is made at the level of networks that trained with protocols that simulate conditioning procedures. Such protocols are defined in terms of the behavioral categories that are used in conditioning research. In Pavlovian conditioning, they are CS, US, CR, UR, and the various CS-US temporal and contingency (probabilistic) relations.

## Network Aspect

Figure 11.3 depicts the three networks used in the simulations, labeled as NL ("no lesion"), V1L ("V1 lesion"), and NL2 ("no lesion with twice the ventral hidden layers"). I propose NL and NL2 as neural network interpretations of the part of the two-stream hypothesis enclosed in the square in Fig. 11.1, where NL2 has a larger ventral stream. I propose V1L as a neural network interpretation of the absence of V1 (and hence both streams), to simulate cortically blindness. NL and V1L were used in Simulation 1 (section "Simulation 1: Pavlovian Blindsight"). NL2 was used in Simulation 2 (section "Simulation 2: Pavlovian Masked Conditioning").

Figure 11.3. Neural networks used in the simulation, designed after Fig. 11.1. *NL*: no lesion. *V1L*: V1 lesion. NL2: no lesion with twice the number of ventral hidden layers. $s_1$, $s_2$ (squares within dashed rectangle): inputs whose activations simulate sensory effects (arrows) of the CS on the pulvinar nucleus via the superior colliculus (SC, not depicted). $s_3$, $s_4$ (pentagons within solid rectangle) in NL; $s_3$, $s_4$, and $s_5$ in NL2: inputs whose activations simulate sensory effects of the CS on V1 via the lateral geniculate nucleus (LGN, not depicted). V1L lacked the V1 inputs, to simulate a V1 lesion. $s*$ (hexagon): US input unit. Circles: computational units (all excitatory). Thin lines with button endings: initially weak variable feedforward connections. Dotted connections (NL, NL2): dorsal stream. Dashed connections (NL, NL2): ventral stream. Thick lines: fixed maximally strong connections. $S''$: polysensory layer, divided into posterior parietal (PPC, dorsal stream) and inferotemporal cortex (ITC)

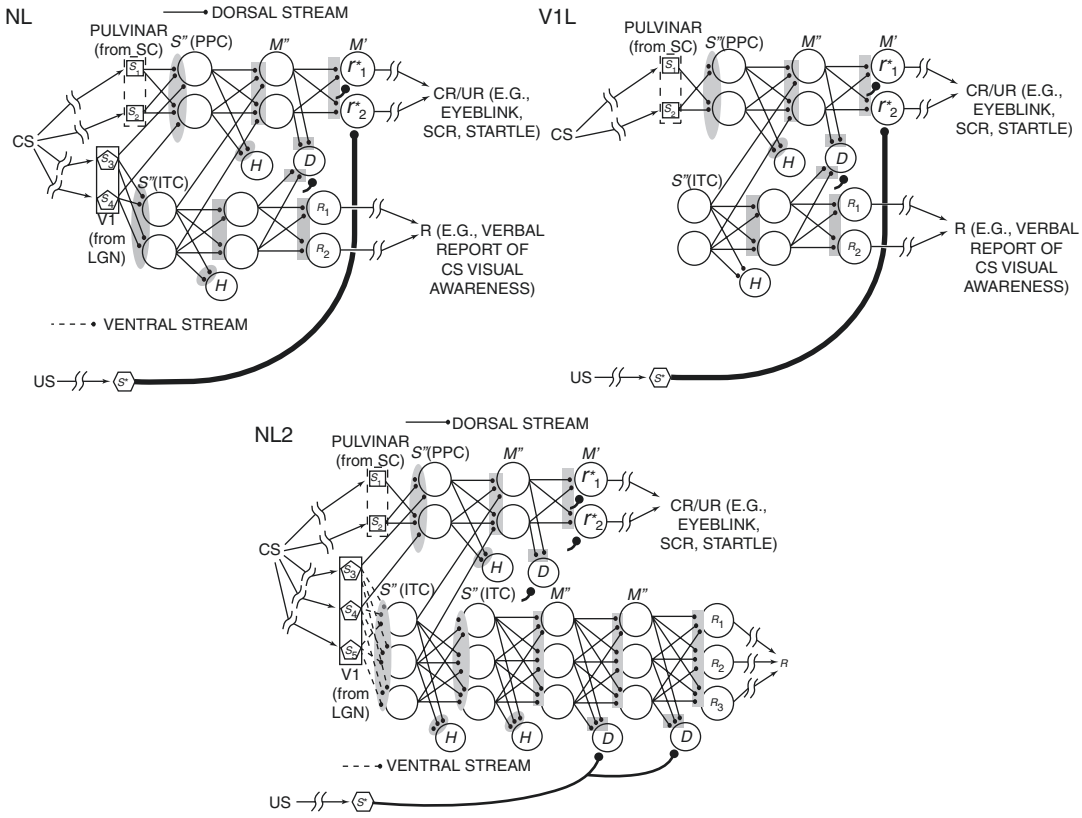


**Fig. 11.3** Depicts the three networks used in the simulations, labeled as NL ("no lesion"), V1L ("V1 lesion"), and NL2 ("no lesion with twice the ventral hidden layers")

units (ventral stream). *H*: hippocampal-like unit. Gray ellipses: hippocampal modulating signal. *M″*: layer of secondary motor-like units (two per stream). *D*: dopaminergic-like unit. Gray rectangles: dopaminergic modulating signal. *M′*: primary motor (output) layer. $r^*_1$, $r^*_2$: outputs that simulate primary motor precursors of a conditioned response (CR) or unconditioned response (UR). SCR skin conductance response. $R_1$, $R_2$ (NL, V1L), $R_3$ (NL2): outputs that simulate primary motor precursors of a conditioned response that is not elicited by the US (R). Pairs of wavy lines: convenient theoretical simplification by exclusion of key structures (e.g., retina, SC, LGN, various effectors such as muscles and glands)

The three networks are very simple and abstract, so I do not intend them as complete emulations of any natural brain circuits. I only intend them as very incomplete, minimal networks that simulate a few aspects of the phenomena of interest. They have a basic feedforward organization in that units are organized into input, hidden, and output layers (from left to right in each network), where input connect to hidden, and hidden to output units. Computational units are depicted as circles, and their activations are computed according to the activation rule. Initially weak variable connections are depicted as thin lines with button endings, and their weights change according to the learning rule.

However, the networks differ from typical feedforward networks in some important respects. First, inputs are divided into three types that are intended to simulate neuroanatomically distinct sensory structures: squares labeled as $s_1$ and $s_2$; pentagons labeled as $s_3$ and $s_4$ (NL), or $s_3$, $s_4$, and $s_5$ (NL2); and a hexagon labeled as $s^*$. A key feature of NL and NL2 regarding the part of the two-stream hypothesis enclosed in the square

in Fig. 11.1 is the distinction between $s_1$ and $s_2$, on the one hand, and $s_3$ and $s_4$ (NL), or $s_3$, $s_4$, and $s_5$ (NL2), on the other. I mean this distinction to capture the distinction between the pulvinar nucleus (simulated by $s_1$ and $s_2$ in the three networks) and V1 (simulated by $s_3$ and $s_4$ in NL and by $s_3$, $s_4$, and $s_5$ in NL2), according to the hypothesis.

Activations of $s_1$ and $s_2$ are thus intended to simulate specific activations of the pulvinar nucleus by the CS, via the superior colliculus (SC, not included in the networks). Activations of the V1 inputs are intended to simulate specific activations of V1 by the same CS, via the LGN (not depicted). V1L had no V1 inputs and their connections to PPC and ITC, to simulate the absence of V1 in cortically blind organisms. Multiple input activations are intended to simulate distributed sensory effects of the same simple CS. Another working hypothesis is that some such effects (those on the pulvinar nucleus) remain relatively intact in Pavlovian blindsight (and blindsight in general) while others (those on V1) do not.

Unit $s*$ is a special-purpose input unit. Its activation is intended to simulate sensory effects of the US (more on this in the fifth point below). Input activations are not computed through the activation rule but assigned manually according to a training protocol that simulates a Pavlovian conditioning procedure of interest (in the present study, a forward-delay procedure). For simplicity, I will assume that $s*$ activations simulate an appetitive US (e.g., food, water). Aversive USs (e.g., electrical shocks, loud noises) raise further complications that are better left for future research. This emphasis departs from the one on aversive conditioning, which dominates research on blindsight and masked conditioning.

Second, only some units in a layer are connected to only some units in its target layer, in contrast to feedforward networks that have complete layer-to-layer connectivity. Thus, $s_1$ and $s_2$ in the three networks are connected only to the upper pair of units (labeled as PPC, for "posterior parietal cortex") of the first hidden layer ($S''$, for "polysensory"), while $s_3$ and $s_4$ in NL are connected to the lower pair (labeled as ITC, for "inferotemporal cortex") in the same hidden layer ($s_3$, $s_4$, and $s_5$ in NL2 are connected to the lower three units of its first $S''$ layer). I intend PPC and ITC to simulate parts of the corresponding polysensory areas.

I propose such separation between two sets of input units connecting to different sets of $S''$ units in NL and NL2 as a neural network interpretation of the distinction between the dorsal stream (connections from $s_1$ and $s_2$ to PPC, depicted as dotted lines) and the ventral stream (connections from $s_3$ and $s_4$ in NL, or $s_3$–$s_5$ in NL2, to ITC, depicted as dashed lines), according to the part of the two-stream hypothesis enclosed in the square in Fig. 11.1. Strictly, V1L has neither stream, as this network lacks the V1 units and their connections to PPC and ITC, and insofar as such connections define both streams.

Third, in contrast to typical feedforward networks in connectionist modeling, these networks have two other special-purpose kinds of units (in addition to $s*$), labeled as $H$ and $D$. They are intended to simulate the roles of hippocampal ($H$) and dopaminergic ($D$) systems in conditioning. In the learning rule, such roles are hypothesized to partly consist in providing diffuse discrepancy signals that modulate changes in efficacies of different synapses. These signals are depicted in the networks as gray ellipses ($H$ signal; $d_{H,t}$ in the learning rule) and rectangles ($D$ signal; $d_{D,t}$ in the learning rule). The $H$ signal modulates changes in the weights of the variable connections from input to $S''$, and $S''$ to $H$ units. The working hypothesis here is that the hippocampal formation sends a diffuse discrepancy signal that modulates efficacies of synapses from the pulvinar nucleus to PPC and from V1 to ITC.

There is some neuroanatomical evidence for projections from the hippocampal formation to both polysensory areas such as the PPC [44, 45] and ITC [46], although their precise synaptic structure and function remains unknown. The model assumes this structure to consist of feedback axo-axonic synapses, which often serve a modulatory function (the same is assumed for the $D$ signal). Each pair of $S''$ units is connected to its own $H$ unit because this has allowed for better simulation results in the past (see [40]). The $D$

signal modulates changes in the weights of the $S''$-$M''$, $M''$-$D$, and $M''$-$M'$ connections and amplifies the $H$ signal. $D$ receives connections from all $M''$ units because this has allowed for better simulation results in the past. In these networks, then, it is assumed that hippocampal representation is more fine-grained than dopaminergic representation.

As a fourth feature, the networks have multiple hidden layers, in contrast to typical feedforward networks that have one. NL and V1L have two hidden layers (one $S''$ and one $M''$), whereas NL2 has four (two $S''$ and two $M''$). The $M''$ units are intended to simulate parts of secondary motor (or motor "association") areas such as prefrontal and premotor cortex (not distinguished in Fig. 11.3). For my present purposes, these units can be viewed as adding a motor component to the two-stream hypothesis. The working hypothesis, then, is that PPC and ITC project to different parts of secondary motor cortex. It would be premature at this point to speculate about whether such parts correspond to the same or different secondary motor areas (it might be a complex combination of both). I thus will leave this open for further research.

The key working hypothesis is that there is sufficient motor separation between the dorsal and ventral streams to allow for significant behavioral differences between Pavlovian blindsight and normal Pavlovian conditioning. Following this hypothesis, different sets of $S''$ units are connected to different sets of $M''$ units. The ITC units are also connected to the upper pair of $M''$ units, to simulate a polysensory to secondary motor relation between the two subnetworks. No connection from PPC to the lower $M''$ units was included because this would not simulate Pavlovian blindsight. The working hypothesis here, then, is that if there is any relation between the two subnetworks at all, it should be from the ventral to the dorsal subnetwork, not vice versa.

Fifth feature is that the networks also include maximally strong fixed connections (thick lines from $s*$ to $D$, $r*_1$, and $r*_2$). These connections are intended to simulate innately strong synapses that mediate between the US and primary motor precursors of the UR (activations of $r*_1$ and $r*_2$ by $s*$) and the US and dopaminergic systems (activations of $D$ by $s*$). Only $D$, $r*_1$, and $r*_2$ can be activated by $s*$. They can also be activated by the other inputs (via hidden units and variable connections) after some learning (see activation and learning rules above). In $r*_1$ and $r*_2$, their activations by the other inputs are intended to simulate primary motor precursors of a conditioned response (CR) to the CS, a response which is acquired during Pavlovian conditioning. Typically, CR is similar to the UR, hence the CR/UR label, which I intend only to denote the two ways of activating the $r*$ units according to the activation rule (by $s_1$–$s_4$ via the hidden units, or by $s*$, respectively), not an identification of CR with UR or adoption of a stimulus substitution hypothesis. In any case, for simplicity, I will assume that the UR denotes a response that is elicited by an appetitive US (simulated as an $s*$ activation), and that CR denotes a response that is similar to the UR and learned through Pavlovian contingencies. Responses to aversive stimuli raise further complications that are better left for future research.

No other unit can be activated by $s*$. In particular, the $R$ units ($R_1$ and $R_2$ in NL and V1L; $R_1$, $R_2$, and $R_3$ in NL2) comprise a type of output unit that can be activated only by the other inputs (via hidden units and variable connections) and only after some learning. These units are intended to simulate primary motor precursors of some collateral responding that is learned during Pavlovian conditioning but never elicited by the US. There is evidence for such responding [47], although whether it is Pavlovian or operant remains unclear, as it has features of both (Pavlovian because it is learned through a Pavlovian contingency, instrumental because it is not elicited by the US). I cannot discuss this issue here, so I will just label such response neutrally as R. For this investigation, my working hypothesis is that at least one R is learned in normal Pavlovian conditioning but impeded in Pavlovian blindsight and masked conditioning.

Unfortunately, there is not sufficient evidence to constrain this hypothesis much further. Nonhuman Pavlovian blindsight studies thus far have not reported any collateral response that is impeded in cortically blind subjects. At present, the only evidence that suggests a somewhat more

constrained interpretation of R is the occurrence of verbal reports of CS visual awareness in humans without a V1 lesion that receive an unmasked CS [12, 48]. Such reports are hindered in humans with a V1 lesion that receive an unmasked CS [9, 10] and humans without a V1 lesion that receive a masked CS [12, 48].

On this basis, I interpret R as including some sort of report or aspect of a report of CS visual awareness and *R* activations to simulate some primary motor precursors of such a report. In human preparations, I further hypothesize that such aspect includes (but is not restricted to) verbal reports. The implication is that verbal reports of CS awareness are more substantially mediated by the ventral than the dorsal stream. There is neuroimaging evidence in favor of this hypothesis [49]. In animal preparations, I hypothesize that R includes the kinds of nonverbal responding that are taken as "reports" (e.g., operant or instrumental responses, such as pulling a lever or pressing a pad). Such responding too, I hypothesize, is mediated more substantially by the ventral than the dorsal stream.

## Simulations

Two simulations were run. In Simulation 1, NL and V1L were used to simulate Pavlovian blindsight. In Simulation 2, two tokens of NL2 were used to simulate Pavlovian masked conditioning. The simulator was designed and coded by the author with Delphi© for Windows©. The executable file, all necessary simulation files, simulation data files, and source code are available without cost upon request to the author.

### Simulation 1: Pavlovian Blindsight

NL and V1L (see Fig. 11.3) received separately and independently a training protocol that was intended to simulate a standard Pavlovian forward-delay procedure. In this protocol, the CS was defined as the simultaneous maximal activation of all the sensory inputs of each network ($s_1$-$s_4$ in NL; $s_1$, $s_2$ in V1L) for six timesteps. The US

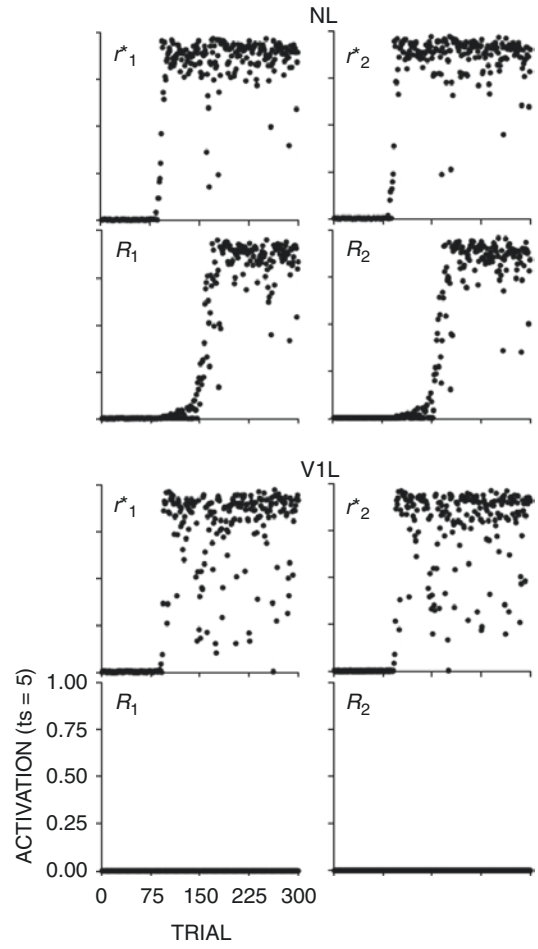


**Fig. 11.4** Depicts the results in terms of changes in the activations of the different sets of output units ($r^*$ and $R$) at the second-to-last timestep of each CS trial for each network during conditioning

was defined as the maximal activation of $s^*$ at the last CS timestep, for an ISI of five timesteps. Both networks received 300 CS-US trials. For simplicity, the intertrial interval was not simulated but assumed to be sufficiently long to allow for all activations to decrease to spontaneous activations (Eq. 11.2). Initial weights were set to 0.2 or 0.1 for the input-$S''$ and $S''$-$H$ connections (depending on whether the units received two or three connections, respectively) and 0.01 for the rest of the connections (see [34]). The update of activations and weights was asynchronous and random.

Figure 11.4 depicts the results in terms of changes in the activations of the different sets of

output units ($r^*$ and $R$) at the second-to-last timestep of each CS trial for each network during conditioning. The results are consistent with the behavioral evidence. NL showed high activations of all output units after approximately 75 CS-US pairings, although noticeably faster in $r^*_1$ and $r^*_2$ than in $R_1$ and $R_2$ (where acquisition took about twice the number of trials). V1L showed high output activations only in $r^*_1$ and $r^*_2$, although their maintenance was noticeably less stable than NL's. More importantly, V1L's $R_1$ and $R_2$ activations were nearly zero, which simulates the absence of a report of CS visual awareness.

Figure 11.4. Changes in activations of all outputs at the second-to-last CS timestep (ts) across training trials for NL (no lesion) and V1L (V1 lesion) in Simulation 1. $r^*_1$, $r^*_2$: dorsal output units that can be unconditionally activated by the US (UR) or by the CS after sufficient learning (CR). $R_1$, $R_2$: ventral output units that can be activated only by the CS after sufficient learning (R)

The model can thus simulate a simple form of Pavlovian blindsight as the occurrence of Pavlovian conditioning (increment of $r^*_1$ and $r^*_2$ activations by $s_1$–$s_4$) to a visual CS, despite the absence of a V1 area and its detrimental effect on reports of CS visual awareness (near-zero $R_1$ and $R_2$ activations). The explanation is equally simple. Pavlovian conditioning in NL allowed sufficient learning in both subnetworks for $s_1$ and $s_2$ to activate $r^*_1$ and $r^*_2$, and $s_3$ and $s_4$ to activate $R_1$ and $R_2$. R (simulated reports of CS visual awareness), thus, was not impeded in NL, as this network had V1 input units. In contrast, Pavlovian conditioning in V1L allowed sufficient learning in the upper subnetwork for $s_1$ and $s_2$ to activate $r^*_1$ and $r^*_2$. However, V1L's $R_1$ and $R_2$ units could not be activated due to the lack of the V1 inputs.

## Simulation 2: Pavlovian Masked Conditioning

Previous simulation research has shown that this model predicts networks with more hidden layers to require longer optimal ISIs than networks with fewer hidden layers. The reason is that the propagation of activations from inputs to outputs through more hidden layers is slower and hence requires longer optimal ISIs than propagation through fewer hidden layers. In all networks, long ISIs promote more weight loss than short ISIs, because long ISIs have more timesteps without the US. This effect, however, is more deleterious in networks with fewer than more hidden layers. This result is consistent with evidence that different preparations require different optimal ISI (see [50, Fig. 11.1]). This evidence is explained in this model by hypothesizing that different preparations involve neural circuits with different numbers of hidden layers and that preparations that involve fewer layers require shorter optimal ISIs (e.g., the nictitating membrane response in rabbits involves fewer hidden layers than conditioned suppression in rats).

For this simulation, the working hypothesis was that if a single network combined subnetworks with different numbers of hidden layers, then a very short ISI could simulate a masked CS that allowed for learning in the smaller subnetwork but be too short to allow for learning in the larger subnetwork. A moderate ISI could allow for learning in both subnetworks. NL2 was designed with this hypothesis in mind. The dorsal subnetwork was thus assumed to have the right number of hidden layers to allow for learning with a short and a moderate ISI. The ventral subnetwork was assumed to have a number of hidden layers to prevent learning with the short but allow for learning with the moderate ISI.

Two tokens of NL2 received separately and independently training protocols that were intended to simulate a standard forward-delay procedure. In this protocol, the CS was defined as the simultaneous maximal activation of all NL2's sensory inputs ($s_1$–$s_5$) for either two timesteps (one token of NL2) or six timesteps (another token of NL2). The US was defined as the maximal activation of $s^*$ at the last CS timestep, for an ISI of either five timesteps or one timestep. Both networks received 300 CS-US trials. For simplicity, the intertrial interval was not simulated but assumed to be sufficiently long to allow for all activations to decrease to spontaneous activations (Eq. 11.2). Initial weights were set as in Simulation 1. The update of activations and

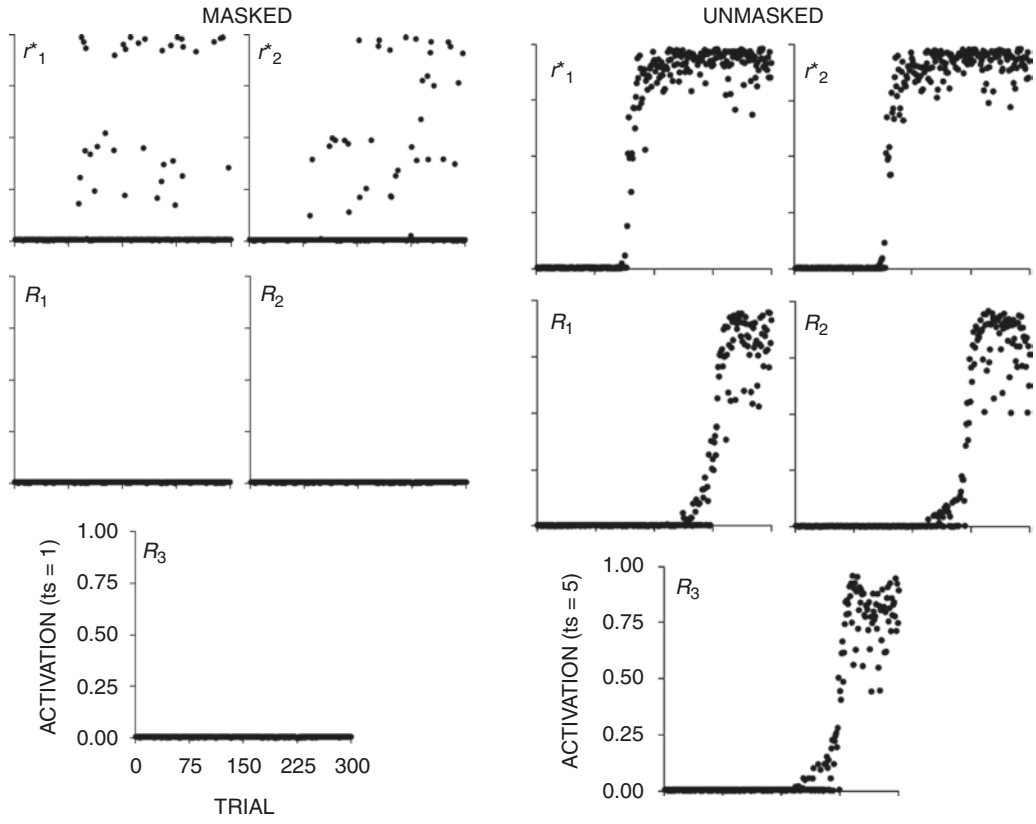


**Fig. 11.5** Shows the results in terms of the output activations at the second-to-last timestep (one for masked, five for unmasked) of each trial

weights was asynchronous and random. Figure 11.5 shows the results in terms of the output activations at the second-to-last timestep (one for masked, five for unmasked) of each trial.

The results were as expected. NL2 simulated a more detrimental effect of a masked (short) CS on *R* activations (which simulate primary motor precursors of some behavioral report of visual awareness of the CS) than on *r** activations (which simulate primary motor precursors of Pavlovian conditioning of a UR-elicited response). The reason was that the ISI in the masked condition was too short to allow for learning in the ventral subnetwork but was sufficiently long to allow for learning in the dorsal subnetwork. The longer ISI (unmasked CS) was sufficient to allow for learning in both subnetworks. Also, Pavlovian conditioning with the short ISI was substantially weaker than Pavlovian conditioning with the longer ISI. This result simulates evidence of the detrimental effect of too short an ISI on Pavlovian conditioning [51].

Figure 11.5. Changes in activations of all output units at the second-to-last CS timestep (ts) across training trials for NL2 in the masked (left panels) and unmasked (right panels) conditions in Simulation 2. Masked: the CS lasted for two timesteps, the US was presented at the second, and output activations were recorded at the first. Unmasked: the CS lasted for six timesteps, the US was presented at the last, and output activations were recorded at the fifth

An implication is that masked Pavlovian conditioning occurs without a "report" of visual awareness of the CS because the ventral stream is longer (consists of more hidden layers) than the dorsal stream. Although more detailed evidence might be needed to confirm it, the implication seems plausible in view of the available evidence.

The ventral stream is typically depicted as being longer than the dorsal stream [13, 52]. There also is some neuroimaging evidence that supports this difference [49]. The difference would explain why a masked CS does not allow for learning in the ventral stream, with the consequent absence of R reports of CS awareness (whether or not verbal), under the hypothesis, formulated in section "Network Aspect", that they are more substantially mediated by the ventral than the dorsal stream.

## General Discussion

The model thus provides a unified connectionist account of Pavlovian conditioning (simulated as above-zero $r^*$ activations) without CS visual awareness (simulated as zero $R$ activations), whether due to the absence of V1 underlying blindsight (simulated in V1L as the absence of certain input units) or a masked CS (simulated in NL2 as too short an ISI to allow for learning in the ventral subnetwork). Of course, the simulation is very simple, but then again, at this stage it would be premature to attempt a more realistic simulation, as there is not sufficient evidence to further constrain the account. The results should thus be taken only as a very short, suggestive, and tentative step toward increasingly more realistic connectionist models. Despite this, the results have implications that could inspire new empirical research.

One implication is that CR maintenance in Pavlovian blindsight across trials is less stable than Pavlovian conditioning in a visually healthy organism. This effect was due to the fact that each PPC unit in NL and NL2's dorsal stream received more inputs (from $s_3$ and $s_4$), which provided a stronger input activation vector that simulated a more intense (salient) CS. This result seems to be inconsistent with evidence that the CR in monkeys with bilateral ablation of the occipital lobes is not significantly different from that of monkeys without any lesion [8]. However, this evidence refers to the acquisition, form, amplitude, and frequency of the CR, not its stability across trials. No systematic observation of this stability has been made thus far in Pavlovian blindsight.

A second implication is that Pavlovian masked conditioning is substantially weaker and less stable than Pavlovian unmasked conditioning, as simulated with NL2. This implication is consistent with evidence from Pavlovian conditioning research on the effects of the ISI. It is well known that strong conditioning requires an optimal ISI, below and above which conditioning weakens. The present model simulates this effect to depend strongly on network size (specifically, number of hidden layers), such that optimal ISIs are longer in larger networks.

A third implication is that at least one response (or aspect of a response) R is learned during Pavlovian conditioning in the experimental situation with an unmasked CS, without being elicited by the US and without a V1 lesion but impeded by a V1 lesion or a masked CS in the absence of a V1 lesion. Again, this is highly hypothetical, as there is not much evidence for such a response. At present, the most direct evidence refers to verbal reports of CS visual awareness, which is impeded in humans with a V1 lesion that receive an unmasked CS and humans without a lesion that receive a masked CS. This evidence suggests an interpretation of R as simulating the ability to give such report or some behavioral aspect of it.

One problem with this interpretation is that the simulation predicts the acquisition of R during conditioning. Intuition, however, dictates that healthy adults come to the experimental situation with the ability to give verbal reports of CS awareness upon request, without the need of conditioning. To make an interpretation of R as a verbal report of CS visual awareness more plausible, the initial connection weights in the ventral subnetwork could be set to sufficiently high values, so that no learning is necessary in the conditioning experimental situation for the V1 inputs to activate the $R$ outputs in NL and NL2, but not in V1L (another simulation with NL confirmed this expectation). Still, the model predicts that visually healthy organisms learn at least one other collateral response as a result of Pavlovian conditioning, without being elicited by the US, and that this response is impeded in cortically blind

organisms. This hypothesis seems sufficiently interesting to deserve further examination. One possibility is to use autoshaping [53], the acquisition of a response (e.g., pecking a key) that is not strictly elicited by the US (e.g., food) but still is acquired under Pavlovian contingencies. Using this preparation with humans (whether in blindsight or in masked conditioning) could provide a way to test the proposed hypothesis.

Another problematic prediction is that the activation of the V1 inputs after learning suffices to activate the *R* outputs (via hidden units and variable connections) in NL and NL2 with the unmasked CS. Obviously, normal humans do not give a report of CS visual awareness whenever the CS occurs, without any request. They normally give a report only when requested to do so. Moreover, cortically blind humans do report something upon request: not being visually aware of the CS. These networks thus exclude numerous aspects of verbal reports of CS visual awareness.

The model also excludes some structures that have been linked to Pavlovian conditioning (e.g., cerebellum, amygdala, hippocampus-prefrontal projections, etc.). The amygdala, in particular, has been linked to both streams, although more directly to the ventral stream (see [54], for a recent review). This link, however, has been made primarily in relation to fear responses that are learned through aversive conditioning (e.g., conditioned suppression). But then again, my emphasis here has been in appetitive conditioning, because aversive conditioning raises further complications that are better left for future research. Admittedly, such emphasis departs from the one found in Pavlovian blindsight and masked conditioning research, which has been conducted with aversive conditioning, thus leading to an emphasis on the amygdala as a key structure.

In the meantime, I will only say that there is evidence that the amygdala is less involved in appetitive conditioning of the US-generated CR [55]. Not that the model makes a fundamental distinction between aversive and appetitive Pavlovian conditioning. In principle, the very same activation and learning rules could be used to simulate aversive conditioning. Rather, the difference would be made at the level of the network between two types of *s** (one to simulate an appetitive US, the other to simulate an aversive US), as well as between two types of *r** units (one to simulate primary motor precursors of responses to an appetitive US, the other to simulate primary motor precursors of responses to an aversive US). This work remains to be done.

Many other structures of the visual system are also excluded, such as the retina, LGN, SC, V2, and V5/MT, among others. For example, it is known that the pulvinar also projects to V2, and this contributes to blindsight and masked conditioning. But then again, such exclusions are intended only as a strategic simplification to focus on minimal networks that can simulate a few features of the phenomena of interest, as a first step toward more realistic networks.

Despite its limitations, the model is highly heuristic in that it allows for systematic manipulations of numerous features of network architecture (number and connectivity of different types of inputs, hidden layers, units per layer, and output units; different numbers and connectivity of *H* and *D* units, etc.). This aspect of the model provides a wide range of theoretical possibilities about neuroanatomical substrates that could be tested in simulations to derive predictions for further empirical research. The differences between the three networks used in the simulations exemplify this, but many more manipulations are possible. For example, the model allows for networks with different numbers of inputs and/or output of different kinds, to simulate different degrees of blindsight. Systematic manipulations of the number and connectivity of *H* and *D* units are also possible, providing a means for theorizing about the possible roles of hippocampal and dopaminergic systems in Pavlovian blindsight and masked conditioning, which remain to be investigated.

The model also allows for systematic manipulations of the input activation levels to simulate different intensities of the CS. Such manipulations provide a way to distinguish between subliminal (low input activations) and supraliminal (high input activations) visual stimuli from a

neural network perspective. For example, NL and NL2 could simulate subliminal Pavlovian conditioning by activating their V1 inputs less strongly than their pulvinar inputs. NL2 with pulvinar inputs activated at 0.9 and V1 inputs activated at 0.5 successfully simulated this. The assumption underlying this simulation is that a weak CS activates V1 more weakly than on the pulvinar. To the best of my knowledge, this is an entirely novel prediction for which there is no evidence. It would thus be premature to commit too strongly to it, let alone any particular hypothesis about possible underlying mechanisms, although some possibilities are conceivable. For example, V1 could be more weakly activated by a weak CS because it is farther away from the retina and hence more susceptible to signal degradation than the pulvinar. Another possible mechanism (compatible with the former) is that pulvinar neurons activation thresholds are lower than those of V1 neurons, so that a weaker CS tends to activate pulvinar neurons more strongly than V1 neurons. There could be other mechanisms. Of course, all of this is very speculative. However, it is empirically testable, at least in principle.

Finally, neither Pavlovian blindsight nor masked conditioning has received any attention from theories of visual consciousness. Of course, phenomenal consciousness is a very complex topic that I cannot do discuss here. However, a few remarks are in order, if only as first step toward theorizing about phenomenal consciousness with the present model. Of course, such theorizing would fall within the category of connectionist approaches to phenomenal consciousness [6, 56–58].

A major issue is which units could simulate phenomenal consciousness in this model. One possibility, as a working hypothesis, is that visual phenomenal consciousness could be simulated at least by the activations of the V1 input, perhaps plus the pulvinar, PPC, and ITC unit activations. The corresponding structures have been linked to visual phenomenal consciousness, so the activations of those units are the best candidates to simulate phenomenal consciousness in this model. This possibility is compatible with the so-called "true neural stance on consciousness" [59]. This stance proposes to take behavioral (or psychological) and neural considerations (observations, arguments, definitions, methods, explanations, etc.) as equally relevant to an understanding of phenomenal consciousness, instead of relegating the latter to mere "correlates."

Such a stance can be formulated more strongly in terms of some form of the so-called identity theory or reductive physicalism, which hypothesizes phenomenal consciousness to be strictly identical to a brain process [60–62]. This identification entails dispensing with talk of neural "correlates" in favor of talk of neural "constituents" of consciousness. It also entails that the absence of behavioral reports of visual consciousness does not imply the absence of phenomenal visual consciousness per se. If pulvinar and posterior parietal cortices are as constitutive of visual consciousness as V1, then visual consciousness is possible without V1 and verbal reports of visual awareness. The present account is consistent with this reasoning.

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# Anthocyanins in Nutrition: Biochemistry and Health Benefits

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## Introduction

Society is constantly changing its eating habits. The new trend of consumption is for the "natural and healthy," which includes vegetables and fruits in the diet. In this sense, a healthy diet is the one that allows rebuilding the body's defenses, provides us with enough energy for our lives, and, at the same time, helps us to prevent diseases (cholesterol reduction, weight control or decrease in sugar level in blood, and blood pressure control, among other factors related to health).

The search for plants with medicinal properties continues to receive attention, as they are known to have a variety of nutraceutical activities, which range from physical to mental health. Bioactive compounds are normally accumulated as secondary metabolites, which are found in a wide range of plant species. Tendencies go toward foods in which the phytochemicals are present, rather than a purified phytochemical consumption, improving human diet and trending to a naturist lifestyle. This has led to the concept of functional foods. Among many foods, red grape berries constitute a great candidate to this target because of their high phenolic content.

Fruits typically contain a mixture of pigments, including the green chlorophylls; yellow, orange, and red carotenoids; red, blue, and violet anthocyanins; and yellow flavonoids. In this sense, grapes are important not only as fresh consumption fruit but also as processed nourishment found in wine and food colorants. Grape phenolic, non-flavonoid compounds such as hydroxycinnamates, hydroxybenzoates, and stilbenes, as well as the more abundant flavonoid compounds including flavan-3-ols, flavonols, and anthocyanins, play a major role in their nutraceutical properties and deserve special attention over other compounds.

## Anthocyanins: Chemistry and Biological Aspects

Anthocyanins (Greek anthos, flower; and kyáneos, blue) are a type of flavonoid polyphenolic pigments responsible for many of the red-orange to blue-violet colors present in plant

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tissues. Chemically, they are glycosylated polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium salts.

Edible plants rich in anthocyanins include the blueberry, raspberry, black rice, and black soybean, among many others that are red, blue, purple, or black. Some of the colors of autumn leaves are derived from anthocyanins, and their color depending on their pH may appear red, purple, or blue. Usually anthocyanins are associated to fruit, but they are also present in vegetables, roots, legumes, and cereals as well [1, 2]. They are water-soluble pigments, and this characteristic is important for their large-scale extraction [3]. Red grape and wine have phenolic compounds present in the berry skin and the solution of wine, and they are responsible for their blue and red color.

These compounds are excellent antioxidants because they are easily oxidized under circumstances of stress, with reactive oxygen species present. This faculty is very important as it contributes to the fruits' and vegetables' protective effect of human heath, regarding degenerative and chronic diseases [4–7].

In relation to human consumption, the extract of some plants and fruits with high phenolic compounds content demonstrated to act as mutagenic and carcinogenic inhibitors as well as anti-inflammatory agents. This promotes the prevention of cholesterol-induced atherosclerosis, including microcirculation diseases [8–11]. Indeed pills powered rich in polyphenols and made out of grape berry skins are already available in the market and are preferred by naturists over conventional medicine.

Anthocyanin biosynthesis is regulated not only genetically but also physiologically. These metabolites are synthesized via the phenylpropanoid pathway, and phenylalanine is the initial compound. The pathway has a branching nature and produces intermediates that act as precursors to generate an enormous diversity of compounds, including anthocyanins and *trans*-resveratrol (Fig. 12.1).

The first enzyme in the pathway is phenylalanine ammonia-lyase (PAL), a key enzyme since it is the first control point of the route. After *p*-coumaric acid is formed, the pathway branches either toward flavonoid synthesis through the action of chalcone synthase (CHS), which produces anthocyanins, or toward the synthesis of stilbenes via stilbene synthase (STS), producing trans-resveratrol. Downstream in the synthesis of anthocyanins, the UDP-glucose:flavonoid 3-O-glucosyltransferase enzyme (UFGT), the last enzyme in the route, adds a glucose molecule to the anthocyanidins that were generated, coloring them and producing the anthocyanins proper.

Once anthocyanins are formed, they may be acylated in their glucose residue, incorporating an acetyl or a coumaroyl group, and introduced into a vacuole by anthoMATE (for *antho*cyanin, *M*ultidrug *A*nd *T*oxic *E*xtrusion transporter family), a membrane transporter [12]. This modification provides stability, an important feature of wines produced for cellaring. The enzymes involved in this pathway response to the expression of two types of genes, the structural genes and the regulatory genes. The structural genes codify the enzymes which participate directly in the synthesis, and the regulatory genes encode elements that control the structural genes.

In grapevine, the transcriptional regulation of structural genes is mainly exerted by a ternary complex (MBW) that involves transcription factors from the R2R3-MYB, MYC-like basic helix-loop-helix (bHLH), and tryptophan-aspartic acid repeat proteins (WDR, also known as WD40) [13]. The expression of most structural genes begins few weeks after bloom except for UDP-glucose:flavonoid 3-O-glucosyltransferase (UFGT), which is regulated independently and begins at veraison (veraison corresponds to the change in the berry skin color, from green to red-violet) [14]. UFGT expression is controlled principally by the transcription factor VvMYBA1 [15], which is mutated in white grapes.

The different anthocyanins are distinguished by the nature, number, and position of the chemical groups attached to the aromatic rings and by the aliphatic or aromatic acids attached to the sugar residue (Fig. 12.2). The basic chemical "backbones" that make up the anthocyanins are called anthocyanidins and have no sugars attached to the aromatic rings. Essentially, in the nature 27 anthocyanidins are known, but there are six common in plants: pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin.

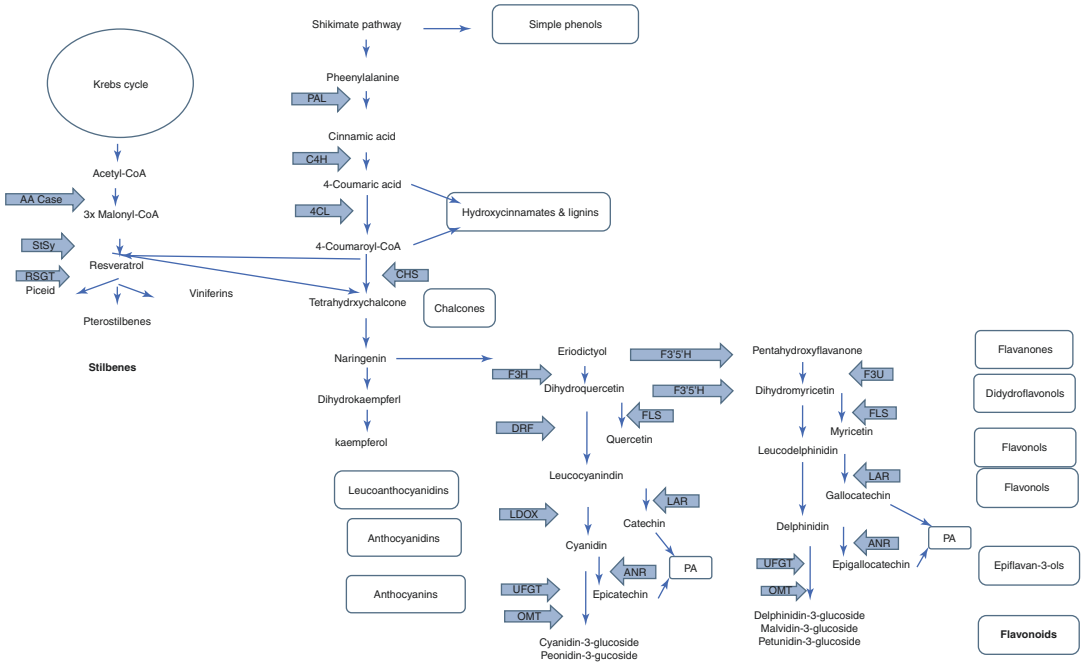



**Fig. 12.1** *V. vinifera* pathways for phenolic and terpenoid biosynthesis. (**a**) *V. vinifera* general pathway for phenolics biosynthesis leading to stilbenes (C6-C2-C6) and flavonoids (C6-C3-C6). For each enzyme, the gene copy number is reported in brackets. The following enzymes involved in the pathway are shown: *PAL* phenylalanine ammonia-lyase, *C4H* cinnamate 4-hydroxylase, *4CL* 4-coumarate-CoA ligase, *CHS* chalcone synthase, *StSy* stilbene synthase, *RSGT* resveratrol glucosyltransferase, *CHI* chalcone isomerase, *F3H* flavanone 3-hydroxylase, *F3′H* flavonoid 3′-hydroxylase, *F3′5′H* flavonoid 3′,5′-hydroxylase, *DFR* dihydroflavonol-4-reductase, *FLS* flavonol synthase, *LDOX* leucoanthocyanidin dioxygenase, *LAR* leucoanthocyanidin reductase, *ANR* anthocyanidin reductase, *UFGT* UDP-glucose:flavonoid 3-*O*-glucosyltransferase, *OMT* *O*-methyltransferase, *ACCase* acetyl CoA carboxylase. PA refers to proanthocyanidins. Enzymatic steps that have not been experimentally confirmed are marked with an asterisk (*)

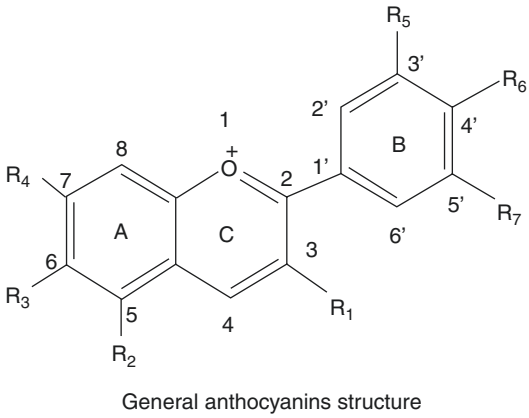


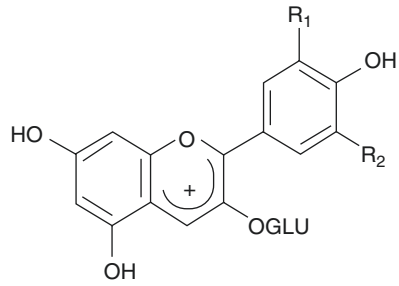

**Fig. 12.2** General anthocyanins structure [16]

Each of these anthocyanidins can be glycosylated and acylated at different sites and with different sugars and acyl groups, and so there are many more anthocyanins than anthocyanidins [16].

The numerous possibilities for the substitution of nucleus B and hydroxyl functions give the anthocyanins specific properties, namely, color and stability, which are directly linked to the structure (Fig. 12.3). The color tones can also be modified by the level of methoxylation, the increase of which leads to more violet compounds such as malvidin 3-*O*-glucoside.

The color of the anthocyanins in solution depends on the pH medium; in fact, the anthocyanins exist in solution under various forms in equilibrium, of different colors. This equilibrium depends on the pH of the medium. At pH less than 2, they are red, and at pH 7 they are violet [17].

There are five out of the six common anthocyanins in grapevine: cyanidin, peonidin, delphinidin,




Cyanidin-3-GLU ($R_1$ = OH, $R_2$ = H)

Delphinidin-3-GLU ($R_1$ = OH, $R_2$ = OH)

Peonidin-3-GLU ($R_1$ = $OCH_3$, $R_2$ = H)

Petunidin-3-GLU ($R_1$ = $OCH_3$, $R_2$= OH)

Malvidin-3-GLU ($R_1$ = $OCH_3$, $R_2$ = $OCH_3$)

**Fig. 12.3** Five anthocyanins in grape berries

petunidin, and malvidin, but pelargonidin has not been detected for this species. Acylations of anthocyanins in grapevine normally occur by esterification of the C1 of the glucose substitution with a cinnamic or aliphatic acid, usually acetyl, coumaril, or a caffeoyl residue. They absorb visible light (maximum peak between 465 and 550 nm) and UV range (between 270 and 280 nm) [18].

## Anthocyanins Synthesis and Abiotic Factors

The anthocyanins are naturally produced by plants in response to biotic and abiotic stresses. In grapevine, the anthocyanins are synthesized in red berry skin cultivars and are localized in different tissues (roots, petioles, leaves, peduncles, berries) and in white berry skin in petioles, leaves, and peduncles.

During berry growth, the synthesis of anthocyanins and accumulation in the skin begins at veraison (veraison is the technical term for the change of color in grape berries and indicates the onset of ripening). Many of the enzymes involved in their synthesis, including PAL, could be regulated by abiotic factors through non-transcriptional mechanisms [19, 20]. The accumulation varies with the cultivar; the environmental conditions, especially light intensity and temperature [21, 22]; plant growth regulators [23–27]; and vineyard management practices [28]. For instance, cultivar Pinot noir was recorded as containing 33 mg/100 g fw of anthocyanins in berries, whereas the cultivar Vincent contained 439 mg/100 g fw [29].

Visible light (400–750 nm) stimulates the synthesis of anthocyanins, although is not necessary for the fruit to be directly exposed to sunlight [11, 30–35]. However, the light is very important for the net photosynthesis. The photosynthesis produces sugar, and the synthesis of all acids and phenolic compounds is dependent on sucrose in berries. Cloudy days slow down the accumulation of anthocyanins and may result in fruits with lower anthocyanin content [32]. These days modify the profile of the anthocyanins (modification of the relative proportion of each anthocyanin). In grapes grown under cloudy conditions, malvidin predominates because it seems to be the anthocyanin less sensitive to radiation intensity [32]. When shading is severe, genes encoding anthocyanin biosynthesis appear to be suppressed [36, 37].

It is estimated that in the cluster area, only 100 $mmol.m^{-2}s^{-1}$ of light intensity is enough to produce anthocyanins normally. In clusters exposed directly to light, temperature is the limiting factor for the synthesis of these compounds [32, 38, 39]. Besides, too much radiation (UVB) can even inhibit the production of anthocyanins or induce degradation, perhaps due to the formation of hydrogen peroxide ($H_2O_2$) as a consequence of oxidative stress.

Temperature is the most important climatic factor influencing coloration of grapes from diverse regions. Temperature control experiments have shown that exposing whole vines or clusters to high temperature (30 °C) inhibits anthocyanin accumulation [22, 24, 40, 41]. Researchers have found that temperatures above 35 °C combined with high light intensities produce low concen-

tration of anthocyanins in the berry [31, 34] and their consequent diminution in wines. Other authors give great importance to the relationship between high nocturnal temperatures in the maturation period and the less content of phenolic compounds [42].

On the other hand, anthocyanin accumulation is enhanced by the exogenous or endogenous plant hormone ABA and water stress [23, 36, 43, 44]. The application of ABA to grapevine increased the content of anthocyanins in berries [36, 44], becoming an efficient strategy to obtain grapes rich in polyphenols.

In the world, water availability for irrigation tends to decrease. So that controlled management of water stress without affecting yields has become a key point in grape production. It has been demonstrated that in vine, water availability affects the concentration and composition of anthocyanins produced by the plant. Post veraison moderate water restriction increases the total anthocyanin content in berries, wines, and organoleptic fraction of wine [43, 44].

## Climate Change and Anthocyanins Content

Global warming and in consequence the climate change affect life in the planet and have impact in the global ecosystems. Since the beginning of the twentieth century, $CO_2$ levels in atmosphere as well as the global temperature have increased. This climate change will affect every region in different manners (www.metoffice.gov.uk/food-insecurity-index), and the viticulture vulnerability will be different. In 2010, Jones and Webb [45] expressed that in the future, the premium wine grape production will occur within very narrow climate ranges (and one factor of premium wine grape is polyphenol content). In the last 55 years, most grape-growing areas were affected. The main causes are the increases in temperature and $CO_2$ levels, as well as the variations in the precipitation regimes [46].

The Intergovernmental Panel on Climate Change in its latest report and update (IPCC 2007 and 2013) informed that during the twentieth century, the land surface temperature has risen globally near $0.6 \pm 0.2$ °C [47, 48], and this increase has occurred mainly in two periods, between 1910 and 1945 and between 1976 and 2000. On a smaller scale, the change has been different depending on the region. In Europe, the greatest changes have occurred at the end of the last century [49]. The increase in temperature has been accompanied by variations in the intensity and frequency of precipitation. It has also been projected that this warming will go together with by extreme events such as heat or cold waves, as well as torrential rains.

This change may affect the metabolic composition of grape berry in terms of their anthocyanin proportion and the sugar content altering then, the alcohol percentage of the obtained wines and modifying their quality. In field, numerous complex factors regulate grape berry development. Because of this, berries with very different outcomes are obtained depending primarily on the cultivar characteristics but also on the timing of the stress, which can be from fruit abortion to earlier maturation [50, 51].

When the environmental stresses occur in multiple years, the frequency represents a risk to the crop yield and quality. During the growing season, temperatures greater than 35 °C can severely damage leaf photosynthetic efficiency and berry metabolism [52]. Water deficit affects berry quality during ripening [53] as well as canopy development, thus exposing the clusters to other environmental hazards (e.g., heat, wind, and solar radiation).

## Anthocyanins and Wine

During wine elaboration, especially in fermentative maceration by diffusion process, phenolic compounds are transferred from the berry skin to the solution. The phenolic concentration in the berry skin and the technological process applied at the winery affect the rate and extent of their extraction and the final content in wine [54].

Other *Vitis* species (not *vinifera*) accumulate colored compounds also in the mesocarp (corresponding to the pulp of the berry); these grapes

are called "teinturier" and present high anthocyanin content. The use of this kind of berries along the maceration process of winemaking would yield highly colored wines, rich in anthocyanins. But these species are not allowed to be use in winemaking, because the OIV (International Organization of Vine and Wine) acknowledges that "wine" is the product made only with *Vitis vinifera*. However two varieties of *Vitis vinifera*, Aspirant Bouschet and Alicante Bouschet, are teinturier grapes and are extensively used to increase wine color.

The content of polyphenolic compounds and especially that of anthocyanins at consumption moment of the different types of wine depends on how the wine has been cellared after elaboration (bottled or aged in barrels). Therefore, the color varies along with the anthocyanin content and how they form complexes with other compounds. The young wine has red and violet intense color. The aged wine, in contrast, has red-orange color [55, 56].

The anthocyanin content in grapes and wine is important from a commercial point of view for wine industry but also for pharmaceutical industry, as a functional food with high antioxidant content, and for food colorants industry, as healthier and safer alternative to synthetic dyes (e.g., FD&C Red 40). Although the wine concentration is influenced by winemaking and maturation processes, it depends largely on the quantity and type of anthocyanins present in grapes [57].

## Anthocyanins as Nutraceutical Compounds

Regular consumption of fruit and vegetables is associated with reduced risks of cancer, cardiovascular disease, stroke, Alzheimer's disease, and some of the functional declines associated with aging. Functional foods have acquired importance in the prevention of these kinds of pathologies, and the consumption of products which contain significant amounts of bioactive components such as grape and wine in moderate quantities is encouraged by medical personnel. Based on their ability to trap singlet oxygen, anthocyanins can interact with the host to confer a preventive benefit by regulating enzymes important in metabolizing xenobiotics and carcinogens, by modulating nuclear receptors and cellular signaling of proliferation and apoptosis, and by acting indirectly through antioxidant actions that reduce proliferation and protect DNA from damage [58].

Specifically, red wine consumption has been inversely correlated to coronary heart disease in many epidemiological studies, such as the research on French paradox made by Renaud and de Lorgeril [59]. This effect has been attributed to the antioxidant activity of flavonoids found in red wine [60], which are mostly anthocyanins. Anthocyanins also have some positive therapeutic effects as anti-inflammatory agents and the prevention of cholesterol-induced atherosclerosis, including microcirculation diseases [9, 10]. Moreover, recent studies have pointed the potential benefits of phenolic compounds and polyphenol-rich foods or beverage consumption in attenuating adipose inflammation and insulin resistance in experimental models of metabolic syndrome and in inflamed adipocytes [61–65]. However, grape berries treated with salicylic acid increased the anthocyanin levels in Syrah red wine but had lesser beneficial effects on metabolic syndrome alterations than control red wine [66]. This suggests that the excess of anthocyanin consumption does not directly leads to an improvement in health benefits.

## Anthocyanins and Bioavailability

For oenology industry and for functional foods, the relative proportion of each anthocyanin is important. In aqueous solutions as in the wine, anthocyanins exist in four different molecular forms that are in dynamic equilibrium. The most abundant molecular form at pH 1–3 is the red flavylium cations. When pH increases, the proton is lost and the blue quinonoid structure is generated. Around pH 4–5, colorless hemiketal forms are predominant that further tautomerize through an opening of the C-ring to generate the yellow chalcone forms in alkaline solutions. In the solution coexist different proportions of molecular structures of anthocyanins and they depend on pH, temperature, and time [67].

During the digestion anthocyanins from wine or plant extracts, their characteristic C6-C3-C6 backbone is converted into a wide range of structures and/or new metabolites. The type and quantity of these chemical forms depends on the dietary compounds consumed and transported along with the anthocyanins through the digestive lumen with them (e.g., proteins and lipid-rich matrices) [68]. As a consequence of their properties, absorption kinetics, general bioavailability, metabolism, and, consequently, the biological response of a human to the ingestion of anthocyanins, including the ability of anthocyanins to modulate human health, are affected.

The evidence linking consumption of anthocyanins from the diet to beneficial human health outcomes has been presented over multiple experimental platforms and disease targets [69–72]. However, anthocyanins (along with some other prominent flavonoids contributed in a fruit and vegetable-rich diet) have long presented a paradox to health research scientists. It is generally assumed that to confer health benefits, dietary phytochemicals (phytoactive compounds in plants) must be bioavailable; that is, once administered as components in foods, the digested phytoactives must be able to reach target tissues or organs in the human body to elicit an effect. And yet, as measured by most of our routine, standard laboratory and clinical instruments, after ingestion of foods or supplements rich in these pigments, anthocyanins and their predicted metabolites appear to be only sparingly present in human plasma [73, 74].

"When superior animals consume these functional foods or wine, the anthocyanins are absorbed in the digestive tract. The absorption is different for each anthocyanin and thus varies with the anthocyanin profile and the food/beverage matrix ingested ingested [74]. It has been shown that the possible transporter of anthocyanins is associated to a bilitranslocase in the gastric epithelium points [75–77].

Investigations reported that the aglycone form of anthocyanins is absorbed by bilitranslocase. However, its function as a differential anthocyanins transporter, according to the kind of anthocyanin, was also demonstrated. In this matter, peonidin and malvidin show the highest values in affinity and absorption efficiency for the transporter, followed by cyanidin and petunidin, and lastly delphinidin which presents the lower values [74].

This differential affinity may be led by the steric interactions between the molecules and the transporter. The absorption of acylated anthocyanins is not clearly elucidated yet, but slower assimilation than simple anthocyanins has been observed for them [75]. These anthocyanins should release their acyl groups before they can be taken by the bilitranslocase. Within red wine, anthocyanins are more stable when in vitro digestion is assessed, compared to other phenolic compounds present in this beverage [78]. Part of these anthocyanins is decomposed, and products from phenolic acid degradation are recovered. However, they exert their well-demonstrated bioactive benefits as intact flavonoids assessing their numerous health outcomes, which have been well validated and are noteworthy [78–80].

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# 13 A Very Promising Molecule: Resveratrol, Induced Synthesis, and Health Benefits

Liliana Martínez, Martín Durán, Emiliano Malovini, María Inés De Rosas, Leonor Deis, and Juan Bruno Cavagnaro

Grape (*Vitis vinifera* L.) is one of the fruits most widely cultivated around the world. Global grape production currently amounts to more than 75 million metric tons per year. Today there are well over 7.28 million hectares of cultivated vineyards worldwide. Italy is the greatest grape-producing country in the world, with an annual grape production of 8,307,514 metric tons. France and the United States are not far behind, with annual productions of 6,740,004 and 6,206,228 metric tons, respectively. Spain and China each produce well over 5 million metric tons each year. Turkey produces 3,763,544 metric tons annually. Argentina, Iran, and Chile have an annual output of more than 2 million metric tons, and South Africa produces a solid 1,587,913 metric tons each year [1].

Much of the world's grape cultivation is intended for the production of wine, and nearly all of the countries on this list are among the world's top wine producers.

Argentina is an emerging player on the international wine market. It is also the seventh largest grape-producing country in the world [1].

In recent years, consumer's awareness and interest in healthy eating has been on the rise [2]. Currently, more than 500 compounds have been identified in *Vitis vinifera* grapes and wine to date [3, 4]. Wine typically contains alcohols and phenolic compounds, which are cyclic benzene compounds possessing one or more hydroxyl groups associated directly with an aromatic ring structure.

Wine-derived phenolic compounds include the non-flavonoid classes of compounds such as hydroxycinnamates, hydroxybenzoates, and stilbenes, as well as the more abundant flavonoid classes of compounds including flavan-3-ols, flavonols, and anthocyanins, and also contain polymeric condensed tannins and pigmented tannins that represent the majority of the red wine phenolic compounds; however, their large size precluding its absorption is unlikely that this compound contributes to any biological mechanisms [5].

Grapevine stilbenes include many compounds such as *trans*- and *cis*-resveratrol, their glycosides (piceid or polydatin), viniferins,

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pterostilbene, astringin, piceatannol (astringinin), and other resveratrol trimers and tetramers. These substances are present in soft tissues, as induced compounds, and in woody tissues, as constitutive ones [6, 7]. Of these, resveratrol appears to have been the most widely examined phenolic compound over the past decade [8].

## Resveratrol

Resveratrol (trans-3,4′,5-trihydroxystilbene), a polyphenolic phytoalexin, is an abundant stilbene very common in our diet and in dietary supplements [8]. It can be found in a large number of plant products, including the skins and seeds of grapes, wines, peanuts, soybeans, pomegranates, mulberries and dried roots of the medicinal plant *Polygonum cuspidatum* [9]. It can also be introduced into the diet through Itadori tea, which has long been used in Japan and China as a traditional herbal remedy for heart disease and strokes.

In plants, this compound acts as a phytoalexin, a class of defense molecules that protects against infection of bacteria and fungi and damage from exposure to ultraviolet irradiation (UV) [10, 11] and extends the life span in different organisms, including yeast and vertebrates [12, 13].

## Chemical Structure

According to its chemical structure, resveratrol exists as two geometric isomers: *cis* (*Z*) and *trans* (*E*) (Fig. 13.1). The *trans* form can undergo isomerization and the *cis* form when exposed to ultraviolet irradiation [14], a process called photoisomerization [15].

*Trans*- and *cis*-resveratrol can be either free or glycosylated [16], hydroxylated, methylated, or converted into more complex compounds. Other well-known stilbenes are pterostilbene and 3′-hydroxypterostilbene.

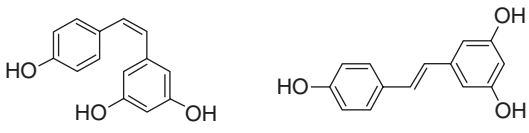


**Fig. 13.1** Chemical structure of *cis*- and *trans*-resveratrol

## Resveratrol Biosynthesis

Resveratrol biosynthesis in plants occurs via the phenylalanine pathway, where phenylalanine ammonia lyase (*PAL*), cinnamate-4-hydroxylase (*C4H*), coumaroyl-CoA ligase (*4CL*), and stilbene synthase (*STS*) play a core role in the synthesis (Fig. 13.2) [17]. The end product is synthesized in the *trans* form, which may isomerize into *cis* form, as described before, or even be transformed to *trans*- and *cis*-piceid by enzymes resveratrol 3-O-beta-glycosyltransferases (O-3-*GT*) [18]. P-Coumaroyl-CoA is a product of *PAL*, which is abundant in plants and used as a precursor for the synthesis of both *trans*-resveratrol and chalcone. Therefore, in stilbene-synthesizing plants, *STS* competes with chalcone synthase (*CHS*) for the usage of this precursor compound during *trans*-resveratrol synthesis [19]. Furthermore, stilbene synthesis pathway is the side chain of phenylpropanoid, which also can be treated as an extension of the flavonoid pathway [20]. Transcriptional factors, *Myb*14 and *Myb*15, have been found to regulate the expression of *STS* multigenic family in *Vitis vinifera* L. [21, 22].

The accumulation of resveratrol in grapes varies according to the cultivar, genotype, locations, environmental conditions, and growing season [17]. Varying amounts of resveratrol have been reported in berry skin, seed, stem, shoot, bud, root, and leaf [23, 24], ranging from 0.16 to 3.54 μg/g [8]. However, relatively higher amount of resveratrol can found in grape skin, about 24 μg/g. Resveratrol is also present in cranberry raw juice, which contains about 0.2 mg/L. In other natural foods, the concentration of resveratrol varies in the range of μg/g (peanuts and pistachios) to ng/g (bilberries, blueberries) [25]. The *trans*-isoform is most common in plants [26].

Resveratrol biosynthesis and accumulation in grape tissues is often low under natural growing conditions and is related to veraison stage [27]. Before veraison, resveratrol content is very low;

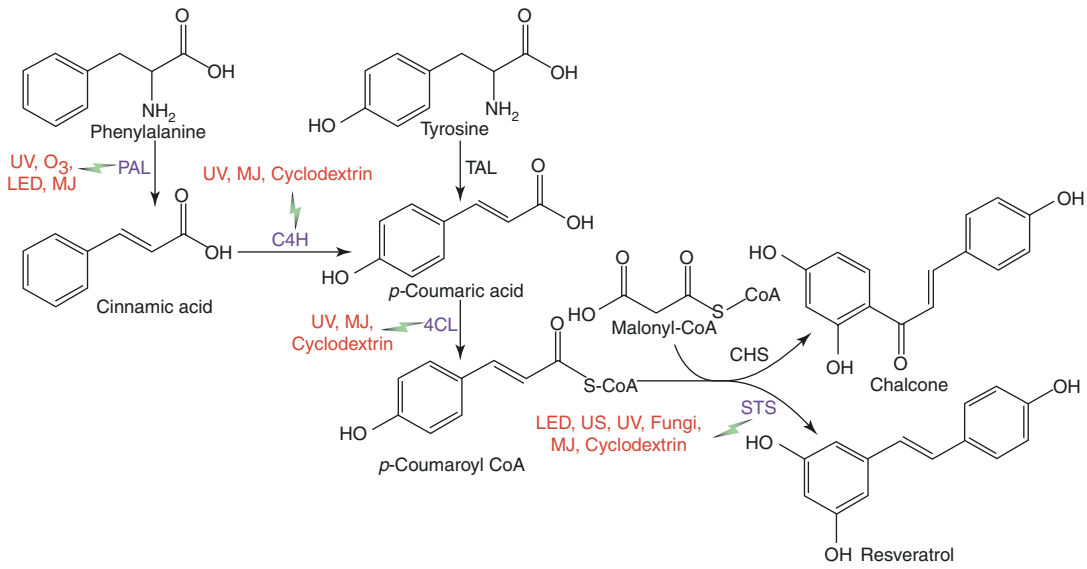


**Fig. 13.2** *Trans*-resveratrol biosynthesis pathway, enzymes involved, and factors eliciting or inducing resveratrol synthesis

however, total resveratrol increases about 500 % from veraison to maturity in the main forms of piceids. *Cis*-resveratrol was not detected throughout the developmental period. In regard to total resveratrol, *trans*-resveratrol, *trans*-piceid, and *cis*-piceid content in "Beihong" (*V. vinifera x V. amurensis)* remained almost unchanged until a week after veraison. Moreover, there were no significant differences among *trans*-resveratrol, *trans*-piceid, and *cis*-piceid contents. However, total resveratrol content rapidly increased from 2 weeks after veraison to maturity [27]. The accumulation of piceids varied during maturity. *Trans*-resveratrol content was nearly unchanged, while *trans*-piceid content gradually increased until 2 weeks after veraison, and subsequently remained relatively stable. In contrast, *cis*-piceid content dramatically increased to maturity.

The expression levels of *PAL*, *C4H*, and *4CL* appeared to reach maximum levels after veraison, respectively. However, high expression levels of *STS* and *Myb*14 were obtained before veraison. During most of the developmental period, the expression level of *O-3-GT* was relatively stable until 98 days after anthesis (DAA), when it began to increase [27].

## Elicitation of Resveratrol

Several methods have been studied to improve resveratrol content in grapevine. Resveratrol can be induced by biotic factors, i.e., fungi, and abiotic factors, i.e., UV-C irradiation, jasmonic acid, salicylic acid, $H_2O_2$, $O_3$, and $CaCl_2$ [27].

Although stilbenes are constitutively present in all parts of the grape plant, elicitation of resveratrol can be provoked by pathogen infection including *Botrytis cinerea*, *Plasmopara viticola*, *Rhizopus stolonifer*, *Uncinula necátor* [17], and *Lasiodiplodia theobromae* [28]. Resveratrol content increased threefold around the infected leaf area of *B. cinerea* and disappeared as the disease advances further [17]. *In vitro* assays conducted in our group, Cesari 2015, inoculating grapevine microplants with *Lasiodiplodia theobromae*, a fungus that provoke a kind of trunk disease called "pelargonium sheet" ("hoja de Malvón"), produced an early and enhanced production of *trans*-resveratrol, *trans*-resveratrol glycosylated, and *cis*-resveratrol glycosylated in *Vitis rupestris* compared to Malbec cultivar, which resulted in a more susceptible one. *Plasmopara viticola*-infected grapes accumulated five times more res-

veratrol than healthy grapes, and the accumulation increased with the degree of infection [29].

All these results can be explained with the synthesis of pathogenesis-related protein-phytoalexins as a part of plant defense mechanism [30].

Light can affect the production of primary and secondary metabolites. Resveratrol synthesis by phenylpropanoid pathway and the induced expression of *PAL*, *CHS*, *CHI, STS1*, and *STS2* were observed by irradiation with blue, red, and white light sources [17].

Ultrasonication treatment of grape skins of Campbell Early, MBA, and Kyoto varieties increased resveratrol in grape juices by 1.53, 1.15, and 1.24 times, respectively. This action might occur due to mechanical stress, by increasing the expression of *STS* and *PAL* [17].

Important induction of resveratrol accumulation has been reported in grapes by direct spray of jasmonic acid (JA) or methyl jasmonate (MJ), a JA derivative. MJ was found to cause a threefold elicitation of *trans*-resveratrol in cell suspension culture, following 18-h incubation, whereas MJ and sucrose together elicited the accumulation of *trans*-resveratrol by sixfold after 6 h of incubation. In addition, MJ/sucrose treatment was found to produce a two-fold extracellular yield of resveratrol than MJ alone [17]. Induction of resveratrol with JA was found to be consistent with the upregulated expression of *PAL* and *STS*, showing the transcriptional control of the synthesis of resveratrol [17]. Duran et al. (2015) demonstrated that MJ sprayed at bunches level induced the synthesis and accumulation of *trans*-resveratrol in Malbec and Pixie berries' skins and increased the relative expression of *STS* genes, while significantly reducing total anthocyanin content [22]. This reduction was most likely due to the activation of stilbenoid biosynthesis pathway and the end use of precursor compounds common to both anthocyanin and stilbene synthesis.

Other reports suggested that salicylic acid (SA) was found to induce the resveratrol accumulation in cell suspension culture, but negative effect of the combined use of SA and JA was observed on the accumulation of resveratrol, verifying the inhibitory effect of SA on the synthesis and signal transduction of JA [17].

An industrial-scale increased production of resveratrol was obtained by the combined treatment of resin, JA, and glucane in cell suspension culture [31].

UV-C lights, ranging from 200 to 280 nm wavelength, are very popular in the field of enhancing the production of the resveratrol in grape berries [17]. An optimization of UV irradiation treatment was developed and patented according to the following conditions: light source distance at 40 cm, irradiation time of 30 s, source power of 500 W, and storage time of 3 days. This resulted in 3.4 times higher resveratrol in Flame cultivar and 2.315 times in Red Globe cultivar compared to the untreated controls [17]. In "Beihong" (*V. vinifera x V. amurensis*), UV-C irradiation significantly stimulated the synthesis of resveratrol, mainly in the form of *trans*-resveratrol. Response of berries to UV-C irradiation was also related to berry development stage. Among the six typical developmental stages, 2 weeks before veraison was the most sensitive to UV-C irradiation. Along with developmental factors, the sensitivity of resveratrol synthesis to UV-C irradiation gradually declined, which may be associated with a regulation of *STS* by *Myb*14 [26]. UV-C irradiation combined with $CaCl_2$ showed significant upregulation of *PAL*, *4CL*, *CH4*, and *STS*, parallel with resveratrol accumulation, suggesting that $Ca^{+2}$ may participate in the signal transduction pathway triggered by UV-C stimulus [32].

Bavaresco et al. (2016) reported that independently from the biotic and/or abiotic elicitation conditions, tissue levels of resveratrol (and its glucoside derivatives piceids) are affected by grape variety, clone, meteorological conditions, soil type, and cultural practices [33]. Resveratrol is present in ripe grapes of both red and white varieties, being higher in red berries than white ones. Clone can also play a role, as reported in a pot trial with different clones of *Cabernet Sauvignon* cultivar. Cooler, as opposed to warmer conditions during ripening, over several years, increased grape resveratrol concentrations; this is also true for higher vineyard elevation. Calcareous and alkaline, as opposed to noncalcareous and

neutral, soil is favorable for increasing resveratrol concentration in berries at harvest. Increasing nitrogen supply has a negative effect on resveratrol levels in berries [33], which explains why vines fertilized at high nitrogen rates are more susceptible to diseases. The effect of removing leaves at veraison in the cluster zone of three varieties was studied in a field trial over 4 years [33]. Resveratrol concentration in grapes at harvest was affected in different ways depending on the genotype and the meteorological conditions. In cooler years (during ripening time), leaf removal improved resveratrol values over untreated vines, while in warmer years an opposite pattern occurred. Cluster thinning improved resveratrol concentration as well as its antioxidant capacity in *Barbera* wine from the Colli Piacentini production area [33]. Both high crop load versus low crop load and irrigation versus non-irrigation reduced resveratrol concentrations in wines from Sicily [33]. It is difficult to compare data (from literature) on resveratrol concentration in grapes affected by diverse biotic/abiotic elicitors and viticultural factors because of the different extraction methods and units of measurements used [33].

## Resveratrol in Wine

According to Bavaresco et al. (2016), resveratrol is contained in considerably higher amounts in red wines than in white wines because it is mainly present in berry skin and white wines are usually produced with no or limited maceration with the pomace [33]. Concentration of resveratrol ranges from 0.1 to 14.3 mg/L in various types of red wine, while white wines contain only about 0.1–2.1 mg/L of resveratrol. Both *trans*- and *cis*-piceids are present in grapes, and their hydrolysis, occurring during fermentation, releases *cis* and *trans*-resveratrol. In addition, *trans-cis* isomerization can influence the balance between two resveratrol isomers in wine, and their levels can be affected by light. For example, *trans*-resveratrol is stable for months if protected from the light; however, *cis*-resveratrol is stable only near pH neutrality when completely protected from light. Moreover, yeast choice can influence the final content of resveratrol in wine due to the different actions of β-glucosidase enzymes, which transform piceids into resveratrol. To some extent, winemaking practices can also potentially affect resveratrol in wine. Different processing techniques including maceration have great impacts on the improved extraction, ultimately leading to an increased resveratrol concentration in grape juice, and wine maceration was found to increase resveratrol extraction in wines by ten-fold compared with slightly pressing for a very short time on grape skins [34]. Prefermentation cold-soaking significantly increased *trans* and *cis*-resveratrol in free-run press in Cabernet Sauvignon grape must during alcoholic fermentation [35]. In addition, maceration time, yeast type, used enzyme, and $SO_2$ concentration were also found to be important factors influencing the final resveratrol concentration in wine [36, 37].

In general, the low levels of fining agents usually added to stabilize red wines do not significantly reduce the level of *trans*-resveratrol [38], and it is a relatively stable compound that can remain for years in properly stored wines (i.e., avoiding exposure to excess heat and presence of normal levels of exogenous antioxidants such as sulfur dioxide) [39]. On the other hand, unusual winemaking processes and aging can induce relevant losses of resveratrol. For instance, sherry wines showed great losses of resveratrol due to oxidative phenomena and a combination with acetaldehyde and "flor" biofilm growth [40].

Food products contain both *cis*- and *trans*-isoforms of resveratrol, mostly in the glycosylated forms. The *trans*-isoform is more common in plants. Glycosylation prevents enzymatic oxidation, thereby increasing stability and bioavailability of resveratrol [8].

Resveratrol initially gained much attention as an explanation for the famous "French paradox" which suggests that French individuals have a relatively low incidence of coronary heart disease, in spite of their diets rich in saturated fats, due to the consumption of wine, which contains antioxidant compounds such as anthocyanin, tannins, and resveratrol [41].

Extensive biochemical, pharmacological, and physiological evidence supports the existence of a causal relationship between regular moderate wine consumption and cardioprotection.

## Biological Activities and Effects of Resveratrol

In the past few years, the interest in resveratrol extensively increased due to its nutritional and medicinal value, and a lot of scientific evidence has demonstrated that resveratrol exerts a plethora of biological function, especially cardiovascular protective [42], antiplatelet [43], antioxidant [44], anti-inflammatory [45], blood glucose-lowering [46], anticancer [47], antiaging [48], and anti-obesity activities [49].

By increasing the production of nitric oxide, resveratrol inhibits platelet aggregation and stimulates vasodilation [50]; also protects against some neurodegenerative diseases, such as Alzheimer's disease [51]; and is effective in the management of osteoporosis in postmenopausal woman without an increased risk of breast cancer [52].

Because of its multiple biological effects, resveratrol is currently used as a nutritional supplement.

Its biological effects are mainly caused by the abundance and diversity of molecular targets that this compound has, like cyclooxygenases/lipooxygenases, a wide range of various kinases, sirtuins [25], transcription factors, cytokines, DNA polymerase, adenylyl cyclase, ribonucleotide reductase, aromatase, and others [53]. It is hypothesized that resveratrol provides a complex physiological activity because of its capability to modulate different pathways in a micromolar range [53].

Chronic inflammation has been recognized as the root cause of various human diseases [48]. The inflammatory processes may induce DNA mutations in cells via oxidative or nitrosative stress, which lead to inflammatory diseases and cancer [54]. It was demonstrated that resveratrol significantly suppressed inflammation markers such as inducible nitric oxide synthase and tumor necrosis factor-alpha. Resveratrol could act as biological enhancer to strengthen the anti-inflammatory activity of apigenin [55].

A relevant number of researchers have considered the anticarcinogenic effects of resveratrol in breast cancer, via inhibition of cell proliferation and promoting death via multiple pathways including apoptosis, cell cycle arrest in the S-phase, and autophagy. Related to prostate cancer, resveratrol treatment has caused significant reduction of prostate tumor growth and the incidence and number of lung metastasis in SCID mice, and it has shown great potential as a useful agent for the treatment of colon cancer [48].

Resveratrol has been reported to have beneficial effects in diabetes and diabetic vascular complication [48]. Chronic resveratrol administration in rodent models improved hyperglycemia, glucose tolerance, and dyslipidemia and protects against pancreatic beta-cell failure as well as diabetic cardiomyopathy [48]. It has been demonstrated that oral supplementation with resveratrol (250 mg/day) for 3 months significantly reduced the hemoglobin $A_{1c}$ and systolic blood pressure in type II diabetic patients [56].

Similarly, Kim et al. [57] reported that resveratrol supplementation effectively reduced the body weight gain. It also significantly reduced abdominal subcutaneous adipocyte size in a human study conducted by Konnings et al. [58].

Calorie restriction in certain conditions may delay the onset of age-related disease. Resveratrol possesses the potential of life span extension in various organism and animal models [48]. Most reports suggested that the mechanism regarding longevity promotion by resveratrol is related to calorie restriction. This compounds enhanced DNA stability and prolonged 70 % life span of budding yeast *Saccharomyces cerevisiae* by activating Sir2, a member of sirtuin family induced by energy restriction, mimicking the effects of calorie restriction [59]. They also showed a marked reduction of diverse signs of aging, including improved insulin sensitivity, cardiovascular function, bone density, and motor coordination, as well as reduced inflammation, apoptosis in the vascular endothelium, and cataract forma-

tion. Daily oral administration at 20 mg/kg of body weight of resveratrol to aged rats for 60 days significantly induced modification of dendritic morphology in prefrontal cortex, dorsal hippocampus, and dentate gyrus, and these changes could explain the therapeutic effect of resveratrol in aging and Alzheimer's disease. It also lengthens the life span of annual fish, reducing the level of ROS, enhancing the activities of antioxidant enzymes, and decreasing the degree of oxidative damage, which were induced by aging [60].

## Pterostilbene

Pterostilbene (trans-3,5-dimethoxy-4′-hydroxylstilbene) is a natural dimethylated analogue of resveratrol and is a stilbenoid phytochemical compound primarily found in blue berries, grapes, and *Pterocarpus marsupium* tree wood [48]. Pterostilbene content varies from different types of berries. *Vaccinium ashei* contains 99 ng/g dry sample, while *Vaccinium stamineum* contains 560 ng/g dry sample [61]. Substantial studies demonstrate that pterostilbene has diverse pharmacological activities for the prevention and treatment of diseases including inflammation, cancer, diabetes, and dyslipidemia [48]. Recent reports indicate that pterostilbene possesses high potential in bioactivities and much better bioavailability than its analogue resveratrol, based on its chemical structure.

## 3′-Hydroxypterostilbene

3′-Hydroxypterostilbene (trans-3,5-dimethoxy-4-dihydroxystilbene), one of the metabolites of pterostilbene [62], can also be isolated from whole plant of the herb *Sphaerophysa salsula*, a shrub widely distributed in Central Asia and Northwest China [63]. A recent study indicated that this compound possesses anti-adipogenic, inflammatory, oxidant, and Sirt-1 inhibitory activities [64]. However, there are few studies involving biological activities of 3′-hydroxypterostilbene.

## Absorption, Bioavailability of Resveratrol and Pterostilbene, and Its Metabolism

Low solubility of resveratrol in water, caused by its chemical structure, affects its absorption [65]. In animals and humans, resveratrol is quickly metabolized in the liver. In plasma it binds to lipoprotein and albumin, and this facilitates its entry to cells [66].

Orally or intravenously administered resveratrol has high absorption (at least 70 %) but rapid and extensive metabolism leading to formation of conjugated sulfates and glucuronides [8]. It was reported by Walle et al. (2004) [67] that sulfation of resveratrol might limit the bioavailability of this compound. In humans and rats, *trans*-resveratrol rapidly undergoes conjugation resulting in 1 % of the oral dose being observed as free *trans*-resveratrol in blood plasma [68]. *Trans*-resveratrol efficiency depends on a sufficient level of active molecule in bloodstream and target tissue.

The maximum peak in plasma concentration of native resveratrol was reached after 30–90 min after oral intake. Appearance of the second peak 6 h after resveratrol intake indicated that the enteric recirculation of conjugated metabolites by reabsorption takes place. In addition, it was found by Ortuño et al. (2010) that bioavailability of resveratrol from wines and grape juice is much higher (six-fold) compared to that from tablets [69].

Different strategies have been assessed to improve *trans*-resveratrol bioavailability: (a) co-administration of *trans*-resveratrol metabolism inhibitor, (b) use of naturally chemically synthesized *trans*-resveratrol analogues, and (c) new *trans*-resveratrol delivery systems.

Bioavailability of *trans*-resveratrol has been improved using lipid solution, microsomes, or other vectorized forms. Nguyen and his group (2017) have shown that a single dose (40 mg) of a soluble form of *trans*-resveratrol in a suitable lipid vehicle elicits micromolar concentration in the blood of human volunteers. In contrast, the dry powder form was unable to elicit efficient blood level at any time. At the

dose 40 mg, *trans*-resveratrol was well tolerated, and no toxicity was reported [68, 69].

Data from animal studies suggest that grape- and wine-derived phenolic compounds are absorbed and accumulated in the brain in measureable amounts after multiple or repeated oral doses [70, 71]. Wine-derived phenolic compounds, and particularly resveratrol, have been shown to be cerebro- or neuroprotective in various models, *in vitro* and *in vivo*, and potential mechanisms have been proposed. Data from similar studies using different varieties of red wines with different profiles of phenolic compounds, as well as studies comparing different phenolic compounds, suggest that the individual classes of phenolic compounds may exhibit differential effects in the brain [72, 73]. From Scholey et al. (2014), the consumption of 100 mL of red wine with a relatively low concentration of resveratrol resulted in better performance by elderly subjects during Series Threes of Cognitive Demand Battery tests, compared with consumption of that same wine enriched with 100 mg resveratrol, while the resveratrol-enriched red wine resulted in better performance during Serial Sevens [74]. Serum analysis confirmed absorption of resveratrol and its metabolites.

Different biological mechanisms of action have been proposed for the observed benefits of light to moderate wine consumption on cognitive function in later life [75].

By increasing the production of nitric oxide, resveratrol inhibits platelet aggregation and stimulates vasodilation [50]. Recently, published data have shown that resveratrol protects against some neurodegenerative diseases, such as Alzheimer's disease [51] and obesity [49], as well as is effective in the management of osteoporosis in postmenopausal woman without an increased risk of breast cancer [52].

The hypothesized properties of *trans*-resveratrol include detoxification through antagonization of the aryl hydrocarbon and dioxin receptor, kinase inhibition, and anti-inflammatory, analgesic, and antitumoral activities [68].

In addition, the glycoside form of resveratrol, piceid, has also shown beneficial effects of health. The biological activities of other isomers (*cis*-resveratrol and both piceids) may also have beneficial effects [76].

Given the role that inflammation may play in depressive disorders, anti-inflammatory agents may prove useful as an antidepressant therapy or adjuvant to traditional therapies. Resveratrol has demonstrated anti-inflammatory properties [77, 78] through inhibition of mast cell, macrophage, neutrophil, and microglial production of histamines, cytokines, proteases, nuclear factor-kappa B, and oxidants [79]. These cellular effects are thought to be responsible for resveratrol anxiolytic properties [80] as well as its demonstrated antidepressant efficacy in the forced swim test, single prolonged stress, and Wistar-Kyoto depressive-like rat model [81]. Also, it was demonstrated by Ge et al. (2017) that resveratrol ameliorates the anxiety and depression-like behavior of subclinical hypothyroidism in rats [82].

## Conclusion and Future Prospects

Many people around the world now live longer. According to the WHO, the number of people worldwide aged ≥ 60 years has doubled since 1980 and is forecasted to reach two billion by 2050. The goal is to not only live longer but also to remain healthy as long as possible. However, metabolic disorders, cancers, and cardiovascular and neurodegenerative diseases develop more frequently in older people and decrease quality of life.

Calorie restriction seems to extend the life expectancy of several species (from yeasts to humans) and generally decreases age-related pathologies. Nevertheless, calorie restriction is difficult to achieve in humans. Pharmacological solutions that mimic the physiological phenomena that occur during calorie restriction are being investigated and, in particular, those factors that act on the sirtuin pathway [68]. Among the candidate molecules researched is resveratrol which increases the life expectancy of numerous species and is considered to mimic calorie restriction [48], though this point is still

controversial. Furthermore, *trans*-resveratrol has shown some anticancer properties; it has antioxidant and anti-inflammatory properties and can help protect against ischemia-reperfusion, neurodegenerative processes, metabolic diseases such as glucolipid metabolism imbalance, and cardiovascular pathologies in both in vitro and animal models [8].

Because of the important properties of *trans*-resveratrol, there is an increasing interest in producing grapes or wines with higher contents of this compound and a higher nutritional value. Many biotic and abiotic elicitors can trigger the resveratrol synthesis in the berries. Under the same elicitation pressure, viticultural and enological factors can substantially affect resveratrol concentration in the wine. The production of high resveratrol-containing grapes and wines relies on quality-oriented viticulture (suitable terroirs and sustainable cultural practices) and winemaking technologies that avoid degradation of the compound [33].

In elder in particular, but also in younger adults, light to moderate wine consumption is associated with neuroprotective effects, although binge and heavy alcohol consumption is neurotoxic [75].

However, one major concern is the poor solubility and absorption of resveratrol when is given orally, which may lower its biological effectiveness. Poor bioavailability of resveratrol is attributed to its extensive hepatic glucuronidation and sulfation [68]. Recent studies showed that the methoxylation on the free hydroxyl groups of resveratrol could reduce its metabolization and increase its plasma exposure [68].

Pterostilbene exhibits much better bioavailability and is more biologically active than *trans*-resveratrol, due to the presence of two extra methoxy groups that cause to have relatively higher lipophilicity, which may enhance the cell membrane permeability and increase its oral absorption [48].

Stilbenoid compounds such as resveratrol, pterostilbene, and 3′-hydroxypterostilbene have promising application for the management and treatment of chronic disorders, such as heart disease, stroke, cancer, diabetes, and obesity. However, human studies of stilbenoid compounds are still lacking. Future clinical research for these compounds in chronic diseases is necessary to investigate their physiological and pharmacological effects and safety [43].

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# 14

# Implication of Oxidative Stress, Aging, and Inflammatory Processes in Neurodegenerative Diseases: Growth Factors as Therapeutic Approach

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## Oxidative Stress and Neurodegeneration

Oxidative stress (OS) is defined as the imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system. Living organisms produce ROS from molecular oxygen as a consequence of normal cellular metabolism. In order to prevent damage, cells have an antioxidant defense system constituted by an enzymatic component (including catalases, superoxide dismutases, etc.) and nonenzymatic antioxidants component (glutathione, α-tocopherol, ascorbic acid, etc.). When the levels of ROS exceed cell capacity, it can cause damage in cellular components such as carbohydrates, nucleic acids, lipids, and proteins, thus altering their function. Whenever this imbalance occurs within the central nervous system, it can lead to the development of the neurodegenerative disorders.

Neurodegenerative diseases are characterized by the loss of neuronal cells and, in most cases, by the aggregates of proteins that form intracytoplasmic and intranuclear inclusions in neurons and glial cells. Data on the literature show that there are two possible mechanisms involved in most of neurodegenerative diseases: (1) mutations and/or aggregation of characteristic proteins of each disease such as α-synuclein in Parkinson's disease (PD) or beta-amyloid peptide in Alzheimer's disease (AD) and (2) dysfunction of mitochondrial energy metabolism in neurons. In this section, we will focus on this last one.

In the CNS, mitochondria are in charge of the production of needed energy to drive most cellular reactions through oxidation of glucose under aerobic conditions, ending up in the electron transport chain (ETC) [1]. A loss of mitochondrial function at this level is associated with neurodegenerative processes. Consequently, in view of the susceptibility of the ETC to oxidative damage, loss of ETC activity, due to an increment of ROS levels, has been proposed to be a plausible mechanism for the neuronal cell death associated with PD, AD, and other neurodegenerative disorders [2].

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Furthermore, the "beta-amyloid ($A_\beta$) cascade hypothesis" that dominated the field of AD research for the past decades has been challenged, and a new "mitochondrial cascade hypothesis" has been proposed. The mitochondrial cascade hypothesis states that in sporadic, late-onset AD, loss of mitochondrial function associated with age affects the expression and the processing of APP, initiating $A_\beta$ accumulation [3]. It is known that not only the partial reduction of $O_2$ increases superoxide radical ($O_2^-$) in normal conditions but also complex I participates [4, 5]. Complex I (CI or NADH:ubiquinone oxidoreductase) is the largest ETC enzyme, containing 44 subunits and the main contributor to ROS production. Regarding this, many authors have described that complex I is disturbed in AD and PD [6, 7], increasing even more ROS levels [8]. Moreover, Schapira et al. [9] have reported a decreased activity of complex I in the substantia nigra of nine postmortem patients with PD. Giachin et al. [5] reviewed that neuronal cells are particularly susceptible to ROS-induced damage because they rely mainly on oxidative metabolism for ATP generation, contrary to glial cells, which are highly glycolytic. This overproduction of ROS not only increases OS able to oxidize biomolecules [10–12] but also leads to the activation of poly(ADP-ribose) polymerase (PARP), responsible for the repair of the DNA using NADH, inhibiting the glycolytic pathway caused by a reduction in NAD+ content. This leads to the subsequent compromise of the respiration at complex I where NADH is a key cofactor [13, 14].

Mitochondrial complex IV (cytochrome c oxidase) is also associated with development of neurodegeneration, in particular AD. Some authors described decreased levels of cytochrome c oxidase in neuronal mitochondria of AD postmortem brain patients [10]**.** Moreover, it is also known that $A_\beta$ specifically inhibit cytochrome c oxidase. This decrease could also be able to rise ROS levels [8, 12], leading to neuronal death.

In conclusion, although neurodegeneration is associated with multiple etiologies and pathophysiologic mechanisms, oxidative stress appears as a major part of the pathophysiologic process. Here, neuronal loss is caused by mitochondrial dysfunction and oxidative stress, among other factors. Mitochondrial function declines with age, with a concomitant increase of OS.

## Neuroinflammation and Neurodegenerative Diseases

The central nervous system (CNS) presents a unique microenvironment given to the isolation due to the blood-brain barrier (BBB), which separates the brain from the periphery. BBB maintains chemical balance within the CNS to support neuronal function as well as limits the entrance of invading microorganisms [15]. Moreover, glial cells – microglia and astrocytes – constitute the neuroimmune system monitoring the CNS. These cells participate in various processes, such as phagocytosis, steroid and growth factor release, free radical reduction, and cellular repair, in both healthy and diseased brain [16–19]. Therefore, due to these peculiar characteristics, the CNS could be considered as an immunologically privileged organ.

In the last decades, the average lifespan has increased due to the improvement of medical care and hygienic conditions. This fact comes together with an increment in the incidence of age-related diseases. Alzheimer's disease is the most common neurodegenerative disorder, which is characterized by the presence of extracellular β-amyloid (Aβ) deposits and intracellular neurofibrillary tangles composed of phosphorylated protein Tau, resulting eventually in the characteristic memory loss [20]. The second most common neurodegenerative disease is PD, which is characterized by the aggregation of α-synuclein into Lewy bodies and Lewy neurites and the specific loss of dopaminergic neurons in the *substantia nigra pars compacta*, resulting in the exhibition of tremors, stooped posture, and dementia in some cases [21]. Regarding Huntington's disease (HD), it is an autosomal dominant disease caused by a mutation in the huntingtin gene. Its manifestations include chorea and cognitive and behavioral decline [22]**.**

Neurodegenerative diseases are accompanied by chronic inflammation, where the neuroimmune cells, mainly microglial cells, activate and adopt pro-inflammatory states (known as M1 phenotype).

This state is characterized by the production of pro-inflammatory cytokines, which amplify the inflammatory response by recruiting and activating more microglial cells as well as promoting their proliferation. Many of these cytokines such as tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL-1β) have been shown to lead to neuronal death both in vivo and in vitro [23, 24]. TNFα can induce cell death through (i) apoptosis via activation of caspase-8; (ii) necrosis via activation of receptor-interacting protein 1 (RIP1), receptor-interacting protein 3 (RIP3), and mixed lineage kinase domain-like protein (MLKL); and (iii) inflammation via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Moreover, M1 microglia characteristically expresses inducible NO synthase (iNOS), which produces high levels of NO continuously. These high levels of NO cause neuronal death by inhibition of mitochondrial cytochrome oxidase in neurons, leading to neuronal depolarization [25].

It is worth highlighting that, though inflammation contributes to the development and maintenance of degenerative diseases, it is not an initiation factor. In fact, an inflammatory response necessarily has to occur in order to guarantee the removal of harmful agents and repair of injuries. In this acute inflammation, microglial cells adopt an anti-inflammatory phenotype (termed M2), characterized by the release of anti-inflammatory cytokines such as tumor growth factor beta (TGF- $\beta$) and interleukin 10 (IL-10) and the expression of arginase-1, which inhibit the release of pro-inflammatory factors [26]. Consequently, we can conclude that it is the imbalance between the pro- and anti-inflammatory molecules secreted by microglial cells that defines whether the immune response will be beneficial or detrimental for the CNS.

## Aging and Neurological Dysfunctions

The twentieth century was the century of population growth, and the twenty-first century will go into the history books as the century of aging. Global aging has been accelerating since 1969 when there were 550 million older adults, with a population of 1250 million in the year 2025 [27]. Only in the United States, the number of adults over the age of 64 will grow to 70 million by the year 2030, and they become the fastest-growing segment of the population [28]. With advanced age comes a decline in sensorimotor control and functioning and cognitive and learning impairment. As a consequence, aging is the major risk factor for the development of human neurodegenerative process such as Alzheimer's, Huntington's, and Parkinson's diseases [29].

For instance, dysfunctions in fine motor control, locomotion, and balance affect the ability of older adults to perform activities of daily living and maintain their independence. The causes of these motor deficits are multifactorial, with central nervous declines and changes in sensory receptors, muscles, and peripheral nerves playing a role [30]. As a result, aging drives changes in brain structural regions: an age-related degeneration of the cerebellum [31], which may contribute to deficits in multi-joint coordination and postural stability in older adults [30] and a reduced volume of gray matter, often present with greater ventricular and cerebrospinal fluid volume [32, 33]. Furthermore, the prefrontal cortex is particularly susceptible to gray matter atrophy [34], and the differential thickness in prefrontal and parietal cortices may be relevant to motor age performance deficits in old age because motor control is more dependent on these brain regions in older adults. In 2004, the group of Salat found significant age effects in both the primary motor cortex, contributes to the movement slowing seen with age, and the somatosensory cortex, increased falls, poor balance, and increased reliance on visual feedback for motor performance in older adults, and they marked a potential vulnerability of these regions of the brain to age-related atrophy [35].

Aging also drives changes in neuronal and cognitive function. The hippocampus, a brain region subserving roles of spatial and episodic memory and learning, is sensitive to the detrimental effects of aging at morphological and molecular levels. With advancing age, synapses

in various hippocampal subfields exhibit impaired long-term potentiation [36], an electrophysiological correlate of learning and memory. At the molecular level, immediate early genes are among the synaptic plasticity genes that are both induced by long-term potentiation and downregulated in the aging brain [37]. Besides, age-related cognitive impairment is associated with a specific set of synaptic plasticity proteins with roles in structural and functional synaptic systems [38]. Deak and Sonntag observed that an evolving area of research in brain aging is focused on the balance between excitatory and inhibitory synaptic systems [39, 40], especially in a reduction of synaptic markers [41].

Despite brain structural effects, there are also prominent differences in brain neurochemistry of older adults. For example, dopaminergic system has been most widely studied and appears to have dramatic effects. There is a significant decline in dopamine transmission levels – reduction of neurotransmitters, receptors, and transporters – and due to this general decrease in dopamine levels, the aging brain is often considered to be located in the preclinical continuum of Parkinson's disease. Dopamine also plays a significant role in higher cognitive functions such as working memory [42], which is very important for motor skill acquisition [43]. So, these cognitive impairments associated with dopaminergic degeneration may indirectly contribute to age-related motor dysfunction.

In addition to a dopaminergic decline, a cholinergic reduction with age has been found in the medial forebrain and hippocampus [44]. Several studies have associated cholinergic decline in hippocampus with Alzheimer dementia, which involves severe deficits in learning and memory. Also, there is a serotonergic decline in the cingulate cortex and putamen [45] which has been related to cognitive deficits ([46] and motor dysfunctions [47]. There is a significant reduction associated with age of norepinephrine levels due to a loss of neurons in the locus coeruleus [48].

Aging and age-related disease are a mounting challenge for individuals, for families, and for social, economic, and healthcare systems. Implementation of preventive health strategies to decrease, delay, or prevent these affections may increase health expectancy and allow people to age gracefully and mantain an independent life style, without disability, for as long as possible [49].

## Estrogen as Neuromodulators and Neuroprotectors

Estrogen is a potent steroid of both gonadal and neuronal origin implicated in reproductive functions as well as in neuromodulatory and neuroprotective actions on the central nervous system [50, 51]. Local synthesis of this molecule in the central nervous system may prevent or reduce neurodegeneration. Steroids modulate the expression of neuropeptides such as neuropeptide Y (NPY), galanin, and β-endorphin. NPY regulates the reproductive cycle, and estradiol administration has been shown to decrease NPY expression in the arcuate nucleus [52, 53], whereas the absence of this hormone results in an increase of NPY mRNA levels [54]. β-Endorphin is another peptide involved in energy and reproductive homeostasis. Estradiol stimulates the activity of pro-opiomelanocortin (POMC) cells, increases the levels of POMC mRNA, and even increases the number of these cells [53, 55, 56].

Moreover, estrogens participate in a series of protective function processes. One example is the promotion of cell survival and synaptic plasticity. In vitro studies have shown that the addition of 17β-estradiol to primary cultures of various neuronal populations (hypothalamic, neocortical, hippocampal, and amygdala) increased viability, survival, and differentiation [42, 57–59]. This molecule also regulates the expression and the action of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) and their receptors (trk, p74) [60]. Neurotrophins are a family of proteins that favor the survival, development, and function of neurons, and estrogens can interact with them by convergence (e.g., sharing the same signaling cascade, acting synergistically), by inducing their expression through estrogen response elements, or

by dependence, where the two components are needed to obtain a complete effect [61, 62]. Estrogens exert their functions via the classical nuclear receptors, regulating transcription factors that control the expression of estrogen-sensitive genes and membrane receptors (independent of transcriptional activation), which elicit faster responses than genomic effects. The most well-characterized nuclear receptors are estrogen receptor α (ERα) and estrogen receptor β (ERβ) [61], and among the membrane receptors is G-protein-coupled receptor 30 (GPR30) which, according to in vitro studies in cortical neurons, is involved in neuroprotection against oxidative stress [63].

The preoptic area, the hypothalamus, and the amygdala are the regions with the highest expression of ERs, although expression of these is also observed in regions of the cortex, hippocampus, and midbrain. Although ERα is the subtype with the highest expression in most regions, there are areas such as the mesencephalon, where ERβ predominates [64].

Estrogens can also prevent neuronal dysfunction by alterations in the levels of neurotransmitters, their receptors, and second messengers, through estrogen-binding sites in the plasma membrane [65]. For example, estradiol could regulate the release and uptake of dopamine by decreasing the affinity of dopamine receptors in order to protect the nigrostriatal system from excitotoxicity [66–68].

Several studies evidence the neuroprotective effects of estrogens in neurodegenerative diseases and traumatic damage. In Alzheimer's disease, estradiol could affect β-amyloid aggregation by regulating its metabolism and apolipoprotein E (ApoE) expression [69, 70]. In addition, this hormone could be involved in the regulation of cholinergic and serotonergic neurotransmissions, thus reducing the cognitive and affective symptoms of the disease.

Estradiol has anti-inflammatory effects in the brain that are mediated, at least in part, by a reduction of reactive gliosis [60, 71] and contributing to neuronal regeneration [72–74].

As it has already discussed, there are numerous neuroprotective actions of estrogens that have direct relevance to neurodegenerative diseases. Despite these actions, the promise of estrogen-based therapies for reducing the risk for neurodegeneration remains to be fulfilled. The application of estradiol as a neuroprotectant in humans presents numerous limitations, mainly due to the endocrine actions of the molecule on peripheral tissues, including estrogen dependent tumors. Therefore, as ongoing research continues to address these crucial and immediate concerns, an emerging area of investigation is the development of natural and synthetic hormone mimetics that will preferentially activate estrogen neuroprotective mechanisms while minimizing adverse effects in other tissues.

## Neurological Dysfunctions and Brain's Growth Factors

Neurotrophic factors (NTFs) are diffusible peptides secreted from neurons and neuron-supporting cells. They serve as growth factors for the development, maintenance, repair, and survival of specific neuronal populations, and they act via retrograde signaling from target neurons by paracrine and autocrine mechanisms [75, 76]. NTFs have different functions depending on the stage of life. During development they contribute to the formation of synaptic network [77, 78], neuronal survival, and axonal growth [79, 81]**.** In adulthood they are associated with neuronal survival and maintenance of different neural phenotypes [80].

An additional basic activity of many growth factors in the nervous system is influencing on the proliferation, migration, and differentiation of stem cells in the developing and adult nervous system [81, 82]. These basic properties are also employed by the nervous system in the case of disease and injury and thus constitute a powerful endogenous repair and maintenance system. NTFs act together in a coordination mode, so that any alteration on their local synthesis and/or transport caused by traumas, pathologies, or even aging could lead to neuronal death. Loss or dysregulation of endogenous trophic factors could contribute to the development of neurodegenerative diseases.

Neurotrophic factors are classified in superfamilies, according to their structure or function, as follows: (i) nerve growth factor (NGF) superfamily; (ii) transforming growth factor (TGF)-beta superfamily, consisting of the glial cell line-derived neurotrophic factor (GDNF) family, the TGF-beta family, and the bone morphogenetic protein (BMP) family; (iii) neurokine or neuropoietin superfamily; and (iv) non-neuronal growth factors that include IGF-1 and acidic and basic fibroblast growth factors (aFGF and bFGF, respectively). In the last decade, there have been described two new NTFs that cannot be included in the previous classification. They are cerebral dopamine neurotrophic factor (CDNF) and mesencephalic astrocyte-derived neurotrophic factor MANF [83]. Both are structurally and functionally clearly distinct from the classical, target-derived neurotrophic factors (NTFs) that are solely secreted proteins [82].

The potential for a therapeutic application of these factors has been realized early on, and the last two decades have seen several approaches to exploit this potential in different neurological disorders. The next section summarizes the current data on NTFs and their potentiality as therapeutic agents for neurodegenerative diseases.

## NTFs and Neurodegenerative Diseases: Evidences and Perspectives

There is clear evidence that neurodegenerative diseases course with impairment levels of neurotrophic factors or their receptors. For example, in PD there is a small decrease in staining density for BDNF and dopaminergic projection areas; GDNF levels are reduced (about 20%) in the substantia nigra pars compacta (SNpc) from PD patients compared with age-matched controls. The researchers also found that ciliary neurotrophic factor (CNTF) decreased as compared with age-matched controls, 11.1%/neuron and 9%/neuropil, and markedly increased levels of tumor necrosis factor and interleukin 6 (IL-6) in the nigrostriatal DA regions of PD patient [84].

Respect to the other major neurodegenerative disease, Alzheimer's disease (AD), it had been described increases in NGF and decreases in BDNF in hippocampal and neocortical regions. It was also observed decreases in tropomyosin receptor kinase A (TrkA) in the cortex and nucleus basalis in advanced AD [85, 86].

The well-documented role for neurotrophic factors to prevent cell death and to maintain cellular function has led scientists to investigate their use as therapeutic drugs and benefits. In the last years, there have been numerous preclinical and clinical studies involving treatment of neurodegenerative diseases with NTFs (for review see [84, 87–89]).

Despite the evident heterogeneity, the results from the reviewed studies can aid in conducting human trials applying NTFs. The reviews mentioned highlight that targeted local deliveries of NTFs led to favorable safety and efficacy outcomes when administration regimens successfully target a degenerated neuronal population. The previous works suggest that the application of NTFs is generally safe and well tolerated when administered locally.

In conclusion the strong potential of NTFs to exert pro-survival and pro-functional responses in neurons of the peripheral and central nervous system makes them good target candidates for treatment of a multitude of neurodegenerative disorders. However significant problems need to be overcome before translating the potential of neurotrophic factors into the therapeutic area.

## Insulin-Like Growth Factor-1 as a Therapeutic Factor

As we previously mentioned, neurotrophic factors that prevent degeneration and restore the function of the remaining neuronal populations are currently of increasing clinical interest as targets of therapeutic possibility in the treatment of neurodegenerative diseases. One of these neurotrophic factors is IGF-1. It is known, in rats, that tissue level of IGF-1 and its receptor decrease significantly in the hippocampus and cortical

layers II/III and V/VI throughout life [90]. It is also known that in situations of cytotoxic hippocampal damage, the microglia of this region substantially increases the production of IGF-1 and IGF-binding protein 2, suggesting a neuroprotective role of these molecules in the central nervous system [91].

It has also been documented that IGF-1 protects hippocampal neurons from the toxic effects of amyloid peptides [92] and that treatment with IGF-1 in mice overexpressing a mutant Aβ-amyloid peptide markedly reduces the peptide levels and improves their cognitive ability [93]. In vitro studies have shown that IGF-1 increases the cell survival of primary cultures and hypothalamic neurons [94] and stimulates the differentiation of rat dopaminergic mesencephalic neurons [95]. Also, IGF-1 modulates the inflammatory response of astrocyte cultures treated with lipopolysaccharide (LPS) [96].

There are mechanisms that suggest neuroinflammation is harmful, at least partially, because it avoids the neuroprotective action of IGF-1 [97]. Moreover, a protective effect of IGF-1 on hypothalamic cells exposed to glutathione-depleting agents has also been described [98], as well as in human, dopaminergic culture cells exposed to the salsolinol toxin and in human and murine neuronal cultures exposed to high doses of dopamine [99]. Recently, Rodriguez-Perez et al. [100] demonstrated that IGF-1 participates together with the local renin-angiotensin system to inhibit or activate neuroinflammation (M1-M2 phenotype transition), oxidative stress, and dopaminergic degeneration induced by $MPP^+$ neurotoxin.

Short-term studies of our group revealed that gene therapy with IGF-1 in the senile female rats with DA neurodegeneration is highly effective to restore hypothalamic DA neuronal function, thus correcting the chronic hyperprolactinemia associated with the dysfunction of tuberoinfundibular dopaminergic neurons (TIDA) in senile rats [101]. Also, ICV gene therapy with IGF-1 partially but significantly restores motor performance in this model of spontaneous TIDA neurodegeneration in senile animals [102, 103].

Among the possible effector fields of IGF-1 on synaptic plasticity and hippocampus, it is known that within a glutamatergic synapse, there is a positive effect of IGF-1 on synaptic transmission and consequently a prevention of cognitive deterioration. IGF-1 (as well as ghrelin, GLP-1, and insulin) is reported to be one of the molecules that stimulate glucose metabolism, providing energy for the biosynthesis of neurotransmitters. In this way, it would facilitate hippocampal circuits in terms of plasticity and synaptic structure, as well as participating in neurogenic aspects modifying learning, memory, and cognitive functionality [104]. This indirect mechanism of action would be mediated by the IGF-1 signal receptor that leads to voltage-dependent calcium channel phosphorylation, causing increased calcium and release of neurotransmitters that would facilitate synaptic conduction [105].

Currently, it is unknown whether IGF-1 exerts a direct effect on the mobilization of synaptic vesicles and the core complex of soluble NSF attachment protein (SNARE) proteins during neurotransmitter exocytosis. Interestingly, at the postsynaptic site, IGF-1 could inhibit the activity of glycogen synthase kinase 3 beta (GSK3β), a key factor in the hyperphosphorylation of the microtubule-associated protein (Tau). By reducing the activity of GSK3, IGF-1 could potentially prevent the formation of neurofibrillary agglomerates (an important pathological marker of AD disease). In addition, through phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) activation, IGF-1 may be involved in the incorporation and transport of glutamatergic receptors in dendrites [41].

## Conclusion

It is well known that age is the major risk factor for neurodegenerative diseases, and the endogenous level of neurotrophic factors decreases with age, suggesting that trophic factor loss may contribute to the etiology of neurodiseases. Neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease and even the natural process of aging generate, as we detailed, several cognitive disorders and

motor dysfunctions associated with excessive ROS from cellular metabolism, alterations in growth factor production, in pro-inflammatory cytokines and inflammatory markers, and in neurotransmitter receptors expression, and structural changes in dendritic morphology and electrophysiological properties.

In this context, insulin-like growth factor-1 is an important neurotrophic factor/hormone with receptors widely expressed in the brain. It is affected in a range of neurodegenerative disorders and may play a role in brain dysfunction. It is well known that IGF-1 promotes neurogenesis and synaptogenesis in the postnatal dentate gyrus and acts as fast modulator of brain activity, specifically, in cognitive processes. Also, the chronic administration of IGF-1 or administration of Gly-Pro-Glu, an N-terminal peptide of IGF-1, attenuated loss of TH-immunoreactive cells, terminals, and behavioral deficits in response to 6-hydroxydopamine (6-OHDA) infusion into the dopaminergic axons within the nigrostriatal pathway. Moreover, IGF-1 therapy improved glucose and lipid metabolism, increasing testosterone levels and antioxidant ability and reducing oxidative damage, and it was also associated with a normalization of antioxidant enzyme activities.

Taken together, the IGF-1 action as neuroprotective molecule, the interaction with estrogen as neuromodulators, its crucial role in oxidative stress, and its important function in synaptic plasticity are valuable aspects to study and evaluate in depth of this growth factor considering that it may be a potential therapeutic molecule inside neurodegenerative diseases.

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# 15 A Commentary on the Therapeutic Potential of Melatonin and Its Analogues in CNS Conditions

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## Melatonin and Its Receptors

Melatonin, also known as *N*-acetyl-5-methoxytryptamine or 5-methoxy-*N*-acetyltryptamine, is found in both animals and plants. In mammals, it is mainly produced in the brain by the pineal gland and locally by the retina. The precursor of melatonin is tryptophan. It is first converted to serotonin before being converted to melatonin in pineal parenchymal cells [1] (Fig. 15.1). The production of melatonin in the pineal gland follows a circadian rhythm: production is low during daytime but rises at the onset of darkness and remains elevated through the night [1]. Melatonin activates two high-affinity receptors: $MT_1$ (Mel1a, *MTNR1A*) and $MT_2$ (Mel1b, *MTNR1B*). Both receptor subtypes contribute to the phase shifting of the circadian rhythm [2], reproduction [3], cardiovascular regulation [4] and immune responses [5]. mRNA hybridization and receptor autoradiography have identified areas of high expression levels of $MT_1$ receptors in the suprachiasmatic nucleus, cerebral cortex, hippocampus, thalamus and cerebellum, whereas the expression of $MT_2$ receptors is most prominent in the retina and hippocampus [6]. Using antibodies with selective affinity for $MT_1$ and $MT_2$ receptors, a recent immunohistochemistry study describes a more widespread presence of each receptor type extending throughout the brain [7, 8]. Both $MT_1$ and $MT_2$ receptors are essentially localized to neuronal cell bodies and dendrites [7]. Outside the CNS, melatonin receptors are also found in the small intestine, liver and heart [9]. At the molecular level, $MT_1$ and $MT_2$ receptors are G protein-coupled receptors, encoded by genes on human chromosome 4 (4q35.2) and chromosome 11 (11q14.3). $MT_1$ receptor is coupled to pertussis toxin-sensitive Gi and pertussis toxin-insensitive Gq/11 G proteins. The binding of melatonin to $MT_1$ inhibits forskolin-stimulated cAMP, PKA signalling and CREB phosphorylation and enhances MAP kinase 1/2 and ERK 1/2 phosphorylation and potassium current via Kir3 channels. Activation of $MT_2$ inhibits cAMP and cGMP formation [10, 11], activates PKC in the suprachiasmatic nucleus and releases dopamine in the retina [12].

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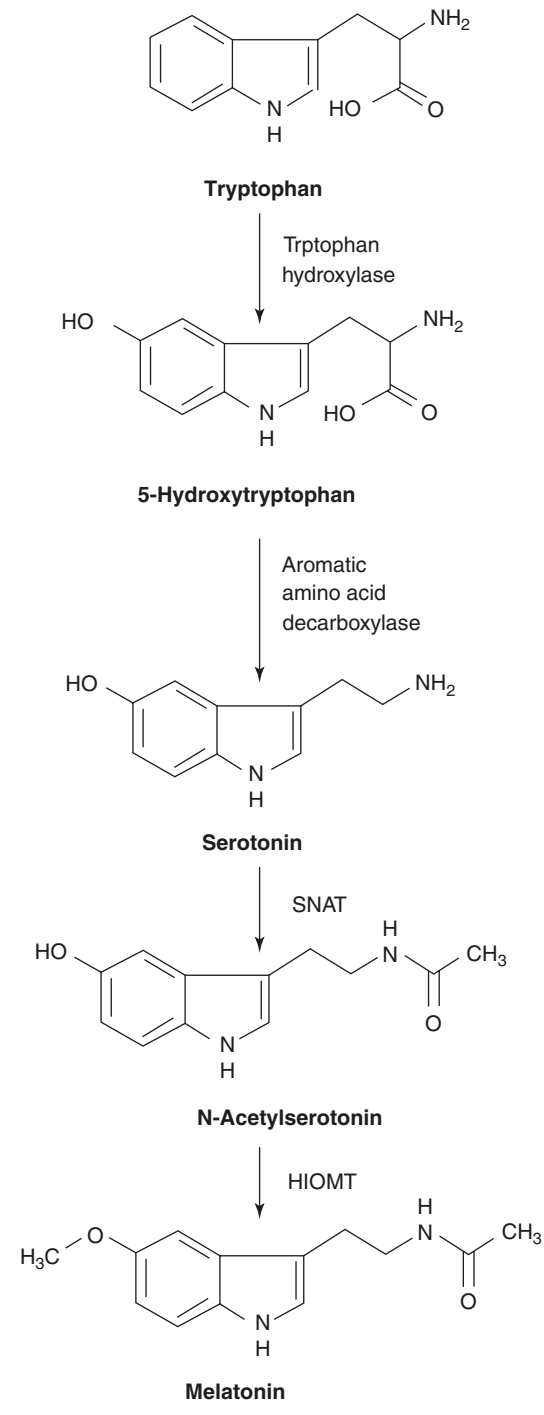


**Fig. 15.1** The biosynthesis of melatonin. First, the essential amino acid, tryptophan, is taken up into pineal parenchymal cells. Tryptophan is converted to 5-hydroxytryptophan by tryptophan hydroxylase and then to 5-hydroxytryptamine (serotonin or 5HT) by aromatic L-amino acid decarboxylase. The final conversion steps depend on two characteristic enzymes of the pineal: serotonin *N*-acetyltransferase (SNAT) and hydroxyindole-O-methyltransferase (HIOMT). Their activities in pineal parenchymal cells rise soon after dark. SNAT converts serotonin to *N*-acetylserotonin, and HIOMT adds a methyl group to the 5-hydroxyl of the *N*-acetylserotonin. A portion of serotonin is liberated from pineal cells after dark, which is deaminated by the enzyme monoamine oxidase (MAO, not shown)

## Circadian Regulation

Melatonin is an important hormonal regulator of the sleep-wake cycle [13, 14]. The elevation of melatonin secretion by the pineal body is directly linked to sleepiness [15]. Melatonin facilitates sleep by inhibition of the wake-promoting system centred on the suprachiasmatic nucleus – the brain's "master clock" – which coordinates the tissue-specific circadian rhythms throughout the body. In response to light input, the suprachiasmatic nucleus produces an alerting signal to enhance wakefulness and actively counteracts the drive for sleep. Coinciding with the onset of nightfall, the rise in melatonin level inhibits the wake-promoting activities of the suprachiasmatic nucleus and triggers sleepiness. It has been shown that phase shift of the circadian rhythm can be directly induced by daily timed administration of melatonin in rodents [16].

## Antioxidant, Anti-inflammatory and Anti-apoptotic Properties of Melatonin

Melatonin is a strong free radical scavenger and antioxidant [17, 18]. It is therefore considered as a prime candidate for slowing the ageing process at the cellular and tissue levels [19], thought to be the results of the age-dependent accumulation of oxidative stress and free radicals [20, 21]. Hence, longevity is associated with increased levels of anti-oxidative enzymes as well as the reduced production of reactive oxygen species induced by low caloric intake. Accordingly, metabolic rate and protective antioxidant activity may explain, to some extent, the variation of lifespan across species. Accordingly, the administration of melatonin or pineal extract has been reported to extend the lifespan of mice, whereas an opposing effect is seen after pinealectomy [22]. Melatonin is an effective scavenger of highly reactive free radicals, singlet oxygen, reactive oxygen species and reactive nitrogen species [17, 18]. Low reactivity free radicals can be scavenged by melatonyl radicals or catalytic action [23–25]. Melatonin also scavenges hydrogen peroxide [26], detoxifies nitric oxide [27, 28] and neutralizes toxic hydroxyl radical [26]. Melatonin can further stimulate the production of antioxidant enzymes like superoxide dismutase [29], glutathione peroxidase and glutathione reductase through augmentation of glutathione recycling [24]. Other indirect effects of melatonin include the inhibition enzymes responsible for the production of free radical within cells [30, 31].

In addition, the anti-ageing effect of melatonin has also been linked to its anti-inflammatory effects. Melatonin can alleviate inflammation by suppressing pro-inflammatory cytokine production through inhibition of NF-ƙB pathways [32, 33]. It also decreases TNF-α production [34]; alleviates phospholipase A2-mediated inflammation [35], which is responsible for the early inflammatory responses; and suppresses the production of inflammatory mediators in the presence of cyclooxygenase and lipoxygenase [36]. In 2004, it has been shown that lymphocytes can synthesized and release melatonin [37]. Importantly, lymphocytic melatonin is critical for the modulation of IL-2/IL-2 receptor system [37, 38]. It has been reported that melatonin can enhance the in vivo antitumor efficacy of IL-2 such that it may be an effective anticancer adjuvant [39].

Lastly, melatonin may promote cell survival by inhibiting apoptosis. This has been reported in precursor B cells and thymocytes in the immune system [40, 41], and thus melatonin is expected to upregulate the immune system [22]. Similar anti-apoptotic effects have been reported in neurons under oxidative stress [42, 43], highlighting its relevance to neurodegenerative disorders [44].

## Protection Against Neurodegenerative Diseases

The decline in melatonin production in aged individuals is considered as a risk factor contributing to the development of age-associated neurodegenerative diseases. It has led to the

suggestion that exogenous melatonin may restore the balance and thus confer neuroprotection [19]. This is consistent with the antioxidant, anti-inflammatory and anti-apoptotic properties of melatonin at the cellular level outlined above. Another hypothesis focuses on the consequence of decline of melatonin production on the stability of the circadian rhythm. The resulting instability is considered a form of *internal temporal disorder* that primes the onset of neurodegeneration [22]. At the pathological levels, melatonin was effective in reducing oxidative stress and preventing lipid peroxidation in an animal model of Parkinson's disease [45, 46]. Its protective effect against Parkinson's disease has also been attributed to the reduction of cytochrome c release, the inhibition of caspase-3 and the prevention of the DNA fragmentation [47]. Amyloid beta (Aβ) is a pathological hallmark of Alzheimer's disease, and melatonin could protect neurons from Aβ-induced toxicity and cell death in vitro by reducing calcium influx [48]. Melatonin treatment was effective in reducing the total Aβ load in the brain of mutant mice that carried the Swedish mutation (Tg2579) in the Aβ precursor protein that leads to the early accumulation of Aβ plaques [49]. The treatment was also effective in improving learning and memory performance in the APP695 V717I mouse model of Aβ pathology in Alzheimer's disease [50]. It was suggested that melatonin inhibited caspase-3 activity and suppressed the upregulation of Bax and prostate apoptosis response-4 in the mutant mice [51–53]. This supports the hypothesis that the anti-apoptotic property of melatonin could halt or delay the degeneration of neurons associated with Alzheimer's disease. Importantly, the neuroprotection effect of melatonin is not limited to age-associated neurodegenerative diseases. There is evidence that melatonin can promote the recovery of spinal cord injury and the alleviation of motor deficits by a reduction of leukocytes at the site of trauma [54]. Similarly, melatonin could prevent ischemic stroke-induced inflammatory responses [55], which may underlie the observed reduction of cerebral infarction in a stroke model based on middle cerebral artery occlusion [56].

## Depression and Anxiety

The application of melatonin treatment for depression and anxiety is arguably more advanced and promising. A growing number of studies have examined the therapeutic potential of $MT_1$/$MT_2$ receptor agonists in patients with depression and anxiety. A prominent candidate is agomelatine developed by Servier. Agomelatine (carries the brand names Valdoxan, Melitor, Thymanax) is a mixed $MT_1$/$MT_2$ receptor agonist and a selective 5-HT2C receptor antagonist. It is active in several animal models of depression [57–59]. Its clinical efficacy has been demonstrated in a large multicentre double-blind placebo-controlled trial with 711 patients of major depressive disorder, which identified the dose of 25 mg/day as being most effective [60]. The same dose was as effective as valproate or lithium in treating acute bipolar II depression [61]. Its efficacy in patients with moderate to severe major depressive disorder was clearly associated with significant improvement seen in the Hamilton Depression Scale and the Clinical Global Inventory [62, 63]. Another study indicated that agomelatine could improve underlying anhedonia and relieve associated symptoms of anxiety in patients [64].

A meta-analysis reinforces the consensus that agomelatine is more effective than placebo and indicates its efficacy is comparable, but not superior, to existing antidepressants [65]. Indeed, the major advantage of agomelatine lies in its relatively more favourable side effect profile as concluded by a recent Cochrane Review [66]. Commonly used antidepressants, of the SSRIs, SNRIs and tricyclics classes, are associated with weight gain, sexual dysfunction and severe withdrawal. In a direct comparison with venlafaxine (an SNRI), agomelatine achieved similar benefits but had demonstratively less severe side effects in terms of sexual dysfunction [67]. Agomelatine is therefore better tolerated, and it should improve compliance and clinical management. In terms of its efficacy against anxiety-related disorder, agomelatine is associated with an earlier and higher clinical response, compared with SSRIs and SNRIs in patients with generalized anxiety disorder [68]. This adds to earlier report on the

use of melatonin in the treatment of sleep disturbance in depression [69]. Another mixed melatonin receptor agonist, ramelteon (marketed as a sleep agent), is also reported to be effective in alleviating anxiety symptoms associated with sleep disturbances [70, 71]. This echoes with a recent clinical trial reporting the benefits of postoperative melatonin treatment in alleviating depression and sleep disturbances in a cohort of breast cancer patients [72]. An anxiolytic effect of melatonin has been consistently reported in several clinical trials focusing on surgery-related anxiety across diverse patient groups. These ranged from preoperative anxiety, separation anxiety and anxiety associated with the introduction of the anaesthesia mask in children [73] to anxiety of topical anaesthesia in patients undergoing cataract surgery [74]. Most studies have reported similar efficacy in comparison with benzodiazepines, such as midazolam [75], but melatonin was relatively free from cognitive and psychomotor side effects by comparison [76]. However, one study reported that melatonin was less effective than midazolam in relieving preoperative anxiety in children at the induction of anaesthesia, but it produced a dose-dependent reduction in emergence delirium post-anaesthesia [77]. In contrast to the impression obtained in clinical trials, a synergistic interaction between melatonin/agomelatine and diazepam has been demonstrated in rats: melatonin and agomelatine have been independently associated with some anxiolytic effects, but the effect became more pronounced and extensive when combined with an ineffective dose of diazepam [78]. Further tentative evidence for a synergism was reported between melatonin and buspirone in ameliorating anxiety and stress-induced oxidative damage in a mouse model of immobilization stress [79].

Finally, it is worth noting that agomelatine has been approved for treatment of major depressive disorder in Europe, but it has yet not been approved by the FDA in the United States. It is therefore worthwhile considering concerns over some clinical trials indicating a lack of synergism between agomelatine and existing SSRIs/SNRIs. One study reported that the efficacy of low-release melatonin plus fluoxetine was limited to improvement in sleep [80]. This is consistent, however, with the known efficacy of melatonin agonists to improve sleep in circadian rhythm sleep-wake disorders [81]. In another randomized double-blind placebo-controlled study, adjuvant slow-release melatonin to current antidepressant treatment failed to significantly improve depressive symptoms compared with current antidepressant alone [82]. Additional large-scale clinical trials are necessary to clarify the use of melatonin and its analogues for depression as an adjuvant medication as well as in the context of monotherapy.

## Modulation of Neurogenesis

Adult neurogenesis in the hippocampus has been linked to the development of depression amongst other psychiatric conditions [83–87]. Suppression of neurogenesis in the dentate gyrus of the hippocampus has been reported in several animal models of depression [84], although blockade of neurogenesis as such does not necessarily induce depressive traits or behavioural disturbances in animals [88, 89]. Thus, the precise causal link, if it exists, remains unclear and ill defined. Nonetheless, the ability to promote hippocampal neurogenesis is considered common amongst many known antidepressant drugs [83, 86, 87, 90, 91] in animal models of depression and anxiety, as well as in patients with depression [92]. Importantly, the therapeutic effect of antidepressants can be blocked if neurogenesis is inhibited at the same time [87]. Hence, findings that melatonin can also enhance hippocampal neurogenesis [93] are supportive of the hypothesized link antidepressant action and promotion of neurogenesis. Melatonin supplement increased the number of neuronal precursor cells in the dentate gyrus in rat after pinealectomy [94] and stimulated adult hippocampal neurogenesis in mice after ovariectomy [95]. In vitro cell proliferation activity in hippocampal precursor cells derived from adult mice can also be triggered by melatonin [96]. Apparently, the proneurogenic effect of melatonin appears even more extensive. The differentiation of midbrain

neural stem cells in rats could also be enhanced by melatonin treatment [97]. Finally, it has been shown that melatonin may regulate neurogenesis following brain injuries, as demonstrated after mild focal cerebral ischaemia in mice [98] and the observation that both proliferation and differentiation of neural stem cells in vitro under hypoxia condition could be facilitated by exposure to melatonin [99]. The latter findings are certainly of relevance to the neuroprotective effects of melatonin against neurodegeneration outlined above [100, 101].

## Future Directions

Here, we do not attempt to provide a comprehensive summary of the plethora of potential application of melatonin and its derivatives in CNS health and disorders, which can be found elsewhere [102, 103]. Instead, it is intended to draw attention to its multifaceted roles beyond the maintenance of the circadian rhythm and, in particular, on its regulatory roles in inflammatory processes, oxidative stress at the cellular levels and the balance between cell death and cell proliferation. Interests in the therapeutic potential of melatonin and its analogues or derivatives are encouraged by the positive outcomes of many clinical trials. Even in areas of application that melatonin does not show superior efficacy than existing medication, its low cost and relatively low toxicity/side effect profile have continued to attract attention. Mechanistic investigation is certainly necessary to guide further refinement in drug development, for instance, in dissecting the contributions between $MT_1$- and $MT_2$-dependent pathways. The identification of the third receptor subtype, $MT_3$, as being equivalent to the intracellular quinone reductase-2 might have opened further opportunities. Not only is quinone reductase-2/$MT_3$ activity directly related to the antioxidant role of melatonin [104], but ligands of the quinone reductase-2/$MT_3$ ligands could also modulate depression-related behaviour [57, 58]. A novel development concerns the epigenetic regulation melatonin receptors leading to the suggestion that we may be able to upregulate the expression of melatonin receptors where they are reduced due to ageing or diseases [105]. Valproic acid has been suggested to be such an agent, which incidentally is also a common mood-stabilizing drug in the treatment of bipolar depression. Finally, the possibility that light-regulated release of melatonin during pregnancy may be associated with foetal programming effects leading to behavioural abnormalities in the offspring in adulthood has been explored in rats [106]. Although the data thus far are still highly tentative, the concept certainly warrants further testing by others. This may yield some significant insights to the reportedly higher incidence of bipolar disorder and schizophrenia amongst winter births [107–109].

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# 16 Lithium Therapy Effects on the Reproductive System

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## Introduction

Lithium (Li) is a drug which has been used for over 60 years for the treatment of bipolar disorders (BD, also known as bipolar affective disorder or manic-depressive illness). Currently, there are no other drugs to completely and confidently replace Li salts in psychiatric medicine. These salts are mood stabilizers and reduce extreme behaviors by restoring the balance of brain neurotransmitters. They are also used in the treatment of manic-depressive symptoms that include hurried speech, hyperactivity, sleep disturbances, aggression, and anger [1, 2]. Despite cross-site variation in the prevalence rates of the bipolar spectrum disorder, the severity, impact, and patterns of comorbidity are remarkably similar internationally [3].

For certain pathologies, the benefits of Li have not yet been overcome by other drugs. However, the safe range of Li levels in blood is very narrow, and a strict control of this medication is necessary in order to avoid undesired effects. The adverse effects are manifested mainly in the kidneys, heart, thyroid gland, and a neurological level. Many of the observed alterations are reversible with the suspension of the treatment [4].

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The toxic effects of Li therapy on the reproductive system are less known and controversial. There are reports in the literature suggesting that these treatments in humans cause a deterioration of sexual functions [5, 6]. In addition, numerous experimental animal studies have demonstrated that Li may have adverse effects on the hypothalamic-pituitary-gonadal axis (HPG) [5–11].

The aim of the present work is to review the history of the discovery of Li as a psychoactive drug, the state-of-the-art study of mechanisms of action, and its adverse effects on human health, mainly in relation to the alterations in the organs of the HPG axis involved in the reproductive processes. Finally, some perspectives on future research on using lithium salts are addressed.

## History of Lithium as a Psychoactive Drug

The discovery of Li is attributed to the Swedish physician J.A. Arfwedson and his teacher, J.J. Berzelius, in the year 1817. They called it "LITHOS," to remember that it was discovered in the mineral kingdom. During the nineteenth century, Li was used as a treatment for gout, since the solubility of uric acid is maximized in the form of lithium urate. In 1873, William Hammond demonstrated the efficacy of lithium bromide in patients with manic episodes. From 1900 onward



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it was used in the prophylaxis of depression and as an antiepileptic or hypnotic [12]. However, a terrible event in the history of Li occurred during the 1940s, because it was indicated as a replacement for dietary table salt (sodium chloride). This practice and Li salt were both prohibited, following publication of reports with details of side effects and deaths. These facts provoked the prohibition of its commercialization in the United States. During the 1950s, the pharmaceutical industry did not show commercial interest in this substance, and it is recalled that in Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (1960 edition), therapeutic applications of Li ion were denied and it was considered a toxic ion [13, 14].

In contrast, in 1949, the Austrian researcher J. Cade assessed the antimanic effects of Li in humans [15]. His work was continued by the Danish psychiatrist Mogens Schou during the 1950s at the Psychiatric Hospital of Aarhus University. He was able to definitively establish the efficacy of this ion [16]. Since 1960, the interest of Li salts increased significantly, and in 1970, their use for the treatment of acute mania and as a prophylactic of BD was allowed by the FDA (Food and Drug Administration or Food and Drug Administration) in the United States. Currently, these salts are used in psychiatric patients as antidepressant and antimanic drugs. This compound is prescribed as a mood stabilizer and reduces extreme behaviors by restoring the balance of neurotransmitters in the brain [1, 2].

## Lithium Chemical Characteristics and Therapeutic Applications

Li belongs to the alkali metal group; it is the lightest solid metal of the periodic table, with an atomic number of 3 and an atomic weight of 6.940 amu (atomic mass units). Li is an extremely active substance because of its electronic structure and the high density of positive charge in its nucleus. Thus, it is not free in nature and it always constitutes different salts. Li is active in the form of a monovalent ion (Li +), so all salts have the same pharmacological action. Of the different Li salts, lithium carbonate is the most widely used in therapeutics; other alternatives are citrate, acetate, sulfate, and lithium glutamate. Lithium chloride is very seldom used because it is strongly hygroscopic [17].

Li salts are chemically simple drugs when compared to the other drugs used in psychiatric therapeutics, and it has other important qualities, such as the fact that it is not metabolized and does not bind to tissue or blood proteins. These properties are essential for the control of values of the active agent by determining its concentration in blood. Li is the only ion that exerts a therapeutic action in psychopharmacology, but it produces undesirable effects, like other drugs. This substance is administered orally, usually as carbonate, and it is excreted by the kidney. Although half of the oral dose is eliminated in about 12 h, the rest is excreted after 1–2 weeks. Thus, Li accumulates slowly over about 2 weeks before reaching its steady state. Li has a narrow therapeutic index, so it is imperative to monitor the patients clinically regarding to circulating concentrations, mainly in the case of patients with low-calorie diets, elderly, adolescents, pregnant women, and drug addicts. The elderly are less tolerant to this ion, and, on the contrary, adolescents are more tolerant to Li than adults, so they may need higher doses to achieve optimal blood concentrations, since the renal clearance of this ion is greater in adolescents than in adults.

Human clinical evaluation indicates that the effective and safe Li serum concentration is narrow: 0.8–1.2 mmol/L (for acute mania) and 0.6–1.0 mmol/L (for maintenance therapy) [18–20]. More recently, a safe therapeutic range between 0.4 and 1.0 mmol/L has been proposed. Below 0.4 mmol/L, it is unlikely to be effective in the majority of patients, while levels above 1.0 mmol/L are increasingly associated with signs and symptoms of toxicity including confusion, seizures, and renal damage [21, 22]. The frequency of occurrence of adverse effects in humans varies with dose, length of treatment, renal excretion ability, and personal sensibility to the drug [23]. In fact, the most adequate schedule of administration of Li is continuously revised

by researchers in each pathology to avoid the appearance of adverse effects [24].

Li was discovered about 190 years ago and introduced in modern psychiatry by Cade and later with clinical experiments by Schou et al. [25] as an effective treatment for manic psychoses. This first study was followed by many more that demonstrated that Li produced beneficial effects between 60% and 80% of manic patients [26]. However, Li salts were not used as a recognized treatment for manic conditions until 1970, when it was approved by the FDA. Despite the passing of time, Li remains the best mood stabilizer, and it is used in long-term pharmacotherapies in patients with affective disorders [1]. Its use has established antimanic effects and prophylactic efficacy against the recurrence of affective episodes [27, 28]. Another advantage of Li is its proven ability to reduce suicide attempts and suicidal death among bipolar patients [29, 30]. One of the most extended hypotheses is the biological correlation between suicide and low serotonin levels. It seems that the main advantage of Li over other psychiatric drugs is the ability of this ion to increase and stabilize the serotonergic function [31]. In addition, recent studies have shown that the combination of Li with other drugs seems to be more effective than monotherapy with this ion [32].

According to the recommendations of the *Practice Guide of the A.P.A. for the Treatment of Patients with Bipolar Disorder*, Li is the first election pharmacological treatment for patients with manic-depressive illness when there is no record of previous renal or cardiac pathologies. Therefore, Li salts constitute the election treatment in the prophylaxis of bipolar affective disorders at long term, with the exception of rapid cycler patients. In the prevention of depressive phases of the unipolar affective disorders and in the treatment of refractory depressions, the use of Li associated with other drugs is recommended. Besides, it is also being applied in schizophrenic disorders, premenstrual disorders, impulse control disorder, episodic aggressiveness, obsessive-compulsive disorders, and alcohol abuse. Finally, the administration of Li salts exceeds psychiatric pathologies, and its application has been reported in granulocytopenia, inadequate secretion of the antidiuretic hormone, hyperthyroidism, migraine, tardive dyskinesia induced by neuroleptics, and in the treatment of some viral infections, such as simple herpes or AIDS, although in all these cases the therapeutic results obtained up to now are in no way conclusive [13].

## Action Mechanisms of Lithium

In recent years, several sites of molecular action for Li have been described, although the exact mechanism of action by which it exerts its effects as antimanic or as mood stabilizer have not yet been fully elucidated [33]. Li appears to modulate intricate regulatory networks via multiple key nodes [34]. Several investigations propose that Li induces multiple biochemical and molecular effects on neurotransmitter receptor-mediated signaling, signal transduction cascades, hormonal and circadian regulation, ion transport, and gene expression [35].

The first studies to establish action mechanisms of Li were aimed at electrolyte balance in BD and recurrent depression. An increase of residual sodium during episodes of depression and mania and its normalization in the course of Li treatment have been reported. In consequence, a reduced activity of NA+-K+ATPase was implicated in the pathophysiological mechanisms of those illness [36–38]. There are studies indicating that Li stimulates Na+-K+ ATPase activity [39], decreasing intracellular sodium (and calcium) via voltage-gated sodium channels [37, 40]. Through this protein, Li is involved in the regulation of different transduction signals, modulation of CREB activity, apoptotic processes, regulation of calcium homeostasis, and lipid peroxidation [41–43]. Moreover, the influence of this ion on other sodium-dependent membrane transporters, for instance, choline transport, has been demonstrated, increasing the intracellular availability of choline and acetylcholine [44].

The effects of Li have been related to the monoaminergic signaling pathways. In animal studies, an increase of serotonin transmission by multiple mechanisms was observed and correlated

with antisuicidal and antiaggressive properties of Li [45]. In human studies, however, the noradrenergic pathway is involved to possibly achieve antimanic and antipsychotic effects [46]. Li administration increases the release of noradrenaline [47] and inhibits increased dopaminergic activity, probably via action on β-arrestin complexes [48]. In addition, it has been reported that Li provokes a decrease in the availability of glutamate by increasing its reuptake while increasing the availability of gamma-aminobutyric acid (GABA) and the $GABA_B$ receptor expression in regions of the central nervous system [49, 50]. Through these actions, Li performs its antimanic actions [33].

Several studies have demonstrated the effects of Li on second messenger systems. The results obtained on the influence of this ion on the adenylyl cyclase pathway involve the inhibition of stimulatory (Gs) or inhibitory (Gi) G proteins, adenylate cyclase (AC), and protein kinase A (PKA) [51]. These studies indicated that Li produces a bimodal action on AC and formation of cAMP to achieve the antimanic and antidepressant effects [50, 52]. Thus, Li is shown to interfere with the neurotransmission of different monoamines (dopamine, serotonin, and noradrenaline) by affecting the cAMP signaling pathway.

Li interferes with another important signal transduction cascade, the phosphoinositide (PI) cycle. Current knowledge supports the hypothesis of Li provoking an inositol depletion, as an initial mechanism able of triggering other subsequent mechanisms. This ion inhibits inositol monophosphatase (IMPase) and inositol polyphosphate-1-phosphatase (IPPase) leading to reduction of myoinositol in the central nervous system. The inhibition of these enzymes is key to the recycling and de novo synthesis of inositol, resulting in a depletion of phosphoinositide (PI), phosphatidylinositol 4,5-bisphosphate (PIP2), and inositol 1,4,5-trisphosphate (IP3). After these facts, a decrease in calcium releasing, diacylglycerol (DAG) activation, and protein kinase C (PKC) activity have been observed [50, 53].

Li also affects several structurally similar enzymes that include the glycogen synthase kinase-3 (GSK3), enzyme that converts glucose to glycogen [54]. GSK-3 has two isoforms, α and β, which have 97% sequence homology in their catalytic domains [55]. Since there exists a high degree of similarity between the functions of these isoforms, it is possible to refer to them collectively as GSK-3. The actions of Li on GSK-3, as well as the biological effects of this kinase, make this enzyme an important target of mood disorder research. This protein is inhibited by Li in therapeutic concentrations [56], leading to multiple pharmacological effects such as regulation of gene expression, embryonic development, neuronal survival, and circadian rhythms by multiple functions on different signaling paths [57]. Li inhibits GSK-3 by two different mechanisms, a direct and fast one that competes with Mg2+ (a mechanism by which it also inhibits different phosphomonoesterases such as inositol monophosphate phosphatase (IMPase) and inositol polyphosphate 1-phosphatase (IPPase), already mentioned) and an indirect inhibition by enhancing phosphorylation of N-terminal serine residues [58, 59]. The decrease in myoinositol and the inhibition of GSK-3 might be responsible for triggering long-term events related to the prophylactic properties of Li and prevent the recurrence of new episodes [32].

The inhibition of GSK-3 causes significant changes in the Wingless-related integration site (Wnt)/β catenin pathway, involved in the guidance of the axonal cone navigation [60, 61]. Wnt signaling plays a role in structural brain processes such as neural development, synapse formation, and neuronal plasticity [62]. Thus, GSK-3 inhibition leads to an increase in cytosolic β-catenins, which are translocated to the nucleus and activate transcription factors and Wnt response genes, as well as a reduction in the phosphorylation of the microtubule-associated protein (MAP-1B) [53, 63].

Inhibition of GSK-3 has also been correlated with reduced apoptotic activity and increased expression of a neurotrophic factor [60, 64]. In addition, the activation of protein kinase B (Akt)

leads to reduction of apoptotic mechanisms, but this protein inhibits GSK-3 activity. There are some questions to be investigated to elucidate if the effect of Li on GSK3/Akt pathway [65].

## Lithium Therapies and Effects on Different Organs and Tissues

Regarding the side effects of Li therapies on the HPT axis, scientific studies have pointed out important findings. It is widely known that thyroid physiology is altered by the consumption of Li salts. The ion is accumulated in the thyroid gland at three- to fourfold higher concentrations as compared to its plasma levels. The most important clinically relevant action is the inhibition of thyroid hormone release through a variation in tubulin polymerization as well as inhibition of the action of TSH on cyclic adenosine monophosphate (cAMP). Inhibition of secretion may result in the development of thyroid autoimmunity, usually goiter, in up to 40% and hypothyroidism in about 20%, but possibly also a state of hyperthyroidism in some cases. In addition, hypothyroidism has been shown to be twice as frequent in female patients with BD, and it has been associated with a delayed response to treatment in bipolar depression [66–68].

The modifications on the HPT axis may be related to Li effects on inhibition of cAMP-mediated cellular events and its inhibitory effect on the phosphoinositol pathway, but the full mechanisms are still not clear. Moreover, Li increases thyroid hormone nuclear binding of T3 in the rat brain. It regulates thyroid receptor gene expression and it affects the cytoplasmic availability of T4 [69, 70].

Earlier studies reported abnormalities in the release of thyroid-stimulating hormone (TSH) [71]. Li therapy in psychiatric patients results in an exaggerated TSH response to TRH [72]. More recently, other researchers have shown a higher rate of TSH abnormality in patients with BD, particularly those taking Li. Moreover, thyroid dysregulation occurs more frequently in female patients. Thus, it has been proposed that the use of low normal range TSH values at follow-up can increase sensitivity in identifying hyperthyroidism in Li-treated female patients and help in preventing the development of subclinical hypothyroidism and an adverse course of illness [73]. Furthermore, hyperparathyroidism and serum calcium elevation were described as side effects of Li [74, 75].

Numerous systems can be compromised with Li therapy. One of the organs most adversely affected by Li treatment is the kidney, and the renal pathologies associated have been studied in detail [76]. These include the nephrogenic diabetes insipidus (NDI), although its mechanisms are not fully understood. A vasopressin resistance of the collecting duct has been described as a possible result of inhibition of GSK-3, impaired cAMP production, dysregulation of renal prostaglandins, altered purinergic signaling, and changes in renal architecture among others [77–79]. Some of the nephrotoxic effects can be reversed by discontinuing Li administration and if damage to the renal parenchyma is no severe [74, 78, 80].

Common acute adverse effects that are usually transient and manageable with dose reduction include gastrointestinal disturbances (nausea, dyspepsia, vomiting, loss of appetite, and diarrhea), fatigue, lethargy, polydipsia, polyuria, and a fine resting peripheral tremor [81]. Cardiovascular alterations have also been observed in adults, for instance, both atrial and ventricular electrical instability, which also normalize when Li intake is suppressed. These changes should be seen as indicators of cardiovascular susceptibility [82, 83]. Regarding dermatological lesions in the 1st weeks of treatment, the prevalence of acne and a lower percentage of cases of Li-associated psoriasis were observed [84, 85]. Cognitive function in patients receiving treatment with Li has also been the subject of some research. However, the real impact of therapeutic blood levels of Li on cognitive impairment has not yet been clarified [86].

Li treatment may also have direct effects on the hypothalamus, stimulating appetite or thirst. Thus, many patients have experienced weight gain. The mechanisms for Li-induced weight

gain remain unclear despite several speculations. It appears to exert insulin-like activity on carbohydrate metabolism, leading to increased glucose absorption in adipose tissue [5, 87].

## Lithium Therapies and Effects on the Reproductive System

Psychotropic drugs affect the regulatory mechanisms of different neuroendocrine axis, mainly of the hypothalamic-pituitary-gonadal axis (HPG) [5] and of the hypothalamic-pituitary-thyroid axis (HPT) [69]. Moreover, some studies have been carried out and confirmed the interaction of different drugs on components of hypothalamic-pituitary-adrenal axis (HPA) in patients with neuropsychiatric disorders [88].

All substances used in psychiatric pharmacotherapy entail sexual side effects, a fact which can be explained by different properties and action mechanisms of the medication. The use of psychotropic drugs is an important question that should always be discussed with the patient before a specific treatment is chosen. Besides, clinicians must be prepared to assess the risks and benefits of mood stabilizers in the context of reproductive events, including pregnancy and breastfeeding.

Although Li has been used in medicine for more than 60 years with beneficial effects, current studies show that adverse effects of Li therapies vary widely considering sex and age, as well as the presence of other pathologies that patients may suffer [89–92]. Studies in laboratory animals and in humans have consistently demonstrated the Li salts impact on the organs that integrate the HPG axis and how they may affect the reproductive behavior, reproductive processes, and gestation.

The data collected from research in animal models (preclinical studies) have demonstrated hypospermatogenesis, altered sperm motility and viability, and a decrease in sperm number in male viscachas, whereas at equal dosis, the testicular tissue and the sperm of rats were not damaged [93]. In this study, the serum Li levels introduced were within the range of human therapies. Other researchers have reported that Li can reduce testosterone levels and spermatogenesis in male rats and increase estrogen levels in female rats [94]. Moreover, Li can impair nitric oxide-mediated relaxation of cavernosal tissue [95]. Recently, it was reported that the Li-induced toxic effects on the heart and testes could be attenuated by administration of *Malva sylvestris* extract [96]. It has been reported that Li modifies the synthesis and/or secretion of gonadotrophins and gonadal hormones in rats and mice [97]. Li treatment in rats and humans decreases blood levels of gonadotrophins, prolactin, and testosterone, as well as ovarian steroidogenic, folliculogenesis, and corpus luteum development [8, 9, 98]. Similar results were found by Jana et al. [99] who observed that a cotreatment with hCG (human chorionic gonadotrophin) might decrease the adverse effects of Li medication on ovarian activity. Mirakhori et al. [100] have demonstrated that Li leads to a disappearance of the antral follicles due to variations in the expressions and activities of GSK-3 which promoted apoptosis and reduces proliferation of granulosa cells in the rat ovary. In sum, several results demonstrate that exposure of Li promotes reproductive system toxicity and reduces fertility [101].

Li treatment remains an important part of the management of many patients with BD, but the incidence of treatment-emergent sexual dysfunction with these salts is uncertain, and little is known about how it might be managed [75]. The literature reveals that the disturbances most frequently provoked by the different substances diminish sexual interest and cause ejaculatory impairment [102]. For example, 30–60% of patients treated with antidepressants are known to develop a sexual dysfunction [103]. A study on the prevalence of sexual dysfunction in patients with BD receiving Li found that approximately one third of the patients experience sexual dysfunction, and this is associated with poor medication adherence [104]. Clinical reports suggest that Li may reduce sexual thoughts and desire, worsen erectile function, and reduce sexual satisfaction [105].

Regarding central neuroendocrine tissues, such as hypothalamus and pituitary gland, it has

been shown that Li is concentrated in both, and, as a result, it may interfere with cell metabolism in other tissues [106]. As to the pituitary and its regulating function on other glands, prolactin secretion in patients with psychiatric disorders receiving Li-therapies and their likely consequences on reproductive disorders has been the subject of numerous studies. Glutamate and GABA are neurotransmitters modified by Li administration. In the pituitary gland, they are expressed in the folliculostellate cells (FSC) to regulate the secretion of growth hormone (GH), prolactin (PRL), and luteinizing hormone (LH) from endocrine cells [107]. Thus, the effects of Li salts on PRL secretion have been controversial. Kusalic and Engelsmann [11] have reported that Li produces an alteration of the HPG axis and thus an increase in PRL, LH, and testosterone (T) levels but remained within normal limits. After more than 2 years of Li therapy, values of these hormones are similar to healthy volunteers, indicating adjustment to Li action over time, as well as an absence of a cumulative effect. However, later studies have demonstrated that Li may constitute a safe option in BD patients with high risk of increased PRL, especially during long-term treatment [108–110]. Other researchers did not observe a difference in PRL levels and gonadal hormones in male and female subjects under Li treatment, suggesting that the sexual dysfunction should be interpreted independently from PRL level [6].

Most patients who used Li as a drug reported experiences of infertility, due to alterations in normal ovarian physiology [7]. Studies of reproductive endocrine function in women with BD receiving therapy with the mood stabilizer (such as Li) observed menstrual abnormalities, including amenorrhea, oligomenorrhea, and prolonged or irregular cycles [111]. However, a high rate of menstrual dysfunction prior to onset of psychiatric illness has also been reported. In contrast, some women with BD may have neuroendocrine and menstrual dysregulation due to psychiatric illness prior to the disease, increasing their susceptibility to aggravated abnormalities following psychotropic treatment [10]. Thus, further investigation should be performed to establish the potential contribution of dysregulation of the HPG axis in the clinical endophenotype of BD in women. The increased menstrual disturbances in women with affective disorders and the consequent development of an endometrial proliferative disorder have been related to the induction of DNA synthesis resulting from the inhibition of GSK-3 [112]. Thus, this induction is also associated with the possibility of developing other disorders such as hyperplasia and carcinoma [113].

Li is currently considered a first-line treatment for BD during pregnancy and postpartum, although it was associated with teratogenicity, mainly when it was used during the first trimester. The risks and benefits of Li use must be carefully assessed in pregnancy and breastfeeding [114]. Li freely crosses the placenta, and its exposure was associated with an increased risk of cardiovascular anomalies of Ebstein type [115] and others, some of which can be solved spontaneously [116, 117]. Li toxicity has also been manifested in neonates as cyanosis and lethargy [118], toxicity to the fetal thyroid and goiter [119], and nephrogenic diabetes insipidus [120].

Li-associated perinatal complications have been observed [121, 122], but no cases of infant death have been reported in association with late pregnancy Li exposure [123]. There is limited data on the long-term effects of exposure to Li in utero. The neurodevelopment and behavior were normal when the children were evaluated at ages 3–15 [124]. The Li dose should be readjusted and controlled throughout pregnancy due to the risk of dehydration and other complications such as preeclampsia [125]. While there is consensus on the teratogenic and toxic risk of using Li during pregnancy and breastfeeding, there remains a diversity of views as to whether or not the benefits outweigh the risks. The risk of congenital abnormalities with Li use is estimated to be 1 in 1000, while the risk of a recurrent episode of bipolar illness during pregnancy if Li is discontinued in the first trimester is 1 in 2 [126]. Other studies suggest that the risk of side effects from Li during pregnancy is lower than it was previously believed, and the risk of teratogenicity and fetal toxicity can be minimized, but not completely eliminated [127].

## Perspectives for Future Research

Li is a drug which has been used for decades in psychiatric diseases. At present there are no other drugs to completely and confidently replace it in psychiatric medicine. However, future studies on Li should address a number of unresolved issues such as the adverse effects of treatment on different human body systems. Recently, it has been observed that Li produces changes in hippocampal cell proliferation, at least in part, by protein kinase C (PKC) inhibition. A rapid cell proliferation increase in the dentate gyrus is a common feature of Li and other drugs, to achieve reduction of manic behavior [128]. In addition, the potential use of Li in acute brain injury and chronic neurodegenerative diseases makes it even more interesting to the medical field and thus potentially extends its usefulness in clinical medicine for the future [76].

In recent years, surprising Li neurotrophic and neuroprotective effects have been described. The neurotrophic effects are related to strategies intended to augment cell proliferation, differentiation, growth, and regeneration. The neuroprotective effects are defined as those that halt or slow the progression of neuronal atrophy or cell death following the onset of disease [129].

Several studies have been performed on Li efficacy as a novel therapeutic in various disease models. It is a neuroprotective agent for the treatment of acute brain injury (e.g., glutamate-induced excitotoxicity, ischemia-induced neuronal damage) as well as chronic neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's [130–132]. Li was used in preclinical research for inhibition of GSK-3 which is one of the key components in apoptosis signaling. It might increase cell survival by inducing brain-derived neurotrophic factor and thereby stimulating the activity of antiapoptotic pathways and upregulation of Bcl-2 protein. Thus, beyond its current clinical use in BD, the neuroprotective ability of Li implies that it could be used to treat or prevent brain damage following acute injury or chronic neurodegenerative diseases [64].

It has been demonstrated that at clinical dose of Li, treatment improves axon regeneration and promotes locomotor functional recovery in rats [133]. Li has also been reported to be capable of inhibiting apoptosis of neural progenitor cells [134], exerting neuroprotective effects against various insults, and promoting proliferation and differentiation of neural stem cells [133, 135].

Li promotes proliferation and neural differentiation of mesenchymal stem cells in vitro, enhances cell survival and differentiation of these cells into more oligodendrocytes, astrocytes, and neurons, and promotes neural regeneration in rat spinal cord. These data suggested that Li could be a potential drug to increase the therapeutic efficiency of mesenchymal stem cells transplantation therapy in central nervous system disorders [136].

However, other researchers have described a mechanism underlying Li action, which was not related to the inhibition of GSK-3 activity [137]. Indeed, Li modulates signals impacting on the cytoskeleton at multiple levels, including signals from GSK-3b, cyclic AMP-dependent kinase, and PKC. These actions may be critical for the neural plasticity involved in mood recovery and stabilization [52].

Breast cancer is one of the most prevalent types of cancer among women, and it was reported to occur with higher rate in women with BD. Lithium chloride (LiCl) was indicated to decrease the radioresistance of a breast cancer cell line by decreasing DNA repair through a GSK-3β and β-catenin pathway [138]. These authors propose that this salt might be used in combination with radiotherapy for eradicating breast tumors.

The treatment with Li salts has been shown to be effective in in vitro studies in multiple cancer types, though in vivo studies are limited. Lubner et al. [139] have performed a phase II trial of LiCl in neuroendocrine tumors but failed to demonstrate a convincing clinical response. Different results may be due to the supraphysiologic doses used in preclinical studies. Different types of GSK-3 inhibitors including Li show promising results in suppressing tumor growth in different animal models of prostate cancer. It is important to highlight that clinical use of Li is associated

with reduced cancer incidence in psychiatric patients. Taken together, GSK-3 inhibition might be implicated in prostate cancer management as a preventive treatment. Besides, Li promotes apoptosis in human leukemia NB4 cells by increasing the level of Ser9-phosphorylated glycogen synthase kinase 3β(p-GSK-3β) and decreasing the level of Akt1 protein in a dose-dependent manner [140]. Novetsky et al. [141] have demonstrated in vitro that LiCl and cytotoxic agents at physiologically achievable drug concentrations reduces ovarian cancer cell metabolism but does not appear to affect cellular proliferation. More recently, a study demonstrated that Li had no significant effects on tumor growth in vitro and in vivo; in contrast, it may inhibit lymphangiogenesis in tumors. In addition, Li inhibited colon cancer metastasis by blocking the transforming growth factor-β-induced protein (TGFBIp) expression and thereby TGFBIp-induced lymphangiogenesis, in primary tumors [142].

Thus, it is worth emphasizing that the use of Li salts in affective disorders has presented important and conclusive results throughout history, despite the adverse effects that it produces. It is necessary to carry out careful evaluations and follow-ups in patients treated with Li in order to prevent the appearance of other pathologies associated with long-term therapies. The development of further preclinical research is fundamental because there are still many questions to be elucidated and new actions or effects of this ion are continuously discovered.

Finally, human and laboratory animal studies are also necessary in order to arrive at conclusive results in different aspects of Li's mechanisms of action that interfere in the functioning of the hypothalamic-pituitary-gonadal axis, altering possibly the human reproduction.

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# 17 The Role of Interneurons in Cognitive Impairment in Schizophrenia

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## Introduction

Learning and memory are considered high-order executive functions that the brain performs in order to generate the most appropriate behavior. The mechanisms of learning and memory are still under research, and unraveling the molecular and cellular components could foster a better understanding of the pathophysiology of neurological and neuropsychiatric disorders that present cognitive alterations. Deficits in cognitive control are core features of schizophrenia, which appear to emerge from impaired inhibitory signaling [1, 2]. Disturbances in GABAergic interneurons, like reduced expression of parvalbumin and glutamic acid decarboxylase 67, in postmortem brains of schizophrenic patients represent a major hallmark of the disease [3–5]. Therefore, perturbed excitatory/inhibitory balance results in cognitive impairment, suggesting that interneurons could be key regulators of cognitive processes.

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GABAergic interneurons account for approximately 20% of all neuronal cells in the brain and display multiple phenotypes. However, different classification criteria do not correspond completely, and some features overlap. This has resulted in a lack of proper classification criteria that has hampered the study of the role of interneurons in learning and memory [6]. It seems that the rich diversity of interneurons renders the brain with an extensive computational power thereby enabling interneurons to carry out multiple tasks [6]. Interneurons are crucial for regulating the complex interaction between principal cells for network operations. However, they not only maintain a matched inhibitory input to prevent runaway excitation. Interneurons are also involved in complex network processes, such as response selectivity, gain control, shaping spatiotemporal firing patterns of excitatory cells, and generating brain oscillations [7]. In healthy brains, all of these actions are dynamically regulated to appropriately respond to external demands.

Increasing body of evidence suggests that experience-dependent modification of neural circuits depends on alterations in synaptic efficacy. It dates back to 1964 when Young highlighted for the first time the relevance of inhibition/disinhibition interplay for learning and memory formation [8]. However, the exact molecular mechanisms that contribute to plastic changes remain largely unknown, and we are just



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beginning to understand the role of interneuron-driven inhibition for learning and memory and its importance during development and adult behavior. With the advent of sophisticated technology, it is possible to identify and manipulate genetically defined cell types. Using these technologies, it has been observed that interneurons regulate diverse forms of plasticity and might be key regulators of learning and memory processes.

This chapter briefly summarizes the microcircuit and network functions that interneurons accomplish, as well as the current knowledge supporting the notion that interneurons might be engaged in different stages of learning and memory processes. Therefore, interneurons might be the cellular substrates for therapeutic intervention for cognitive impairment in schizophrenia.

## Coordinated Brain Inhibition as the Substrate for Network Operations

Balancing excitatory drive by exerting proper inhibition is critical for the stability of neural networks. At its most basic level, inhibition exerted by interneurons serves to avoid uncontrolled excitation on principal cells [9]. However, basic microcircuit functions (i.e., feedforward and feedback inhibition) represent the building block to support more complex computations, such as orchestrating the action of multiple principal cells for spatiotemporal precision of firing patterns, generating response selectivity, gain control, providing salience of sensory input, or inducing network oscillations [7, 10–14].

## Basic Microcircuit Function

Feedforward inhibition narrows the coincidence detection window of excitatory inputs in pyramidal neurons. Afferent glutamatergic cells synapse with principal cells and GABAergic cells in parallel [10] (Fig. 17.1). If the increase in inhibitory conductance and principal cell deporalization are not simultaneous, a transient excitatory/inhibitory imbalance will lead to excitatory postsynaptic potentials (EPSPs) in principal cells before inhibition takes over. This imbalance lasts on the timescale of milliseconds. Contrarily, if the inhibitory input arrives before glutamatergic-induced pyramidal cell depolarization, feedforward inhibition will maintain membrane potential below threshold and prevent excitatory cells from firing any action potential. Consequently, interneurons are able to shorten the temporal summation of EPSPs in principal neurons but also regulate the timing of action potential generation.

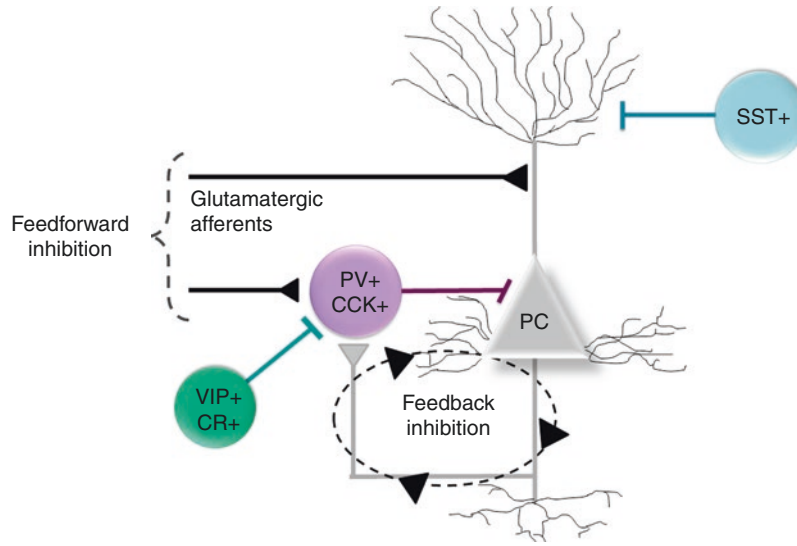


**Fig. 17.1** Basic microcircuit function. Feedforward inhibition: afferent glutamatergic inputs target interneurons and pyramidal cells in parallel. Feedback inhibition: excitatory inputs from principal cells regulate the inhibition exerted by interneurons. CCK cholecystokinin, CR calretinin, PC principal cell, PV parvalbumin, SST somatostatin, VIP vasointestinal peptide

Interneurons that exert perisomatic inhibition on principal cells are a major source of feedforward inhibition. In the neocortex and hippocampus, parvalbumin-positive (PV+) and cholecystokinin-positive (CCK+) basket cells constitute the primary interneuron populations that target perisomatic domains [15, 16]. Nevertheless, some hippocampal GABAergic cells appear to be specialized in feedforward signaling, which mainly signal inhibition to dendritic shafts [17–19]. As a result, feedforward inhibition might control the output signals of excitatory cells or might reduce dendritic spikes, depending on the pyramidal cell domain the interneurons contact with.

The abovementioned PV+ and CCK+ basket cells also participate in the generation of feedback or recurrent inhibitory loops (Fig. 17.1). PV-expressing axo-axonic chandelier cells, similar to PV+ basket cells, display fast-spiking properties and are involved in feedback inhibition. In LII/III of the neocortex, another subtype of interneurons expressing somatostatin (SST), namely, Martinotti cells, target the apical dendrites of principal cells and contributes to feedback inhibition. In the hippocampus, there is a population of interneurons analogous to neocortical Martinotti cells, whose soma is located in *stratum oriens,* and send axons to *stratum lacunosum-moleculare* (OLM, *oriens lacunosum-moleculare* cells). Hilar perforant path-associated cells (HIPP cells) are equivalents to OLM but in dentate gyrus. In feedback inhibitory mechanism, the activation of pyramidal cells recruits the postsynaptic inhibitory neurons, whose discharge would in turn prevent further action potential firing of principal cells [20].

Each PV+ interneuron is able to form synapses with thousands of pyramidal cells, and a single pyramidal cell can receive inhibitory input from several perisomatic-targeting basket cells. Consequently, PV+ basket cells are crucially positioned to decide if the output of the target neuron occurs, and this is of particular interest for synchronizing the firing rate of principal cells [21]. On the other hand, as SST+ interneurons target apical dendrites of pyramidal cells distally, they gate or sculpt the inputs arriving onto dendritic spines. PV- and SST-expressing interneuron-mediated inhibition is complementary. Early inhibition is carried out by perisomatic-targeting fast-spiking cells, which are sensitive and respond rapidly to the stimulus in timescale of milliseconds. Nevertheless, during sustained sensory input, the inhibition exerted by PV+ interneurons decreases. SST+ interneuron-mediated inhibition will then take over, as the onset of their inhibitory impact is slower and is said to be involved in late inhibition [11].

Besides, some types of interneurons make synaptic contacts exclusively with other interneurons, the so-called interneuron-specific interneurons. These interneurons usually express the calcium-binding protein calretinin and/or the vasointestinal peptide (VIP) [22, 23] (Fig. 17.1). In medial prefrontal cortex (mPFC), they usually target SST+ and PV+ interneurons [23], whereas in the hippocampus, they predominantly contact with CB+ interneurons and other CR-expressing interneurons [22, 24], presumably those that co-express somatostatin [22, 24, 25]. Moreover, a specific subtype of SST-expressing interneurons in layer IV seems to preferentially contact PV+ interneurons locally [26]. Those SST+ interneurons are different from Martinotti interneurons, which are primarily located in layer II/III and send projections to apical dendrites of pyramidal cells in layer I [26]. In fact, layer IV SST+ interneurons are X94-like cells and have quasi-FS properties. Interneuron-selective interneurons send GABAergic inputs onto other interneurons to regulate their membrane potential, control synaptic efficacy, and consequently determine the occurrence of plastic changes.

## Complex Operations

Basic microcircuit operations of feedforward and feedback inhibition support more complex computations to allow stable tuning and dynamic shifts of the network (Fig. 17.2). These two main properties driven by interneurons are basic fundaments for appropriate sensory perception and experience-dependent learning. For example, interneurons of visual cortex are essential for

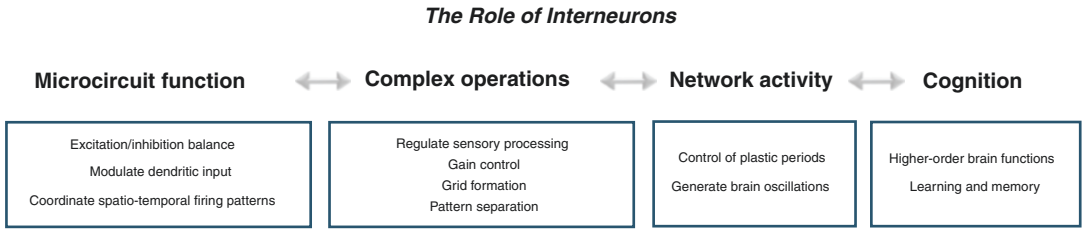


**Fig. 17.2** The role of interneurons in basic microcircuit function that lay the foundation for complex operations and network activity for proper cognitive functions

response selectivity and dynamically regulate the sensitivity to process specific inputs to boost discrimination. Stimulation of PV+ interneurons in primary visual cortex increases orientation and direction selectivity and improves perceptual discrimination [27]. Their activity is also important for recognition of familiar stimuli [28]. SST+ interneurons in supragranular layer of visual cortex contribute to the surround suppression, a basic operation that is needed for size tuning [29], curvature detection, and orientation discrimination [30]. Moreover, the SST+ interneurons contribute to the amplification of deviant stimulus in visual mismatch negativity task, reflecting their relevance in proper sensory processing [31]. There is substantial evidence for dysfunction of sensory processing systems in schizophrenia, including visual processing deficits [32, 33]. Although there is a lack of studies investigating the number of interneurons in the visual cortex of schizophrenic patients, GABA levels are found to be reduced and correlate with altered visual processing [34]. Animal studies further support the notion that visual dysfunction of schizophrenia is related to altered function of interneurons in visual cortex [31].

Interneurons also modulate the gain of sensory responses. They keep the amplitude of output signals of principal cells in certain boundaries despite drastic environmental changes. Large changes in the input that result in small changes in the firing output of neurons provide a broad range of stimulus intensities that can be encoded in a narrow range of firing rates. Gain control is mostly carried out by perisomatic connections of PV+ interneurons and is primarily concerned with controlling the dynamic range of neural responses [35]. Gain control studies in schizophrenia have been mainly carried out in the visual system and clearly show that patients have difficulties in adapting and optimizing their neuronal responses to stimuli within a particular surrounding context [32]. These difficulties are mainly associated to low-contrast stimuli and motion processing and have been related to higher-level problems in perceptual organization [32].

More recently, optogenetic manipulations have demonstrated the relevance of inhibitory cells in hippocampal functions. One of the main characteristics of the hippocampus is its ability to encode the external environment. Place-, grid-, and head-direction cells are devoted to integrate spatial information, but their mechanisms to encode spatial representations are still unclear. In this respect, the involvement of interneurons has been intensively investigated. Optogenetic manipulations have shown that PV+ and SST+ differentially suppress the firing rate of place fields, suggesting that inhibitory cells regulate the shape of place and grid fields [36]. Moreover, feedback inhibition is the mechanism implicated in grid formation [37] and in grid-to-place switch [38]. Recurrent inhibition has also been suggested to be engaged in pattern separation – the ability to distinguish overlapping input patterns [39]. Likewise, in medial entorhinal cortex, PV+ interneurons modulate the firing rate of grid- and head-direction cells [40]. According to the work of Mesbah-Oskui and colleagues [41], mice with a schizophrenia-like endophenotype exhibited simplification of the ensemble place codes for individual locations and consequently presented impaired encoding of spatial location in the hippocampus, which might explain poorer navigation skills of schizophrenic subjects [42].

These results indicate that inhibitions carried out by different types of interneurons are crucial for proper sensory processing and participate in diverse computations related to cognitive functions that are altered in schizophrenia.

## Network Oscillations

Brain oscillations are patterned rhythmic activity in the range of 0.05–500 Hz often measured extracellularly with local field potentials. Coupling of inhibitory neural network to principal cells generates synchronous activity that is well characterized in the hippocampus and neocortex. Although the computational value of brain oscillation is still unclear, the synchrony of neural activity generated by recurrent activation of feedback loops is crucial for network operations, as it temporarily organizes cortical activity for efficient transmission of information.

Rhythmic activity in different frequencies is correlated with distinct behaviors. For example, theta frequency (4–12 Hz) occurs with exploration and navigation [43]. Gamma (40–100 Hz) oscillations arise during perception, sensory association and working memory [44–46], and segment information in different phases of their cycle, so items are coded and separated in sequence. Sharp-wave ripples (140–200 Hz) are irregular bursts of high frequency that are believed to be necessary for information consolidation and transfer. Different concomitant oscillations might occur at the same time. In those cases, low-frequency oscillations govern high-frequency oscillations. This phenomenon is termed as cross-frequency coupling. It was first described between theta (4–9 Hz) and gamma (30–90 Hz) oscillations, but later a relationship was also found between gamma oscillations and sharp-wave ripples [47]. There is a growing recognition that neuronal oscillations are important in learning, memory, and attentional processes and interneurons play a key role in the generation of these oscillations. Parvalbumin-expressing fast-spiking interneurons of the hippocampus participate in theta, gamma, and ripple activity [13, 48], whereas OLM and HIPP cells of the hippocampus mainly contribute to theta oscillation generation [13].

Reduction in gamma oscillation power and synchronization has been found in schizophrenic patients that are independent of medication [49]. More precisely, schizophrenic patients show reduced power in gamma oscillation in auditory cortex after a train of clicks [50] and in visual cortex when the scenery needs a perceptual organization [51]. Similarly, schizophrenic individuals failed to identify stimuli related to emotional perception, like determining emotions in faces, and these findings were correlated with poor gamma oscillations [52]. Furthermore, during working memory tasks, gamma oscillations increased in healthy individuals, but a neural oscillation abnormality in this frequency in frontal lobe was found in schizophrenic patients [53]. Gamma oscillations have been extensively correlated with information transfer across multiple brain regions to provide a "whole value" to the combination of different parts of the same. This coincides with the "dysconnectivity hypothesis" of schizophrenia, in which a lack of proper communication between brain regions is believed to underlie cognitive impairment. Nevertheless, theta oscillations also allow binding and processing of information and occur simultaneously to gamma oscillations and modulate this band [54]. Thereby, gamma oscillation abnormalities in schizophrenia could emerge from alterations in background oscillations of lower frequencies. On the other hand, hippocampal sharp-wave ripples have been termed as cognitive biomarkers for episodic memory and planning [55]. Studies from basic research support the view of altered ripples in animal models of schizophrenia that can contribute to cognitive impairment [56].

While the implications of neural oscillations and cross-frequency interactions to cognitive abnormalities of schizophrenia are open to debate, it is undeniable that inhibitory interneurons constitute an essential substrate for oscillatory synchronization and therefore their dysfunction might be directly responsible for the abnormalities in brain oscillations found in schizophrenia.

## Inhibitory Drive for Learning and Memory Processes

Up to date, little is known about the role of activity-dependent circuit refinement for learning and memory. The functional consequences of inhibitory synaptic modifications strongly vary depending on the network activity that each particular interneuron accomplishes. Bridging the gap between synaptic plasticity with learning and memory remains a central challenge in neuroscience. With the advent of high-spatial and temporal-resolution technologies, like optogenetics, it is possible to selectively activate and silence identified types of interneurons. and examine their role in learning and memory processes.

## Interneurons Are Crucial for Normal Cognitive Behavior

There is extensive research documenting the implication of interneurons in learning and memory, although each subtype is differently involved depending on the brain region and the task. Despite the wide diversity of interneurons, PV- and SST-expressing interneurons have been the most intensively studied ones. Interestingly, both subtypes of interneurons are the most affected in schizophrenia [3, 57], so dissecting their role in learning and memory processes could be a major advance for understanding the cognitive dysfunction of schizophrenia.

Perturbations in inhibitory neurotransmission mediated by PV+ interneurons have been implicated in memory impairment. For instance, genetic ablation of cyclin-dependent kinase 5 from PV interneurons leads to hyperinhibition, decreases amygdala-dependent contextual and cued fear memory, and impairs spatial reference memory in Morris water maze [57]. In addition, PV-expressing FS interneurons of medial prefrontal cortex play an essential role in goal-directed behavior, working memory, and cognitive flexibility [58], and their inactivation by optogenetics deteriorates the attentional processing that is required for the acquisition of new information [59]. As demonstrated by functional deactivation of PV+ cells in CA1, these interneurons are required for spatial working but not for reference memory [60]. In addition, knockout mice that have M1 muscarinic acetylcholine receptor genetically deleted from PV+ interneurons exhibit impaired recognition memory and, to a lesser extent, decreased spatial working memory [61]. On the other hand, mutant mice lacking NMDA receptor-mediated neurotransmission in PV+ interneurons show selective cognitive impairments, namely, deficits in working memory and associative learning [62]. Most of these animal models have been used to replicate core features of schizophrenia, pointing to the specific role of PV+ interneurons in cognitive deficits.

Along with parvalbumin deficits, a reduction in somatostatin mRNA and protein levels is consistently observed in postmortem brain of schizophrenic patients [5, 63, 64]. Somatostatin (SST) is a neuropeptide that is released from dense-core vesicles from both axons and dendrites [65] upon repetitive afferent high-frequency firing [66]. The cellular and synaptic effects of somatostatin are fairly well understood, but less is known about the behavioral and cognitive effects [67, 68]. Somatostatin appears to play a role in learning and memory, as KO mice for SST receptor display spatial learning deficits [69–71]. In addition, in aged humans and rats, less SST is found in the cortex, and this correlates with learning alterations in rodents [72]. Moreover, intrahippocampal or intraventricular injections of SST ameliorate spatial learning in different tasks [73, 74]. Functional deactivation of specific interneuron populations has demonstrated the role of SST-expressing interneurons of dentate gyrus in spatial working memory and reference memory precision [75]. In contrast, optogenetic inhibition of hilar interneurons, which are mostly SST+, also disrupted spatial learning and memory retrieval in the Morris water maze, without affecting short-term working memory, motor coordination or exploratory activity [76].

However, different interneuron subtypes are not isolated from one another but rather connected at circuit-level function. Few studies have

addressed the possible interplay between different types of interneurons' high-order cognitive functions. PV-expressing fast-spiking interneurons of medial prefrontal cortex drive goal-directed behavior, but SST+ neurons also contribute. During rewarded working memory task, each subtype of interneuron shows opposite target-dependent delay-period activity [77]. In anterior cingulate cortex, they participate in different phases of rewarded tasks. According to the results of Kvitsiani et al. [78], while SST+ interneurons were activated when approaching to the rewarded area, PV+ interneurons responded at reward leaving and encoded preceded stay duration.

Even though this is a non-exhaustive list of studies, these observations provide evidence for the critical role of interneurons for the expression of normal cognitive behavior and support the notion that the function of different interneuron subtypes is divided spatiotemporally to play complementary roles for appropriate cortical circuit dynamics underlying cognition. Therefore, one intriguing possibility is that the alteration in the expression of PV- and SST-expressing interneurons might be directly implicated in the pathophysiology of cognitive dysfunction in schizophrenia.

## Opposite Regulation of Inhibitory Drive for Acquisition and Consolidation of Memories

Several lines of evidence suggest that the interplay between excitation and inhibition plays a major role in learning and memory formation. Concretely, a transient and specific disinhibition seems to be causally involved in learning-related plasticity. The first evidence highlighted that the basal activity of SST+ interneurons was reduced during movement and active sensation [79]. In recent years, pharmacological and optogenetic stimulations of PV+ interneurons have shown that their activity impairs auditory fear learning [80]. Based on these evidence, some authors have proposed that disinhibition might be a general mechanism that favors synaptic plasticity and learning [81]. In fact, Gambino and Holtmaat [82] directly demonstrated that disinhibition promoted LTP facilitation in somatosensory cortex. Further evidence supporting this hypothesis is that a transient reduction of PV+ interneuron-mediated inhibition or the removal of perineuronal nets from these cells reopens the critical period of visual cortex for ocular dominance plasticity [83]. Against this background, feedforward activation of PV+ interneurons in the amygdala is necessary for fear learning [84]. Similarly, L4 SST-expressing neurons of barrel cortex increase in number during the training period of classical conditioning [85]. However, in those cases, the effect of interneuron activation on the network could lead to the same outcome: the disinhibition of pyramidal cells. Since PV+ interneurons of the amygdala seem to silence SST+ interneurons and L4 SST+ interneurons are probably part of the disinhibitory circuit targeting PV+ interneurons, their activation would unequivocally result in pyramidal neuron firing. In line with these, GABAergic projections from ventral tegmental area halt the spontaneous activity of accumbal cholinergic interneurons to enhance associative learning [86]. Taken together, these results show that disinhibition gates plastic changes during learning, with high specificity, by actively shaping synaptic integration, probably by enabling high-frequency firing of action potentials that are important for inducing experience-dependent synaptic plasticity [87, 88].

Recent observations have led to speculate that increased inhibition may play a role in circuit plasticity after learning completion. The dendritic inhibition mediated by SST+ *oriens lacunosum-moleculare* (OLM) cells of *cornus ammonis* 1 (CA1) is crucial for contextual fear memory formation [89]. Moreover, following associative learning, there is an increase in GABAergic signaling, demonstrated by augmented presynaptic GABA concentrations, upregulation of $GABA_A$ receptor subunit α1 in postsynaptic sites, and increased frequency of spontaneous inhibitory postsynaptic currents [90, 91]. SST interneurons also express more GABA and somatostatin after associative learning [85].

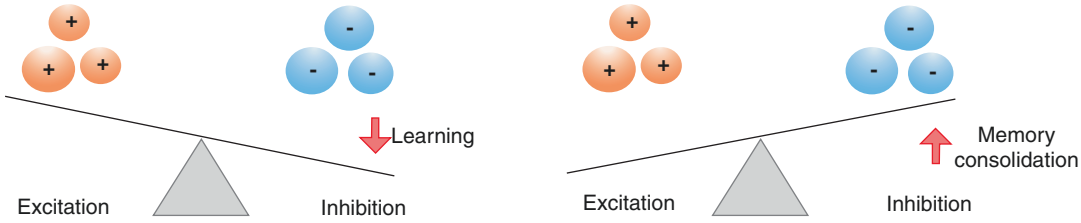


**Fig. 17.3** Excitation/inhibition balance for learning and memory processes. The level of inhibitory tone determines the occurrence of learning-related plastic changes and memory formation. While disinhibition may act as a general mechanism for learning, rule consolidation requires relatively high inhibitory configuration

In the last couple of years, few studies have stated that different subsets of PV+ interneurons might engage in distinct phases of learning and memory processes. According to these experiments, distinct subpopulations of the same interneuron cell type could respond with high specificity to different tasks, suggesting that the inhibitory drive carried out by each interneuron subtype could be further compartmentalized to augment the computational power of the brain. For instance, Donato et al. [92] found that late-born PV+ basket cells were involved in the acquisition of new tasks, whereas plastic changes at early-born PV+ basket cells occurred upon the consolidation of rules. Inhibition exerted by VIP+ interneuron-specific interneurons onto late-born PV+ neurons played a central role in learning-related synaptic plasticity [92]. In line with this, pharmacological inhibition of PV+ interneurons enhanced structural synaptic plasticity, and a similar trend was seen in the training period of maze navigation tasks or when faced to environmental enrichment. On the other hand, activation of PV+ interneurons promoted the consolidation of validated rules [93]. Later, Lagler and co-workers [94] showed that PV-expressing basket cells were recruited into different neuronal ensembles with different firing patterns in a memory-guided choice behavior, suggesting task-associated specialization within a single cell type.

These findings add to a growing body of literature our understanding of the contribution of excitation/inhibition balance to learning and memory. There are compelling evidence indicating that disinhibition enhances excitatory neurotransmission and may act as a general mechanism for learning. On the other hand, rule consolidation requires relatively high inhibitory configuration, [92, 95] raising the possibility that the level of inhibitory tone determines the occurrence of learning-related plastic changes and memory formation (Fig. 17.3). These data indicate that exquisitely coordinated brain inhibition is essential for proper acquisition and storage of information and any perturbation in this balance can be detrimental for cognitive functions.

## Conclusion and Remarks

Interneurons are no longer considered passive bystanders of cortical circuits. Interneuron-driven inhibition lays the foundation for the generation of complex operations that allow appropriate sensory processing, integration, and high-order computations. Nonetheless, a comprehensive understanding of the functional role of inhibition in activity-dependent circuit refinement for learning and memory remains a central challenge in neuroscience. Although it is clear that disinhibition carried out by interneurons plays an important role in experience-dependent learning, it would be necessary to determine if different forms of disinhibition exist depending on interneuron cell type and their subcellular afferent projections and how this is related to computations in projection neurons.

The major cellular hallmark of postmortem brains of schizophrenic patients is the loss of interneuron markers. Cognitive impairment has been attributed to the reduction in inhibitory tone. However, the direct implication of interneurons in cognitive functions has remained somewhat elusive. With the advent of cutting-edge technol-

ogy, we are beginning to understand the relevance of interneurons for sensory processing and normal cognitive behavior. In this chapter, we have reviewed the current evidence regarding interneuron-driven inhibition and its relationship to learning and memory processes. Still, the daunting task of elucidating neural mechanisms of interneuron-mediated complex computations and the interaction of experience in their networks will require several years.

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# 18

# Animal Models of Depression: Validation Criteria and Relevance in Translational Experimental Neurobiology

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*Nature is not only all that is visible to the eye… It also includes the inner pictures of the soul.*

Edvard Munch (1863–1944)

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## Introduction

As an introduction, from the point of view of phenomenology, depression is a heterogeneous pathology, clinically defined as a complex entity which encompasses an important psychological symptomatology, as well as a neuroendocrine corporal dimension. However, a heterogeneity is manifested by the existence of nearly 30% of patients' refractory to conventional treatments [1]. It is also worth considering that this resulting clinical complexity is evidenced by the challenges to be faced as regards the poorly understood neurobiology of this psychiatric disorder, its biomarkers, and its corresponding investigation through experimental models. A translational framework in medical sciences is crucial in terms of overcoming those difficulties, taking into account that it is necessary to bridge the preexisting gaps between the data acquired through basic experimental animal research and the therapeutics of the disease [2]. Therefore, it implies the development of criteria and analytical tools for assessing the application of empirical results



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as well as theoretical conclusions in clinical practice. Correspondingly, it is conventionally agreed that numerous animal models of depression are required for understanding several and different aspects of the disease and for providing convergent evidence of the research findings [3]. Assuming a constructive approach regarding animal models and being concerned about improving methodological aspects rather than discussing philosophical argumentations [2], the present chapter is the first part of a two-chapter series which proposes a classification of animal models of depression by first analyzing their general framework and validation criteria as a way to understand the most relevant paradigms currently accepted.

Following these concerns, a model might be explained in terms of a particular induced state in a nonhuman species which aims at replicating specific human pathological features – including human psychopathology – presenting predictive validity [4]. As a matter of fact, an animal model consists of an independent variable, i.e., the experimental manipulations applied to induce an altered condition and a dependent measure, which is applied to assess the effects of the manipulation [3]. In fact, a test, as a concept categorically different from that of a model, provides only an endpoint, that is to say, a behavioral or physiological measure (readout) designed to assess the effect of a genetic, pharmacological, or environmental manipulation [4].

Furthermore, following the present theory of depression diathesis [1], an animal model is not to be simply reduced to the application of certain pharmacological agents within a specific period of time [2]. Actually, the design of a model fundamentally consists of a comparison between pathological organisms [5], imitating the etiological process of transformation from a healthy organism to a pathological organism through a vulnerability state in time. A present general framework of animal studies takes into consideration the fact that epigenetic mechanisms transform a healthy organism into a vulnerable one. From a genetic perspective, the initial organism might be either vulnerable or non-vulnerable. Next, during adulthood, the presence of specific triggering factors transforms the vulnerable organism into a pathological one. To summarize, three states define the process of transformation from a healthy organism to an adult pathological one, taking into account a vulnerability status related to epigenetic alterations. They are genetic, epigenetic, and triggering factors. The third and final state is to be considered notably contrasting in relation to the first one, bearing in mind that the important divergences between them explain the mechanisms underlying the disease. The pathological symptomatology is presented in the form of behavioral symptoms and biological markers. At this point, the action of a therapeutic agent diminishes the pathological effects, reversing the transformation process back to a vulnerable status [2].

Concerning animal models of depression, it is essential to take into consideration the specific purpose of a model, acknowledging that the intended purpose of a model determines the validation criteria necessary for establishing its relevance and utility in basic experimental research [3]. The validation of a model indicates at what level a model is useful for a particular purpose [3]. Then, added to that, validation criteria are general standards relevant for evaluating any animal model [3]. It is worth mentioning that the main purpose of a model is to understand a human phenomenon, which means, in other words, to deepen our knowledge about the underlying neurobiological mechanisms of a specific disease [3]. Next, the aim of mimicking a human condition diverges into two extremes serving, respectively, for two opposite purposes: modeling a disorder in its entirety or modeling a particular dimension of the disorder [2, 3]. The former requires establishing a homology between the pathology and the induced condition as regards signs and symptoms for determining the experimental manipulation to be applied, which implies the reproduction of multiple interdependent variables. The latter refers to pharmacological isomorphism, defined as a systematic concept for evaluating the effects of potential therapeutic treatments. It is possible to target a particular symptom of the disease as long as it is independent from other symptoms of the same condition [2]. As a matter of fact, limiting the spectrum of a purpose increases the reliability of a model.

Consequently, the confidence in the cross-species homology between the model and a human pathology is heightened [3].

In order to be considered relevant and useful for human pathology, a model of human psychopathology must satisfy a multidimensional series of criteria [2]. As mentioned before, a purpose determines the external validation criteria for evaluating the methods and procedures through which the understanding of a specific human phenomenon might be achieved. Accordingly, depending on the intended particular purpose that a model or test intends to validate, different types of criteria are to be applied [3]. The actual notion of scientific understanding is reflected by the determination of the applicability – through its validation criteria – of a model as a tool for measuring aspects of a disease. In relation to this, the process of validating an experimental model is crucial for the development and establishment of new scientific theories [3]. Since a phenomenon is defined by its correlations with its antecedent and its consequent phenomenon, the only valid scientific observations are correlations [3]. It follows that scientific understanding is the ability to predict, and, therefore, the most important criterion for evaluating an animal model is its capacity for elaborating precise predictions [3].

The ideal animal model should offer an opportunity to understand molecular, genetic, and epigenetic factors that may lead to depression. Nevertheless, regarding the issue of developing and validating animal models of human psychopathology, it is prudent to mention that depression cannot be reproduced in nonhuman animals like rodents [6], because they cannot observe feelings of sadness, guilt, or suicidal thoughts, subjective verbal symptoms mainly limited to humans. The question therefore remains whether we can know if a mouse is "depressed." Only specific measurable behaviors – endophenotypes – can be considered for a model to be relevant for studying human depression. In reality, few models of depression fully fit these validating criteria, and most models currently used rely on either the actions of known antidepressants or responses to stress. Notably, it is not necessary for an "ideal" animal model of depression to exhibit all of the abnormalities of depression-relevant behaviors, just as the patients do not manifest every possible symptom of depression. In fact, anhedonia is the core symptom of depression, and most of the current models only mimic anhedonia.

The next stage, after an introductory conceptual context about validation criteria has been developed above, is to prudently begin with the challenging task of defining them particularly. In the first place, an animal model meets validity as far as it is similar to a human disease. Actually, the numerous aspects of this similarity ought to be determined autonomously [2]. Although the classic criteria – as mainly described by Paul Willner –will be still considered as the axis of the validation analysis, a new proposal by Catherine Belzung and Maël Lemoine is to be introduced in the concepts to come. This more recent approach aims at an integration of Willner's criteria into the general framework of depression diathesis. As a consequence, it is important to anticipate and acknowledge that there will be constant comparative references as regards terminological differences between Willner and the new approach. The evolution of the classical validation criteria is also described taking into account the classification proposed by Mark Geyer and Athina Markou.

The criterion of predictive validity as a concept has undergone specific variations in its extension through years. An evolution of the concept is clearly seen in Willner's publications. He began with an emphasis on pharmacological correlation without observing any attempts to translate aspects of the human pathology to animals. Later, he extended the concept by indicating that a model must respond positively to all available treatments for depression. It implies the inclusion of electroconvulsive therapy, in order that its predictive validity be established. In the latter, a human-animal correlation can be observed in terms of therapeutic outcomes. Following other authors, it can be affirmed that this criterion is assumed in a broader sense, encompassing the capacity of a model to predict specific markers for a disease. According to Geyer and Markou, predictive validity enables the formulation of predictions about a human phenomenon based on the performance of a model. In this case, clearly,

the concept is not limited exclusively to the ability to predict the effectiveness of a particular treatment.

In a stricter sense, when it comes to models of human psychopathology, the criterion of predictive validity must be accepted in terms of pharmacological isomorphism [1–3]. It implies the ability of a model to identify drugs with potential therapeutic value for human beings. Consequently, a valid model of depression should respond positively to effective antidepressant treatments in behaviorally selective doses, as well as to electroconvulsive therapy; and the model should, at the same time, fail to respond to ineffective agents [1]. In other words, a valid design should maximize the identification of true positives and true negatives and minimize the identification of false positives or false negatives [1].

Practically speaking, establishing predictive validity requires an exhaustive pharmacological profile which should encompass not only the traditional antidepressant drugs but new drugs as well [1]. Nevertheless, not every new compound has equal contribution to this validation. It is conventionally affirmed that new drugs which act through serotonin or noradrenaline systems have a limited contribution, while new drugs acting on different systems from the traditional ones might positively contribute to this validation [1]. Finally, an account of antidepressant pharmacological profile is not sufficient for establishing a predictive *discriminative* validity, that is to say, the extent to which a model or test measures a specific aspect of a phenomenon [1, 3]. Since certain antidepressant drugs have been reported to work effectively on models of panic and anxiety, it is generally suggested that a model should not respond to benzodiazepines [1].

According to Belzung-Lemoine's approach, the predictive validity is the alikeness in the connection between the triggering factors and the manifestation of the disease and between the therapeutic agent and the disease. It presents two subcategories: induction validity and remission validity. The first sub-criterion refers to the fact that a model meets induction validity when the etiological factors applied in the animal model produce the same effects both in the model and in the human disease. On the other hand, the latter refers to a resemblance in the effects produced by the treatment applied both in the model and in the human disease. This is the case of the well-known remission after chronic antidepressant treatment in both cases [2].

Predictive validity is to be determined through a "macro-observational" perspective or through biomarkers. Following these authors, the factors that modify the evolution of a biomarker in the animal model ought to predict the result of the same biomarker in humans [2].

In a comparative sense, there is no unequivocal reference to induction validity in Willner's publications. This is because he is mainly concentrated on the connection between the biological mechanism and the consequent symptomatology (which integrates his concept of construct validity). Induction implies a major concern about the causes of the pathological outcome, evident in the new approach. Remission validity seems to extend along Willner's outlook, particularly in his most recent works, in which the effects of treatments take into account non-pharmacological treatments [2].

Construct validity is classically defined as a theoretical standard which explains the etiology of a human pathology and its alignment with the exhibited altered behavior of an animal model. Geyer and Markou define construct validity as the accuracy with which a model measures what it is intended to measure [3]. According to Willner and Mitchell, construct validity refers to a theoretical analogy between the etiology of the human pathological condition and the altered animal behavior [1]. This second definition encompasses the notion of both construct validity and etiological validity as separately described by Geyer and Markou. The animal behavior is evaluated and confronted by the pathophysiological explanation of the etiology of the disease.

The aspects commonly studied in relation to a theoretical paradigm of depression are etiology and psychological and neurobiological mechanisms [1]. However, the state of the theories about depression as a pathology and its etiology remain preliminary in some senses. As mentioned before, the neurobiological mechanisms of the disease are yet poorly understood. This results in an intrinsic limitation toward any possible evaluation

of an animal model of depression. Nevertheless, there are known factors with proved implications in the etiology of depression, such as psychological factors – unfortunate or undesirable life experiences, chronic mild stress, adverse situations during childhood, and aspects of personality – and biological factors, like genetic influences (depressive diathesis), physical pathologies, and pharmacological treatments [1]. However, there is limited knowledge about how these processes might influence the physiological mechanisms that explain mood [1].

It has been suggested that the pathogenesis of depression is interpreted as the consequence of an accumulation of several risk factors [1]. It is interesting to comment that this observation has not been taken into consideration in the development of most animal models, which happen to work with one single causal factor [1].

Given the assumption that the possibilities for evaluating a theoretical construct of the animal models are limited because of the absence of a theoretical structure at a clinical level, several generalizations are possible in order to establish this validation process [1]:

- Chronic stress regimes increase the possibility of a construct validity because the role of stressful life events in relation to the etiology of depression is proved.
- Social isolation contributes to an inadequate or complete lack of social support, which is to be considered as an important vulnerability factor as regards depression.

Other aspects concerning construct validity are related to the correct use of the terms, the concepts, and their paradigms, that is, whether the behavioral aspects of a model are properly explained according to a certain paradigm [3]. That is the case of the learned helplessness paradigm, the behavioral despair paradigm, and the chronic mild stress-sucrose preference-anhedonia paradigm. Observations regarding each one of these particular constructs will be mentioned in the following description of the current animal models of depression.

In general, some authors appreciate this validation criterion as the most important to be assessed in evaluating a model, while others assume that the validation of a model cannot entirely rely on the construct criterion because of the constant changes in scientific theories and in the conventional classification references that indicate what should be measured [3]. Despite these divergent attitudes, it is evident that the process of construct validity positively contributes to the development and refinement of any model of depression [3].

According to Belzung and Lemoine, the criterion of homological validity encompasses two subcategories: species validity and strain validity. The first criterion refers to the challenges in selecting a particular species for an animal model, depending on the cognitive or biological mechanisms to be studied. On the other hand, strain validity specifically refers to strain differences, that is to say, the anatomical, physiological, or behavioral differences that result from genetic changes within a species [2].

Following the new approach, the criterion of pathogenic validity refers to two contrasting dimensions: ontopathogenic validity and triggering validity. In the first case, the criterion refers to early factors in the environment which interact with an initial organism turning it into a vulnerable organism (a predisposed organism), following the theory of diathesis. On the other hand, a model meets triggering validity when there is similarity of triggering factors during adulthood, which produce a pathological organism after interacting with a vulnerable or a non-vulnerable initial organism. It is paramount to take into consideration that etiological factors are not required to be materially identical but semantically similar instead. This means that the stimuli applied can be of different nature as long as they have the same meaning or effect (semantical similarity) in the animal model and in humans as well [2].

Although the Belzung-Lemoine's concept of species validity is not directly mentioned in Willner's publications, it coincides with the classical notion of homological validity. Strain validity, as well as ontopathogenic and triggering validity, on the other hand, might be integrated in Willner's conception of construct validity (even when they could refer to different constructs), due to their agreement on the relevance of the

genetic predisposition in the etiology of the disease both in animals and humans.

Mechanistic validity refers to the similarity between the mechanism – either cognitive or neurobiological – which is supposed or known to underlie animal disease and the mechanism supposed to be working in human disease [2]. Belzung-Lemoine's conception of mechanistic validity partially extends along Willner's notion of construct validity, since their scheme refers to the specific mechanisms (biological and cognitive) implied in the pathological effects. Willner incorporates other diverse aspects in his view of construct validity, such as etiology and course of the disease, and he does not directly include cognitive mechanisms. In the end, this criterion refers to the mechanism that is presumed to be producing the already mentioned behavioral symptoms and biological markers and might be sensitive to the application of therapeutic agents.

Mechanistic validity is determined through straight examination of what is taking place in the organism's pathological condition. It must be noted that this criterion does not observe the similarity between the effects of the mechanisms but the interaction between one specific mechanism and other mechanisms in the organism. In fact, mechanistic validity and face validity must be observed separately [2].

According to the statistical bibliographical references conventionally established for defining the clinically relevant symptomatology of psychiatric disorders, the concept of face validity is based on a phenomenological (descriptive) similarity between the animal model and the human pathology. Geyer and Markou, as well as Sarter and Bruno, make reference to this phenomenological similarity. On the other hand, following the first definition by Willner, the concept of face validity includes pharmacological similarity. It implies that antidepressant effects must be observed only under chronic administration, due to the fact that chronic antidepressant treatment is generally effective in humans. It implies also phenomenological identity, in terms of features specifically related to depression.

The face validity of a model is doubtful in case of a positive response to acute treatments because of the inconsistency with the known clinical outcomes in humans [1]. Likewise, a valid model of depression responds to chronic antidepressant treatments, and the effective response lasts as long as the treatment is applied [1]. The phenomenological identity already mentioned is formulated in terms of behavioral and cognitive aspects, and it does not refer to the neurophysiological bases of depression [2]. A further definition by the same author mentions the extent of similarity between a model and the human pathology. From this point of view, the main requirement for establishing face validity is symptomatic identity [2]. The direct consequences of this definition have been explained above, since it may be discussed whether a model ought to be developed according to its relevance for a particular human pathology in its entirety or for a limited spectrum of symptomatic dimensions and/or endophenotypes [2].

In fact, it is possible to target a particular symptom of a psychiatric disorder as long as it is independent from other symptoms of the same condition [2]. Anhedonia and depressive mood are the two main symptoms of depression taken into account for the development of animal models of depression [1]. As it is known, the latter cannot be reproduced in animals because it involves a verbal dimension. As a result, anhedonia plays an important role in the process of validating a model of depression. There are subsidiary symptoms that can also be modeled in animals, such as psychomotor, appetite or sleep alterations, and fatigue or loss of energy [1]. Alterations in locomotion are a main behavioral aspect in many models of depression. However, the status of this symptom is rather imprecise since it has been observed to increase and decrease in several validation studies [1].

As regards Belzung and Lemoine, face validity is characterized as the alikeness between the observations in the animal model and the human organism. This conception embraces two subcategories as well, namely, ethological validity and biomarker validity. In the first case, the subcriterion refers to a behavioral similarity in relation to the pathological organism. Once again, the semantic content, and not the material similarity, is most important. Biomarker validity

refers to a resemblance between the biological markers related to the organism, taking into consideration that the function of a biomarker, and not its composition, is most relevant [2].

Ethological validity might be incorporated in Willner's face validity in terms of symptomatic correlation. Nevertheless, the classical conception implies a more extensive notion, encompassing specific aspects formerly integrated in the concept of construct validity, such as similarity in the course of the disease. On the other side, biomarker validity is not to be explicitly detected in Willner's earliest works, but his later notion of construct validity refers to the correlation between the biological mechanism and the symptomatology.

In conclusion, it is sometimes argued that two different species cannot exhibit the same phenomenology or symptoms, even when the etiology of the condition is known [3]. In the second place, observing similarities in particular behavioral and physiological aspects between animals and humans does not necessarily imply the same etiology [3]. Also, some authors consider the face validity criterion to be difficult to establish because they claim an ineludible use of subjective arguments for determining the required mentioned analogies [3].

Finally, it is the complexity of human psychopathology what makes the challenge of a translational approach so relevant. This notion consists of the process of validating experimental models in order to certify the applicability of their findings and abbreviate the distance between basic research and medical practice. Each model serves for a particular purpose, and that defined purpose determines the validation criteria that the model must satisfy in order to establish, in neurobiological experimental research, its utility and consequent relevance.

However, even when a translational approach is not new or recent in medical sciences, the efforts aimed at a "back-translational" approach – that is, in the opposite direction – happen to be rare. This approach is essential in order to investigate therapeutic alternatives once particular mechanisms have been discovered through experimental research.

The fact that the notions about the etiology of depression remain limited and primitive is already common knowledge, in part due to the complexity of the task of designing animal models. Nevertheless, optimism has aroused from the development of new stress-based paradigms and hedonic/anhedonic behavior [7].

In the end, it is paramount to mention that this complexity of the validation criteria and the experimental design ought to find a proper equilibrium in ethical implications expressed in the general structure of animal research. The validation of animal models in neurobiological research, including the development and contrasting analysis of new versus classical conceptions, is as important as the evolution of scientific understanding itself. As a matter of fact, the actual notion of scientific understanding is reflected by the determination of the applicability, through its validation criteria, of a model as a tool for discovering and measuring aspects of a disease. That is the reason why determining the criteria is equivalent to determining what scientific understanding actually is [3].

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# 19 Animal Models of Depression: Classification and Relevant Validation Criteria

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*"For it is then that we have need of pleasure,*
*When we feel pain owing to the absence of pleasure."*

Epicurus (341–270 B.C.)

## Introduction

In this chapter, a classification of the current animal models of depression is proposed (see Table 19.1). The criterion of this organization diverges regarding the classification developed by Willner, in which he describes 18 models following the conceptual rigor of his classical notions about validation criteria [1]. As a matter of fact, in this case, the present classification follows an empirical criterion and is catalogued according to the practical nature of the technical procedures implied in the experimental process. Consequently, this supposes the challenge of constantly keeping in mind the already mentioned differences between the concepts of animal model, test and paradigm, and their singular purposes.

The present knowledge about genetic and epigenetic factors and the study of the associations between specific causes (such as specific forms of stress) and pathological outcomes, i.e., psychiatric symptomatology, besides the primitive notions on the neurobiology of depression, enlighten us and make room for several changes in the conception of experimental models. Nowadays, this conception has been expanded toward the assumption of a transformation process from health to disease within a certain environment. Evidently, following Slattery and Cryan, it may be noted that during the last years, a change in the ways of understanding and applying experimental models has taken place [2]. Therefore, as it was mentioned before, the most recent general framework of animal studies takes

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**Table 19.1** Current animal models of depression

| |
|---|
| Stress models |
| Chronic mild stress (CMS) |
| Social stress |
| Early life stress (maternal deprivation) |
| Sleep deprivation |
| Learned helplessness (electric foot shock)[a] |
| Behavioral despair (FST and TST)[a] |
| Genetic models |
| Traditional genetic models |
| Selective breeding |
| Optogenetic tools |
| Models based on chemical manipulations |
| Neonatal clomipramine treatment |
| Withdrawal from exposure to drugs of abuse[b] |
| Stimulation of the immune system |
| Models involving surgical procedures |
| Olfactory bulbectomy |
| Intracranial self-stimulation (ICSS)[b] |
| Others |
| Change in photoperiod |

[a]FST and TST are tests used for measuring altered behaviors produced by exposure to several forms of stress paradigms. The FST was originally developed as a test for studying and evaluating substances with possible antidepressant effects [3]

[b]The reward paradigm involves stress-induced behaviors, anhedonia, and the mentioned related procedures (ICSS, withdrawal from previous exposure to drugs of abuse, and sucrose preference) for measuring the alterations in the value of rewarding stimuli

into consideration the fact that epigenetic mechanisms transform a healthy organism into a vulnerable one. From a genetic point of view, the initial organism might be either vulnerable or non-vulnerable. Next, during adulthood, the presence of specific triggering factors transforms the vulnerable organism into a pathological one. A posteriori, the design of a model fundamentally aims at imitating the etiological process of transformation from a healthy organism to a pathological organism through a vulnerability state in time.

The complexity of this realization challenges the mere possibility of a reductionism of any model to a simple test for evaluating the antidepressant efficacy of a substance. This is why, as an effect of the theory of depression diathesis, it is proper to pay due attention to the fact that some procedures result into a vulnerable organism which presents predisposition toward a specific pathology (such as early maternal deprivation), which can be manifested later on during adulthood following certain triggering factors. Such triggering factors (e.g., chronic mild stress) are evidently associated with the appearance of the symptomatology of depression.

In fact, because it is known that this presents an important similarity as regards the pathological process in humans, there is a current emphasis on the chronic stress and reward paradigms due to an explicit interest in the biological mechanisms underlying depression [2]. Accordingly, anhedonia – understood as a loss of pleasure – and alterations in the brain reward system, seen as a loss of interest, imply different underlying neurobiological processes.

The next relevant challenge is the frame of reference to be followed in order to explain the assessment of the validation criteria. Despite the fact that Willner's developed conceptual axis is the most relevant and conventionally accepted, some of the newest proposals by Belzung-Lemoine will be taken into account in relation to the paradigms most frequently adopted, following the theory of depression diathesis. As a consequence, it becomes necessary to clarify the difference between ontopathogenic factors (which produce vulnerability) and triggering factors (which produce the specific symptomatology of a disease). In a similar way, the most recent conceptions about validation have consideration for the impairment in cognitive functions besides the commonly described behavioral alterations. This supposes, in effect, an expansion of the classical face validity criterion, as described by Willner.

Having observed the main aspects to be taken into account, it is now proper to comment that in the literature of neurobiological research, it is commonplace to detect original articles which apply more than one procedure during their experimentation processes, depending on the objectives of their studies. In this way, some procedures may be applied in order to induce vulnerability states. Other procedures are destined aiming to produce later specific symptoms.

In the end, it is decisive to analyze the theoretical frames of reference for a deeper understanding

of the neurobiological dimension in the etiology of depression, given the significant statistics in relation to refractory patients, which manifests this pathology's heterogeneity.

The descriptions included will not provide a thorough analysis of the selected models. It is paramount to mention that some of the procedures described below will not only encompass animal models per se but will also take into account some tests commonly related to specific paradigms.

## Stress Models

### Chronic Mild Stress (CMS)

The chronic stress model was proposed by Katz and Hersh in 1981 and was later modified by Willner in order to use milder stressors and generate more realistic conditions [4, 5]. The procedure involves the application of a variety of stressors like cold, disruption of light-dark cycle, foot shock, food or water deprivation, isolation or crowded housing, and dampened bedding, among others, over a relatively long period of time [5–7]. It is acknowledged that exposure to these stressors induces long-lasting changes in behavior and neurochemical and neuroimmune parameters, and, when performed reliably, it can generate important molecular insight into depression [5, 7]. It is important to emphasize that repeated exposure to the same stimuli leads to adaptation, which can be avoided by using an unpredictable sequence [8]. Anhedonia is observed, and, in fact, it is one of the main behavioral changes measured in CMS. Also, there is a decrease in cognitive functions, locomotor activity, grooming, and sexual, aggressive, and investigative behaviors [5, 7–9]. Added to that, Belzung-Lemoine's criteria observe that CMS employs triggering factors and meets mechanistic and ethological validity [10].

This model causes changes in the hypothalamic-pituitary-adrenal axis with an increase in plasmatic corticosteroid levels. Correspondingly, increased adrenal weight, lipid and protein level changes, and decreased activity of antioxidant enzymes were observed too [8, 11]. BDNF levels are reduced and there is an evident attenuation in neurogenesis. However, opposite results have been reported too, suggesting a compensatory mechanism to stress [8]. Anatomic changes such as hypothalamic atrophy have been noticed [9]. When exposure to the stressors is discontinued, the rat will recover after a 4–5-week period, and other episode can be induced later by resuming it again [7]. This reversion of behavioral changes can also be generated by chronic antidepressant treatment [5, 7].

Although this is one of the most verified and realistic models, it is sensitive to subtle variations in design, and numerous factors such as testing time and provider difference, among others, make it difficult to reproduce [5]. Variability in stress response, gender differences, and treatment sensibility differences have been observed as well [5, 12]. The procedure is also claimed to be space and time demanding and it has long duration, making it difficult to be implemented in new laboratories [9].

### Social Stress

Social environment may be considered a source of stress, mirroring stressful events of everyday human life [7, 9]. Perturbations in social structure, like social defeat, subordination, and loss of control function as powerful stressors, are used in validated animal models [6, 7, 13]. In the resident-intruder model, a male is introduced into another male's home cage for a variable period of time from a single occasion to a day–week period [7]. After physical exposure, the intruder is placed in a protective cage before being returned to its home cage [7]. Anhedonic-like state and social withdrawal were observed in animals, along with decreased exploration and locomotor and sexual activity [5, 9, 13]. There are strong responses in heart rate, blood pressure, body temperature, prolactin, and testosterone [14]. HPA dysregulation and autonomic function were noticed. Decreased cell proliferation in the hippocampus and in the medial prefrontal cortex, as well as dendritic morphology alterations, was also shown [5, 15].

Many studies suggest that chronic but not acute treatment with antidepressants can reverse depression-like behavior in these animals [7]. However, this model has some drawbacks. Diurnal time point of exposure is critical, and female rodents cannot be used since they do not fight with each other in the resident-intruder paradigm. Finally, the quantity of aggression is to be taken into account, for excessive physical injuries are irrelevant and unethical [7].

## Maternal Deprivation

The early life stress model is typically applied in the form of maternal separation during the early postnatal period [5]. In this sense, long maternal separation mimics neglect or loss of parents in humans and is one of the most potent stressors during development [8]. Studies have provided evidence that lack of maternal care in early life periods leads to an altered response to stress along with neuroendocrine alterations in the HPA axis throughout the lifespan [5–8].

When animals are submitted to the CMS model, maternal-deprived ones show a vulnerability to develop depression-like behavior. This also happens with the FST, in which these animals have an increased immobility time [8, 9]. As a matter of fact, other abnormalities have been observed, like impaired hippocampus-dependent learning and memory functions along with reduced survival of adult-born neurons. Treatment with antidepressants was able to reverse depressive-type behaviors, promoting an increase in neurotrophin levels and neurogenesis [6, 8, 13]. According to Belzung-Lemoine's conceptions, this procedure meets ontopathogenic validity [10].

## Sleep Deprivation

Sleep deprivation is a common example of circadian disruption, which can alter allostasis and, therefore, can be used as a natural stressor [16]. The procedure consists of gently handling the animals to prevent them from sleeping for a relatively long period of time. A sleep deprivation of 72 h was accomplished in mice using a platform submerged in water. In this manner animals fell asleep, and they consequently fell into the water and must climb back, being forced to stay awake. Although this is not yet a well-established model of depression, many studies show that it alters important stress-related pathways and has consequences for many body systems.

Following sleep deprivation, neurotransmitters, such as dopamine and serotonin, are altered. Likewise, gene expression of several transcription factors as well as genes that encode neurotransmitters and proteins involved in metabolic processes and cellular plasticity is altered. A decrease in cell proliferation has been shown after 96 h of sleep deprivation [8]. As a matter of fact, repeated stress causes structural remodeling in the hippocampus, amygdala, and prefrontal cortex, resulting in impaired memory and increased anxiety and aggression. Increased levels of messenger RNA for interleukin 1b and for cortisol have been observed along with glycogen store depletion and increase in oxidative stress and free radical production in the hippocampus. Classical tests such as the inhibitory avoidance and the water maze test show deficits in learning and hyperactivity as well [8, 16].

## Learned Helplessness

Helplessness is a core symptom in depression. It is a specific deficit in behavior to control aversive stimuli [7]. When animals develop a state of helplessness and are re-exposed to the same stressor with an easy escape route, they will either display increased escape latency or they will fail to escape [5, 6]. In Belzung-Lemoine's criteria, this model shapes triggering factors [10]. The classical model procedure consists of three groups, with two control groups. The first group is exposed to electric foot shocks that can be controlled. The second group is coupled with animals of the first one, taking into consideration that they receive unpredictable shocks of the same amount, duration, and pattern. The third group is not exposed at all [5, 17].

As it has been reported, reduced weight, increased motor activity, reduced libido, cognitive deficits, and changes in sleep have been observed in helpless animals. Following one or more sessions of inescapable shock, rats have been shown to develop persistent changes in HPA axis activity and a loss of spine synapses in the hippocampal regions. Depletion of norepinephrine and serotonin, as well as changes in the norepinephrine and 5-HT1B serotonin receptors in the hippocampus, was reported. Concomitantly, high levels of glucocorticoids and homocysteine, which are found in human patients with depression, have been reported in rats in an animal model of learned helplessness. Animals subjected to this model respond to tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, and electroconvulsive therapy. Response to these antidepressant drugs was observed between 2 and 3 days after the initiation of treatment.

Interestingly, the learned helplessness model can also be used to measure the escape performance of mice with different mutations, showing which target genes for depression may affect vulnerability to develop a depressive-like state. Nevertheless, the major drawback of this model is that most of its depression-like symptoms do not persist long enough following cessation of the uncontrollable shock stimulus [8].

## Forced Swimming Test (FST)

The forced swimming test was described by Porsolt (1977) as a behavioral method for inducing a depressed state [18]. This test is commonly used to investigate antidepressant effects of new compounds, and it consists of placing an animal into a water-filled cylinder, from which it is unable to escape. Initially, the animal exhibits an active escaping behavior that ameliorates within time, adopting an immobile, passive behavior. After 24 h, the exposure is repeated for a shorter period of time and variables are measured [7]. Deficiency of struggling to exit corresponds to a despair-based state of depression [6].

Unfortunately, this test has poor face and construct validity. The time by which antidepressants cause changes in immobility does not correlate with the timing of antidepressant effects on humans, and the mechanism that explains the onset of immobility is hard to interpret. On the other hand, the effect of antidepressants in the forced swimming test is relatively specific since they do not increase motor activity unlike psychostimulants. Besides the effects of antidepressant drugs, the FST can also be used to evaluate the type of depressive behavior which might be exhibited. In this perspective, animals subjected to maternal deprivation show increased immobility time.

Following Belzung-Lemoine's frame of reference, this procedure partially meets the ethological criterion, taking into account that it only mimics one symptom of depression. It is suggested that this device might achieve higher validation scores inasmuch the individuals selected were previously exposed to pathogenic factors, the strain was specifically selected, or stress factors were applied during adulthood [10]. Finally, it is worth mentioning that this test is generally easy to use, has very good reproducibility and is applied for the selection of new antidepressant drugs. However, many factors can alter the outcomes of this test [8, 18, 19].

## Tail Suspension Test (TST)

Designed by Cryan et al. as a model analogous to the forced swimming test, it is usually used in mice which are suspended by the tail manually or through a device during several minutes [6, 18]. Like the forced swimming test, rodents treated with antidepressants show a decrease in immobility time, which is considered a depression-like state based on despair. It is relatively specific to antidepressants and resolves some problems with the previous test, like hypothermia.

Importantly, both the FST and the TST are considered predictive models of antidepressant activity (pharmacological isomorphism), not animal models of depression. More research needs to be done in order to determine their face and construct validity [18].

## Genetic Models

### Traditional Genetic Models of Depression

Genetically engineered rodents make it possible to investigate the consequences of altered functions of genes thought to contribute to the pathophysiology of the disease. Many mutant rodent lines have been developed aiming to this end. There are two main approaches to be chosen: forward and reverse genetics.

In forward genetics, a large number of random mutations are induced in an organism by mutagenic techniques. Then, the individuals are bred and screened for the desired aberrant phenotype. Once the desired genotype is produced, the responsible gene can be identified [20].

In reverse genetics, a genetic manipulation that results in either loss-of-function or gain-of-function mutants is induced. The majority of mutant mice lines created using this approach involve the inactivation of a candidate gene (knockout mice). Most of these genetic models in mice result in an antidepressive-like phenotype; the models that result in depressive behaviors are a lot fewer. Examples of single-gene manipulations in rodents include 5-HT transporter, multiple sub-types of adrenoceptors, corticotropin-releasing factor (CRF), CRF1 receptor, CRF2 receptor, forebrain-specific mineralocorticoid receptors, and brain-derived neurotrophic factor (BDNF).

Lately, sophisticated conditional strategies have been introduced, which enable control of spatial and temporal gene expression. For example, conditional knockout mice that either have lifelong or only adult reductions of BDNF have been produced, making it possible to compare the consequences of BDNF depletion during development with those occurring during adulthood.

These models have limited or no predictive or face validity and have been used mainly because of their etiological and construct validity. An important factor in some of the discrepant findings regarding these studies is the background strain of the mouse. This may resemble the genetic heterogeneity that might contribute to conflicting results in human studies [20, 21].

### Models Based on Selective Breeding

Selective breeding is the process of breeding plants or animals for particular genetic traits desired by the researcher. In these models, animals with specific features are selected and bred over several generations in order to generate inbred strains with specific physiological or behavioral traits. Some of the lines currently used as animal models of depression were originally created for other purposes. In other lines, a specific depressive-like behavior was selected for breeding.

An example of selectively bred models on depression is the Flinders sensitive line (FSL) of rats, which phenotypically resembles a number of depression symptoms and has helped to elucidate the endophenotype of depression. Observations of the behavior of the FSL suggest that it exhibits psychomotor retardation, increased immobility in the forced swimming test, and anhedonia when exposed to chronic mild stress.

Other lines generated by selective breeding are the fawn-hooded rats, reported to exhibit high immobility in the forced swimming test, elevated serum corticosterone, and high voluntary ethanol intake. The Wistar-Kyoto rats present increased immobility in the forced swimming test and dysregulation of the HPA and hypothalamic-pituitary-thyroid axes. The high/low stress reactivity mice and the swim low-active/swim high-active rats are also examples of selective breeding.

Belzung-Lemoine's conceptions observe considerable strain validity in these procedures [10]. They are an important tool to provide evidence for interactions between genes and environment, demonstrating differential vulnerabilities. The combination of genetic models with various stress paradigms is likely to mimic the human condition more accurately. They have good face validity and, in some cases, their predictive

validity has also been proven. Their etiological and construct validities are questionable [20, 22].

### Optogenetic Tools

These methods enable the regulation of neuronal activity with high anatomical, genetic, and temporal precision. Genes encoding for light-sensitive ion channels are inserted into specific groups of neurons, usually with viral vectors. Expression of these ion channels by neurons enables the experimenter to selectively stimulate or silence them. Optogenetic tools have been used to study the role of the mPFC in depression. It has been found that optogenetic stimulation of mPFC neurons restored normal social interaction and sucrose preference in chronically socially defeated mice.

Generally, these models seem to have good face and construct validities. Their predictive validity needs further investigation to be proven. Their etiological validity is difficult to be assessed because these models combine numerous invasive procedures in order to induce the desired effects [20, 23].

## Models Based on Chemical Manipulations

### Neonatal Clomipramine Treatment

This model is claimed to be appropriate for studying the pathomechanisms of the disease because it hypothesizes depression as a developmental disorder. It consists of chronic administration (twice a day, between postnatal days 8–21) of the tricyclic antidepressant clomipramine, followed by behavioral tests applied during adulthood (e.g., FST), that is, approximately 3 months later [24]. It has been reported that rats subjected to neonatal chronic clomipramine treatment develop persistent depression-like symptoms during adulthood. The same effects have been reported in relation to the administration of the selective serotonin reuptake inhibitor (SSRI) citalopram. This phenomenon is known as antidepressant exposure syndrome (NADES). Predictive validity of the model might be established in terms of a proved positive response to chronic and subchronic administration of fluoxetine, demonstrated by reduction immobility and increased swimming in FST [19].

As regards face validity, three aspects are worth mentioning: in the first place, persistent changes in behavior during adulthood are observed, including sleep pattern alterations. In the second place, a pronounced increase in immobility, as observed in the FST procedure, is to be related to a depression-like state. In the third place, interestingly, acute administration of fluoxetine failed to reduce immobility, which satisfies an important requirement for establishing face validity.

In terms of construct validity, in a sense of etiological validity, this model provides a molecular basis for analogous mechanisms proved to be involved in the etiology of depression. According to recent studies, this procedure is known to arise depression-like behavior in adult rats, which results in observable alterations in neuronal and glial network development. The signs of those pathological alterations consist of modifications in cellular proteome during adulthood. In fact, it is empirically affirmed that clomipramine treatment induces long-term alterations in molecular phenotype of cortical cells in an indirect way. This is because it triggers cellular processes during the early development phase of the neonatal brain, processes which progressively evolve to manifest observable alterations in adult mature phenotype. Specifically, the mentioned molecular modifications in proteome affect proteins involved in biological functions of diverse nature, like inflammation, transcription, cell metabolism, and cytoskeleton organization. The most relevant molecular alterations detected are observed in the increased levels of the macrophage migration inhibitory factor (MIF), as well as modifications in the expression of 5-$HT_{1A}$ receptor. These result in sustained pathological changes in the cellular phenotype in the prefrontal cortex, which might configure the molecular basis of depression-like behavioral symptoms in adult rats.

## Anhedonia-Reward Paradigms

### ICSS-Drug Abuse Withdrawal and CMS-Sucrose Preference-Anhedonia Paradigm

Reward stimulation in depressive patients has been observed to present a considerably diminished value. The reward system seems to be altered in the brain, and it expresses a specific psychological process named anhedonia. This symptom is described as an important symptom of depression and a negative symptom of schizophrenia as well. It is defined as a lack of interest, or markedly diminished pleasure, in relation to all or almost all activities for the most part of a day, almost every day. Experimentally speaking, some possible manipulations might be applied to induce an anhedonic state in animals.

Exposure to uncontrollable forms of stress, including chronic mild stress, electric foot shock, or FST and withdrawal from exposure to drugs of abuse were studied.

In the case of FST, as electric foot shock is related to the learned helplessness paradigm, the FST procedure is applied in the sense of a behavioral despair paradigm and not as a test for measuring antidepressant effects.

On the other hand, the tools available for measuring the hedonic value of stimuli which present convergent evidence in relation to the stress-induced alterations are sucrose preference and/or place preference tests, while the intracranial self-stimulation (ICSS) can be used in both stress protocols and in drugs of abuse withdrawal procedure.

The ICSS involves a brief self-stimulation in specific brain regions. The measure of the stimulation value is determined by the psychophysically defined threshold. A decrease in the threshold is interpreted as an increment in the value of a rewarding stimulation, and an elevation of the threshold means a decrease in the value of the same stimulation. A posteriori, an anhedonic state is operationally defined by a decrease in response to the ICSS or an elevation in the thresholds. Generally, the ICSS is considered an important tool for the brain reward system (BRS) research because it operates directly on the neural substrates involved in the rewarding effects of natural reinforcers, as in the case of food and water. In fact, the study of the neurobiology of behavior in relation to ICSS after experimental manipulations allows the understanding of the alterations in reward mechanisms observable in several psychiatric disorders.

#### Measuring Anhedonia After Exposure to Stress

As regards ICSS, because an anhedonic state has been induced, a decrease in the reward value can be noticed. Predictive validity in terms of pharmacological isomorphism is established as stress-induced alterations. They may be reversed by antidepressant treatment. Construct validity is established through the notion of a specific process which appears to be altered in depressive patients, allowing the investigation of its neurobiological substrates. There is also a notable validity in the sense of etiology, since exposure to uncontrollable forms of stress has been associated with depression causality.

In reference to sucrose preference, animals under stress tend to consume less volume of sucrose solution than the control groups. This fact might suggest some anhedonic state caused by stress. This conclusion has been questioned, considering that food restriction was used as a stressor and correlations between less consumption and weight loss were detected. Once the weight variations were leveled and food restriction as a stressor was suspended, some publications reported no difference in sucrose consumption between the experimental and control groups, while others reported the opposite results. In general, this test might not be entirely reliable when a form of stress is applied as experimental manipulation. Antidepressant treatment is seen to revert the effects of stress, while the fact that antipsychotic treatments failed to achieve the same positive results contributes to the establishment of a predictive validity in a sense of pharmacological isomorphism.

The place preference paradigm consists of an association between a neutral environment and a rewarding stimulus. The measure of reward is

determined by the degree of place preference. Control groups manifest preference for the environment associated with the rewarding stimulus (food or drug). Exposure to chronic mild stress debilitates the association between the rewarding stimuli and the neutral environment since the stress-induced state presents a decreased sensitivity to rewards.

### Measuring Anhedonia After Withdrawal from Extended Exposure to Drugs of Abuse

According to this procedure, exposure is interrupted after sustained self-administration of several drugs of abuse, such as cocaine, amphetamine, nicotine, morphine, and ethanol. As regards ICSS measures, during the post-interruption period, an elevation in the threshold is observed. The increase is proportional to the amount of consumed substance. Similar threshold elevations are observed in both cocaine and amphetamine. This confirms reliability of the phenomenon. Also, predictive validity is established because the post-cocaine threshold elevations were reversed after treatment with bromocriptine (dopamine agonist) and desmethylimipramine (tricyclic antidepressant). In addition, traditional antidepressants reverse the altered value of the reward stimulations measured through ICSS after drug withdrawal. Finally, it might be affirmed that potential construct validity is satisfied because human beings generally present anhedonia after interrupting administration of such drugs.

## Stimulation of the Immune System

Inflammatory mediators like cytokines alter neurotransmitters, neural plasticity, and neuroendocrine functions [8]. Animal models involving the immune system have been criticized because of the complexity of immune-brain communications. Specifically, one of these models which used an endotoxin showed behavioral changes, such as anhedonia, sleep alterations, anorexia, and learning alterations. Moreover, neuroendocrine changes were observed, and treatment with antidepressants reduced anhedonia in these animals [8, 25].

# Models Involving Surgical Procedures

## Olfactory Bulbectomy

Olfaction is extremely important in rodents. As a matter of fact, their olfactory system forms part of the limbic region in which other regions contribute to emotional and memory components of behavior [7]. Bilateral olfactory bulbectomy produces behavioral, endocrine, and neurotransmitter changes that mimic human patients. Nevertheless, it is prudent to mention that this procedure does not imitate an etiology of depression, because loss of olfaction is not observed to produce depressive symptoms in human patients. As manifested by Belzung-Lemoine, it produces an alteration in the processing of odors, which is related to the orbitofrontal cortex, rather than to the olfactory bulbs. These authors recognize, however, mechanistic validation, as the procedure induces neurobiological alterations similar to those observed in depressed humans [10].

Specifically, animals submitted to this surgery show an increase in cannibalism and exploratory and locomotor behavior, as well as a decrease in sexual activity and cognitive anhedonic deficits [8]. Noradrenergic, serotonergic, cholinergic, GABAergic, and glutamatergic systems are altered, and there is a marked degeneration of neurons in the hippocampus, cortex, amygdala, locus coeruleus, and raphe nuclei. There is also a reduction in the level of synapses and dendritic morphology in hippocampal and cortical neurons. Finally, chronic (but not acute) administration of antidepressants corrects behavioral, endocrine, immune, and neurotransmitter changes that occur after the procedure [7, 8].

## Changing Photoperiod

Light-dark cycle manipulations could be used for an animal model of depression. In this model, rodents are exposed to an altered cycle for a 2-week period. Fat sand and Nile grass rats show depression-like behavior when maintained under short photoperiods compared to neutral photoperiods.

Accordingly, these animals developed anhedonia and increased motor activity. Increased levels of corticosterone and decreased BDNF levels in the hippocampus were also observed. Antidepressant treatment reversed the induced behavior, except anhedonia. On the other hand, brief or long exposures to light treatment have antidepressant effects on the FST. Although different effects have been described, the interactions between the mechanisms and mood changes in diurnal animals may provide new insight into depression [8].

## General Conclusion

Major depressive disorder is a complex, multifactorial, heterogeneous, and often chronic mental disorder [7]. It imposes a severe social and economic burden globally. As a matter of fact, it is the second leading cause of global disability, and predictions indicate that it will reach first place by 2030 [7]. As mentioned before, this disorder is characterized by a clinical complexity due to its therapeutic heterogeneity. This implies a major challenge for the scientific community: the challenge of investigating a disease through experimental models. Most experimental models employ either genetic manipulations or some type of environmental stress, or the combination of both, producing animals that exhibit phenotypes that are similar to the symptoms of depressed patients. As a consequence, a second challenge is implied, namely, a translational approach, which consists in the process of validating those experimental models in order to certify the applicability of their findings and abbreviate the distance between basic research and medical practice. Each model serves for a particular purpose, and that defined purpose determines the validation criteria that the model must satisfy in order that it's utility and consequent relevance may be established in neurobiological experimental research. It is worth remembering that no model presents 100% of predictability [26].

Honestly, the process of validating experimental models of a disease cannot be oversimplified since it is a central part in the organic evolution of scientific understanding and theories development. Phenomenology generally invites us to look at an object for a second time, because "nature is not only all that is visible to the eye." In fact, it is paramount to take into consideration every aspect that could be relevant for explaining human pathology, even when those aspects are not evident or superficial. This is reminiscent of a metaphor created by Thomas Südhof about a children's play at school. Let us suppose that the children's parents were expected to reconstruct the whole play by using the various movie clips they could take. The question is "would it be possible to reconstruct the play?" Furthermore, if one actor was missing and the audience's reactions were the "symptoms," could they reconstruct the play (e.g., the disease)? The actual notion of scientific understanding is reflected by the determination of the applicability, through its validation criteria, of a model as a tool for measuring aspects of a disease. That is the reason why determining the criteria is equivalent to determining what scientific understanding actually is [26].

Finally, we hope that this conclusion be interpreted in terms of an open conclusion, as our minds are open for future discoveries and new findings in the field of neurobiological research and human phenomenology. An optimistic constructive attitude is recommended for assuming every scientific task.

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# Aggressive Behaviour and Sleep: History, Review, and Perspectives

20

Gabriel Natan Pires, Sergio Tufik, Katsumasa Hoshino, and Monica Levy Andersen

## Abbreviations

| | |
|---|---|
| APD | Antisocial personality disorder |
| BPD | Borderline personality disorder |
| CPAP | Continuous positive airway pressure |
| LSD | Lysergic acid diethylamide |
| RBD | Rapid eye movement behaviour disorder |
| REM | Rapid eye movement |
| SDB | Sleep-disordered breathing |

## Introduction

The global population, and particularly the population of industrialized countries, experiences a constant sleep deficit [1–3]. The main source of this sleep deficit is chronic sleep restriction, which is often associated with impositions of modern life, such as heightened labour demands, an extended workday, increased social and household responsibilities, and a generally fast-paced lifestyle [4–6]. Recent investigations report an 18-min reduction in sleep time compared to 1978 and, overall, a 2-h reduction over the past five decades [7, 8]. Chronic sleep restriction, when compounded by other sleep disturbances, constitutes an important public health issue [9, 10], since sleep restriction and sleep disorders are associated with numerous adverse health consequences [11–19]. Among these, the effects of sleep disturbances on neurobehavioural issues deserve attention. Sleep deprivation [20], sleep-disordered breathing [21, 22], and associated diseases [23] are all linked to both neuropsychological deficits [24, 25] including increased aggressive behaviour and impulsivity, executive dysfunction, memory and attention impairments, anxiety, and depression.

As with sleep, aggression is also influenced by the routine of modern life and by its consequences. The growing exposure to violence, mostly through the media, can be associated with the development of aggressive behaviours and attitudes [26, 27]. Aggressive behaviour is linked in part to factors like fatigue, mood, and other external aspects [28]. In particular, sleep restriction and fatigue are among the stressors that have been found to be relevant in the precipitation of aggressive attitudes and reactions [28–30].

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There is a notable shortage of papers condensing the literature that examines the relationship between sleep and aggression. Indeed, the recent literature has focused mainly on parasomnias, disorders in which violent behaviour may be observed during sleep, neglecting several other points in which sleep and aggression are associated. A paper that investigates the theme thoroughly and comprehensively is timely, given that the topic has been subject to increasing scrutiny in the last decade. Thus, we aimed to review the literature concerning the association of sleep and aggressive behaviour, revealing the interface of these two variables. This review concisely presents basic concepts adopted in this field of study and summarizes its main findings in both animals and humans, highlighting the main research perspectives.

## Historical Overview

The relationship between sleep and aggressive behaviour first came under scrutiny in the 1960s. Increased aggression, expressed in the form of antisocial behaviours, as an effect of total sleep deprivation was analysed in the classic review by Kleitman [31] on sleep and wakefulness. Such a surge in aggressiveness had already been observed by Dement [32] in REM-deprived individuals. Analogous results were observed in rats, in which paradoxical sleep deprivation induced heightened aggressive behaviour as verified through the increase in fights induced by electrical stimulation [33].

The 1970s included a significant number of experiments linking sleep to aggression. Carlini and colleagues saw a causal relationship between sleep deprivation and aggressive behaviour, considering this association as a factor involved in the assessment of the behavioural effects of psychotropic substances [34]. The group has also used this paradigm to evaluate the neurophysiological mechanisms involved in the aggressiveness induced by sleep deprivation [35–39]. This group's body of work is considered a milestone in the investigation of sleep and aggressive behaviour as it added much to what was at the time an incipient field. The work of Hicks and colleagues [40] in the same period must also be highlighted; they found reduced latency and increased frequency of attacks and occurrence of muricide due to paradoxical sleep deprivation, corroborating previous data collected by Morden and colleagues [33].

The work of Tufik and colleagues in the 1980s examined the importance of the dopaminergic

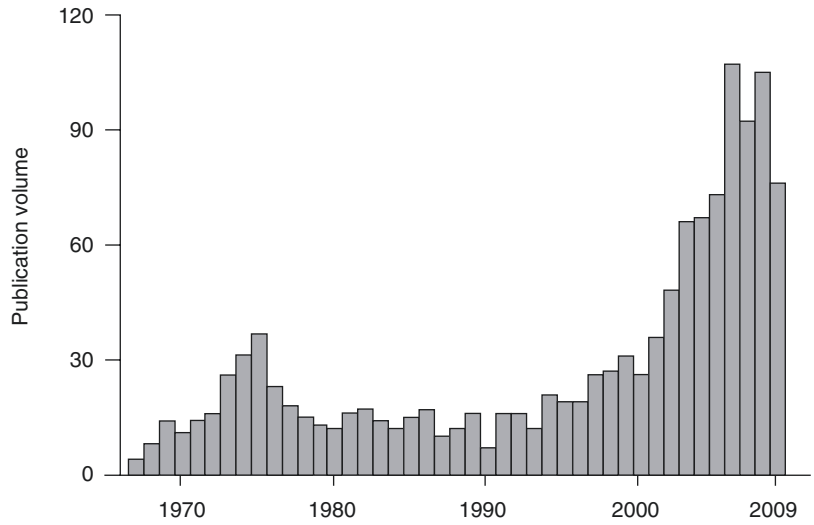


**Fig. 20.1** Publications regarding sleep and aggressive behaviour from 1967 to 2009. Note the temporal evolution of the publication volume concerning the association of these themes. One can observe two peaks in the graph, the first in the 1970s, correspondent to the pioneering studies about this relationship, and the second in the past decade, due to the improvement of psychiatric research concerning sleep and aggression

system in the genesis of aggression induced by paradoxical sleep deprivation [41–43]. These findings continue to be considered one of the hallmarks on the research about the psychopharmacological effects of sleep deprivation, as it set the grounds for the relationship between sleep deprivation and dopamine. This period, however, saw a decrease in the number of publications concerning the relationship between sleep and aggressive behaviour when compared to the 1970s (Fig. 20.1).

Likewise, the 1990s cannot be considered a prolific decade in terms of the amount of research on the relation between sleep and aggressiveness. Still, some works deserve to be mentioned given the relevance of their findings. Among these works are the first clinical studies that yielded useful data about sleep and aggressiveness [44, 45] and several papers examining sleep-related aggression from a legal perspective as well as its implications and juridical interpretation [46–49].

The 2000s were characterized by a revival of interest in the association between sleep and aggressive behaviour, albeit this time with a focus on different issues than those examined previously. The bulk of the literature from this period comes from psychiatric research, especially studies investigating disorders in which aggression is an inherent manifestation, like antisocial [50–53] and borderline personality disorders [54–57]. The efforts of Lindberg and Virkunnen, who investigated the relationship between psychiatric disorders and sleep architecture [50–52, 58–60] are notable. The work conducted by Mitchell concerning aggressive behaviour as well as other cognitive and behavioural characteristics in children with obstructive sleep apnoea is also relevant [61–63].

## Search Strategy and Selection Criteria

For this review, data were obtained in Medline and Scopus databases. Search terms were "sleep", "aggression", "aggressive behaviour", "aggressiveness", "violent behaviour", and "impulsivity". The works that fit the purpose of this review were considered for analysis. Moreover, relevant studies and reviews cited by the first selections also were considered. Articles published in English language were prioritized; however, relevant studies published in other languages were also considered, provided that these articles presented a summary in English.

## Aggressive Behaviour

Aggression is a complex, instinctive, and social behaviour that can be defined as acts performed for specific purposes in sight of or in response to threatening stimuli [64, 65]. This behaviour has both innate and acquired aspects and can be performed in pursuit of food, reproduction, and survival or in defence of an organism's territory or offspring [65, 66].

Aggressive behaviour is modulated through parallel activational and inhibitory pathways in the brain. In rodents, aggressive behaviour is usually triggered by olfactory stimuli, which are processed in the medial nucleus of the amygdala. This nucleus activates the periaqueductal grey, a structure responsible for the promotion of aggression, through the activation of three different brain areas: the anterior hypothalamic area, the bed nucleus of the stria terminalis, and the lateral septum. The inhibition of aggressive behaviour in rodents occurs in two distinct manners, both of which triggered by stressful stimuli: the inhibition of the anterior hypothalamic area due to activation of the paraventricular nucleus and the inhibition of the medial amygdala due to the activity of the orbitofrontal cortex. The circuitry underlying aggression is very similar in non-human primates, although aggressive behaviour is triggered predominately by visual and auditory stimuli and the participation of the lateral septum and paraventricular nucleus is low [66, 67]. Additional structures are also involved in behavioural modulation, with specific roles in subclassifications of aggression [67].

Despite the similarities between human and animal aggression, important differences must be taken into account [68, 69]. Human aggression is more complex than that of non-human primates, rodents, and other animals [65]. These differences emerge through an ethological analysis of animal behaviour, wherein aggression can be triggered

within certain contexts, like the pursuit of food and reproduction. Human aggression, however, must be viewed in light of a psychiatric perspective as being motivated by feelings and emotions such as anger, irritation, frustration, fear, or pleasure [66].

The differences between animal and human aggressiveness are also reflected in their classifications. In animals, aggressive behaviour is classified as predatory aggression, involving the attacking of prey for food [70, 71], or emotional aggression. Emotional aggression is further classified into three subcategories: offensive and defensive aggressions, which are differentiated by the context in which they are performed and by the main sites on the other animal's body that are attacked [65, 70], and maternal aggression, performed by lactating females in protection of their offspring [65, 72]. In addition to these classifications, there is play-fighting behaviour, which is very similar to aggressive behaviour and is displayed by prepubertal and sexually immature rats in which no social dominance or hierarchy is observed [70, 73].

In humans, there are several classifications of aggressive behaviour (briefly reviewed by Liu [74]). The more significant classification, for clinical purposes, distributes aggressive behaviour into two subtypes: the impulsive-reactive-hostile-emotional and the controlled-proactive-instrumental-predatory. The difference between these two categories lies in the fact that the first is impulsive and associated with feelings like anger, while the latter is wilful and directed toward the pursuit of specific objectives [75, 76]. This classification is based in a previous typology proposed by Feschbach [77], which separates aggression into instrumental and hostile categories. Moyer [78] proposed a stimulus-based classification of aggression, in which the behaviour is a response to previous eliciting stimuli. In this case, aggression can be categorized as predatory, intermale, fear-induced, irritable, territorial, maternal, or instrumental. Buss [79] classifies aggression in three different dimensions. According to this author, aggression can be physical or verbal, active or passive, and direct or indirect. Finally, some authors classify aggression as positive or negative. In this case, positive aggression is related to adaptive improvements, consolidation of identity and autonomy, survival, and social acceptance, among other issues, while negative aggression is goal-directed, resulting in harm, personal injury, or property destruction [80].

Certainly, all the classifications aforementioned have practical applicability. Indeed, they seem to analyse the same behaviour from different perspectives. Thus, these classifications are complementary, and, for a broad and complete approach of aggression, all of them should be considered.

## Sleep and Aggressive Behaviour: Animal Models

### Animal Models of Aggression

The main method employed in the investigation of aggressive behaviour in animals is the resident-intruder paradigm. In this paradigm, an animal, usually a mouse, rat, or vole, is kept isolated or in the company of a female. After a period of adaptation, an intruding animal, usually younger, is placed in the cage. In this context, aggressive behaviour occurs to ensure the territorial dominance or sexual success of the dominant animal [65, 81]. However, in the study of the relationship between sleep and aggressive behaviour, the resident-intruder paradigm is usually employed with modifications, like the confrontation of two animals under the same experimental conditions [35, 82]. Moreover, methods like muricide [40, 83, 84] and aggression induced by electric discharges [85] have also been utilized, despite reasonably uncommon nowadays. In cats, which in the past were commonly employed in both sleep and aggressive behavioural research, muricide is the main research method [86, 87]. Nevertheless, it must be noted that muricide among rats is a form of emotional aggressive behaviour, whereas in cats it represents predatory aggression.

### Animal Models of Sleep

Regarding animal sleep research, several techniques can be used, and the choice of a

technique must be contextualized within the aims of a particular study. In general, two groups of techniques can be employed when considering the relationship between sleep and aggressive behaviour. One allows analysis of how aggressive behaviour can modulate sleep, and the other enables investigation of the influence of sleep deprivation on aggressive behaviour.

In the first case, the methods are basically restricted to the recording of sleep, similarly to human polysomnography, by recording the electrical activity of the cortex and hippocampus (electrocorticogram) and muscles (electromyogram). By means of such recordings, one may analyse the sleep stages and trace a hypnogram to assess the sleep/wake patterns of the animal. The second group of methods includes several techniques that allow researchers to observe how the manipulation of sleep affects aggression. Two of the most frequently used methods include paradoxical sleep deprivation, which is commonly performed using a modified multiple platform protocol [3], and total sleep deprivation, which is carried out mostly by the gentle-handling method [88].

## Models of Sleep and Aggression

The involvement of *Cannabis sativa* in aggressive behaviour was first studied at the end of the 1960s [83, 89, 90] and served as the basis for the very first investigation into the relationship between sleep and aggression [34]. In this study, paradoxical sleep-deprived rats treated with extracts of *Cannabis sativa* displayed heightened aggressive behaviour and irritability with shorter latencies during a 4-h period, while the animals that were treated with the same extract but not sleep-deprived presented depressive-like behaviour. Such findings were later confirmed in subsequent studies [35, 38]. This method has developed into a model used to explore the roles of different neurotransmitters, mainly dopamine and noradrenaline, in the relationship between sleep and aggression, as can be seen below.

## Sleep and Aggressive Behaviour

### Neurotransmitters

Several studies have analysed the roles of neurotransmitters and other substances that perform specific actions within the central nervous system relevant to the association of sleep and aggression. A detailed description of studies and findings relevant to this relationship follows.

*Dopamine* The dopaminergic system was one of the first focuses in the study of sleep and aggression. The first work about this neurotransmitter in the context of this relationship [35] was based on other studies that had previously demonstrated enhancement of aggressive behaviour due to cannabinoid [34] and catecholaminergic action [91]. Carlini and Lindsey [35] found that dopaminergic agonists like apomorphine were able to induce aggression in sleep-deprived rats, similar to *Cannabis sativa*, indicating the involvement of dopamine in the modulation of aggressive behaviour in the context of sleep deprivation. Moreover, such effects are blocked by the administration of haloperidol and chlorpromazine, both dopaminergic antagonists [35]. Furthermore, this study concluded that integrity of the dopaminergic system is necessary for the genesis of aggressiveness induced by sleep deprivation in rats. Carlini et al. [36] corroborated these data and suggested that aggression may increase the dopaminergic turnover within that context.

Analysing the dopaminergic response to paradoxical sleep deprivation, Tufik et al. [39] concluded that the dopaminergic system becomes sensitized due to a shortage of paradoxical sleep. Paradoxical sleep-deprived rats treated with apomorphine presented increased body temperature and enhanced stereotyped and aggressive behaviour when compared to non-sleep-deprived animals treated with the same substance [39]. Additionally, Trotta et al. [92] demonstrated that apomorphine administration led to shorter but more intense aggressive attacks in sleep-deprived rats as well as inducing short periods of intense excitability not seen in control animals. These effects are mediated through the dopamine system,

as Troncone et al. [41] described a reduction of apomorphine-induced aggressive behaviour in sleep-deprived rats when pretreated with dopaminergic agonists, like amphetamine and L-dopa. Tufik [42] also verified these findings, showing that the administration of haloperidol 24 h prior to the administration of apomorphine enhances aggressive behaviour, while the administration of haloperidol 2 h prior to apomorphine inhibited aggressiveness. Moreover, bromocriptine and piribedil, both direct dopamine receptor agonists, also enhanced aggressiveness in sleep-deprived rats, demonstrating that this effect cannot be attributed exclusively to apomorphine but rather to the activation of dopaminergic receptors.

Studies report that amphetamines also induced aggressive behaviour in paradoxical sleep-deprived rats [93, 94], although other studies suggest that even high doses of amphetamine induce milder aggression than cannabinoids in sleep-deprived rats [34]. Carbamazepine, an antiepileptic drug, induced high aggressive response in sleep-deprived rats subsequent to the acute administration of the drug alone or combined with amphetamine but reduced aggressiveness after chronic treatment [94]. Together, such findings lead to the conclusion that paradoxical sleep deprivation induces sensitization of the dopaminergic system, but this can be prevented by previous treatment with dopaminergic antagonists.

*Noradrenaline* In 1974, Carlini and Lindsey [35] published a pioneering study examining the importance of noradrenaline in the genesis of aggressiveness by using a variety of adrenergic drugs in the context of the *Cannabis sativa* and sleep deprivation paradigm [34]. Reserpine (vesicular monoamine transporter inhibitor) and α-methyl-p-tyrosine (tyrosine hydroxylase inhibitor) reduced aggressive behaviour, while phenoxybenzamine (α-adrenergic antagonist) and FLA-63 (noradrenaline synthesis blocker) both increased aggressive behaviour in sleep-deprived rats, when compared to non-sleep-deprived animals. These data led the authors to conclude that noradrenaline exerts an inhibitory role over aggressive behaviour elicited by sleep deprivation. This was further supported by the results of Troncone and Tufik [95], who explored several noradrenergic drugs (agonists and antagonists of both α- and β-adrenergic receptors) to detail the role of this neurotransmitter in the modulation of aggressive behaviour in sleep-deprived rats. Only with isoproterenol, a β-adrenergic agonist, reduced aggressive behaviour was observed, suggesting that modulation of aggressive behaviour by the noradrenergic system is inhibitory, relatively weak, and restricted to β receptors.

The results of Carlini and Lindsey [35] also suggested that the dopamine/noradrenaline ratio is important in aggressive behaviour. This hypothesis was corroborated by Musty et al. [38], who observed a concomitant increase in cannabinoid-induced aggressiveness and the dopamine/noradrenaline ratio in sleep-deprived rats pretreated with 6-hydroxydopamine, a neurotoxin that acts on dopaminergic and noradrenergic cells. In addition, intraventricular injections of noradrenaline and the resulting restoration of the normal ratio between these neurotransmitters reduced the aggressive behaviour. These data indicate the importance of the dopamine/noradrenaline ratio in triggering aggressive behaviour within a sleep deprivation paradigm and the role of noradrenaline as an inhibitor of this behaviour.

*Serotonin* Serotonin has a well-known role in the modulation of aggressive behaviour (for review, see Ferrari et al.) [96]. The role of serotonin in aggressive behaviour and sleep was first examined by Carlini and Lindsey [97], who studied the effects of several serotonergic drugs in paradoxical sleep-deprived rats treated with *Cannabis sativa* extract. The results demonstrated that drugs that enhance serotonergic action (tryptophan and fluoxetine) increased aggressiveness, while those that reduce serotonergic action (fenclonine, cinanserin, and cyproheptadine) strongly blocked the same behaviour. Thus, aggressive behaviour triggered by the action of cannabinoids in paradoxical sleep-deprived rats seems to be modulated by serotonergic activity. Similarly, imipramine, in moderate doses (2 mg/kg), led to an increase in

aggressive behaviour in paradoxical sleep-deprived rats, although the same effect was not observed with higher doses (4 mg/kg) or in a long-term treatment (14 days) [94]. The results regarding fluoxetine and imipramine are similar to those demonstrating an increase in aggressiveness after the administration of antidepressants in the absence of sleep deprivation [98]. Conversely, studies examining the effects of serotonergic drugs such as mescaline and LSD have found no effect on aggressive behaviour in sleep-deprived rats [34, 37].

Since fluoxetine and imipramine inhibits serotonin reuptake while LSD and mescaline are serotonergic agonists, one may speculate on receptor-dependent action of serotonin in the proposed relationship. Indeed, 5-$HT_{2a/2c}$ receptors, sites of action of LSD, and mescaline are involved in reduction or extinguishment of aggressive behaviour, whereas other serotonergic receptors induce initiation and increase aggression [99]. Thus, this might explain the aforementioned discrepancies.

## Sleep Deprivation and Aggression

Studies directly associating sleep with aggressive behaviour are limited, and in general, this association is demonstrated by works employing paradoxical sleep deprivation. Among these few studies, Morden et al. [33], who observed aggressive behaviour subsequent to electrical stimuli in paradoxically sleep-deprived rats, and Hicks et al. [40], who observed a reduction in the latency of attacks and increased rate of muricide following suppression of paradoxical sleep, merit attention. In addition, Tufik et al. [39] observed a surge in aggressive behaviour in sleep-deprived rats treated with apomorphine when compared to non-deprived controls treated with the same drug. Finally, ethological analyses allow the conclusion that aggressive behaviour due to paradoxical sleep deprivation is predominately defensive, rather than aggressive, both in male [100] and lactating female rats [101–103].

Feng and Ma [85] recently examined the effect of paradoxical sleep deprivation during the neonatal period upon aggressive behaviour induced by electric discharges in adulthood. These animals displayed less offensive behaviour when confronted with normal rats. These results are interesting compared to those of studies that examine aggressive behaviour immediately after a period of paradoxical sleep deprivation [39, 40]. While the latter investigations found enhancement of aggressive behaviour following paradoxical sleep deprivation, Feng and Ma [85] revealed the opposite with sleep deprivation imposed during the neonatal period. It should be noted that the reported effects are attributed by the authors only to neonatal sleep deprivation, and no discussion about other events that may take place in the period between sleep deprivation and behavioural tests was provided. Nevertheless, the prospect of long-lasting alteration of aggressive tendencies due to precocious sleep deprivation is enticing, since it gives an ontological perspective regarding escalated aggression.

## Aggression Alters Sleep Patterns

When examining aggression as a natural stressor, particularly in the context of social defeat [104, 105], and with the awareness that several stressors may lead to alterations in sleep patterns [106], it becomes reasonable to expect alterations in sleep in animals submitted to an aggressive confrontation. This association was observed by means of social defeat protocols, in which animals exposed to an older and more aggressive rat displayed more slow-wave activity, indicating a higher intensity of non-paradoxical sleep [88]. Similar results were observed in mice, in which heightened activity and duration of slow-wave sleep and a reduction in the duration of paradoxical sleep were observed following social defeat protocol [107]. In addition, Meerlo et al. [108] demonstrated deleterious effects of exposure to social defeat upon the circadian rhythm. Based on these findings, it can be concluded that not only an aggressive animal presents changes in sleep patterns but also those subjected to aggression.

## Sleep, Aggression, and Panic

Furlan and Hoshino [109] suggested an interesting relationship between aggressive behaviour

induced by paradoxical sleep deprivation and anxiety disorders. Based on the relationship between the administration of sodium lactate and the precipitation of panic attacks in patients suffering from panic syndrome [110], the authors hypothesized that enhancement of aggressiveness induced by paradoxical sleep deprivation in rats subsequent to the administration of sodium lactate would be analogous to the panic symptoms in humans. Indeed, rats submitted to paradoxical sleep deprivation and treated with sodium lactate displayed enhanced aggressive behaviour, manifested mainly as upright confrontations and submissions. From these data, the authors concluded that the paradoxical sleep deprivation methodology may itself be a source eliciting panic attacks. Furthermore, the authors suggested that panic reactions may account for cases of domestic violence and social aggression most likely triggered by sleep deprivation [109, 111], a relationship that have been proved true in clinical settings [112].

In a similar context, de Paula and Hoshino [113] investigated the connection between panic attacks, modelled through audiogenic seizures, and aggression in sleep-deprived animals. Audiogenic seizures are a phenomenon that consists of wild running induced by high-intensity sound in rats. The results indicated that the animals displaying aggressive behaviour subsequent to sleep deprivation are more susceptible to audiogenic seizures, the characteristics of which correspond to the fight-or-flight reaction during the panic attacks.

## Final Considerations: Studies Involving Laboratory Animals

The relevance of animal research in the comprehension of the relationship between sleep and aggressive behaviour is evident. However, basic research has yielded few studies on aggression and sleep in recent years, since currently this relationship is mainly studied in humans, from a psychiatric perspective. Another point to be noted is that the main focus of these studies is paradoxical sleep deprivation, while total sleep deprivation has been rarely used.

Based on these studies, the effects of sleep deprivation, mainly paradoxical sleep, on aggression are clear. However, the neurobiology underlying this relationship still requires further explanation. Dopamine and noradrenaline seem to be the most important neurotransmitters to aggression modulation, but it should be kept in mind that studies examining their importance mainly did so in association to drugs, such as *Cannabis*, apomorphine, haloperidol, chlorpromazine, and reserpine, for example. Thus, further studies purely examining the association of sleep and aggression are warranted. Moreover, the role of additional variables in the relationship between sleep and aggression (e.g. panic attacks and social defeat) still requires further investigation. The main relationships between sleep and aggression in animals are resumed in Fig. 20.2.

## Sleep and Aggressive Behaviour: Humans

The segment that follows will examine the main clinical studies investigating the relationship between sleep and aggressive behaviour. The association between variables is taken into account from several different perspectives.

### Research Methods

As in animal experimentation, few studies directly examine the relationship between aggressive behaviour and sleep deprivation in humans. Although this relationship has been poorly explored, its existence is strongly supported since antisocial behaviours and irritability are considered expressions of aggressiveness [45].

Regarding the methods used to investigate sleep in humans, polysomnography is the gold standard in the acquisition of data about sleep, although several studies make use of questionnaires and scales, such as the Epworth Somnolence Scale, the Basic Nordic Sleep Questionnaire, and the Pittsburgh Sleep Quality Index. In some cases, polysomnography is used in conjunction with

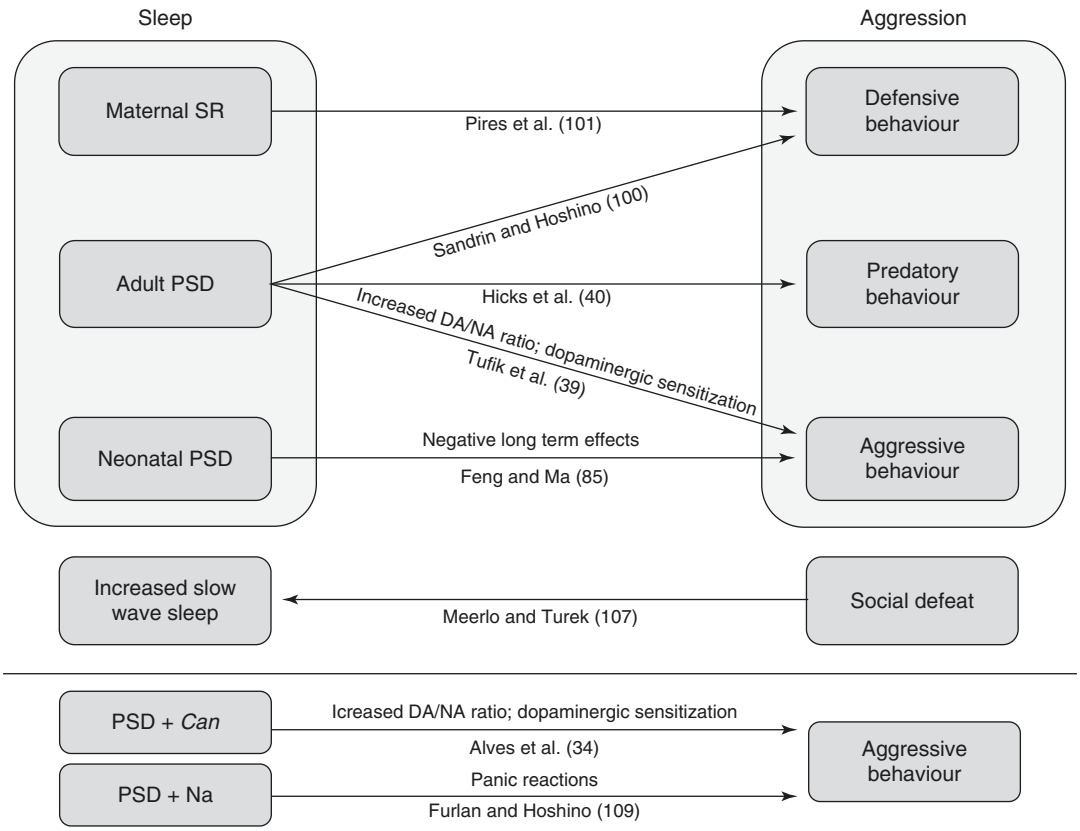


**Fig. 20.2** Relationship between sleep and aggression in animals. The arrows indicate the direction of the association. For each relationship is presented a key reference. Whenever possible, the underlying mechanisms are showed; however, most of the associations are based only in the outcome. SR: sleep restriction; PSD: paradoxical sleep restriction; *Can: Cannabis sativa* extract; Na: sodium lactate: DA: dopamine; NA: noradrenaline

these questionnaires, providing additional information.

Similarly, in order to investigate aggressive behaviour in humans, the majority of existing studies employ questionnaires, while other studies use behavioural observation or responses to specific stimuli [114, 115]. Among these questionnaires, the most utilized is the Aggression Questionnaire, which is specific to aggressive behaviour [116]. In studies involving children, questionnaires are commonly filled out by the parents or legal guardians, as is the case for the Child Behaviour Checklist, Conners' Parent Rating Scale, and the Behaviour Assessment System for Children. In general, such questionnaires are not specific to aggressive behaviour and encompass other behaviours and information of psychiatric interest.

## Aggression and Dreams

Dreams may be defined as the main mental activity that occurs during sleep [117]. This activity, which is predominant in REM sleep [118], is composed of experiences comparable to wakefulness or of a bizarre or fantastic nature [117] and directly involves primary consciousness (which includes perception and emotion), but not secondary consciousness (including self-reflexive consciousness, abstract thinking, willingness, and metacognition) [119]. In this context, some studies have sought to analyse dreams with aggressive content.

Based on five case reports, Hempel et al. [120] proposed a disorder called psychotic dream-related aggression, discussing a possible continuity of the cognitive process through the

sleep-wake cycle. In this disorder, which mostly affects people with psychiatric conditions, particularly paranoid schizophrenia, aggressive episodes can be triggered by dreams or nightmares. The five cases that were reported corresponded to individuals who had committed some form of violent act against another person following to dreams that compelled them to perform the act. In general, the individuals dreamed of something that incited violence and committed the violent act when they awakened. It is relevant to note that at the moment of the violent acts, the individuals were awake but not fully aware of their acts. This differentiates this disorder from other parasomnias, like REM behaviour disorder (RBD), in which aggression occurs when the subject is asleep. As the violent acts happened as a consequence of violent dreams, the authors speculate that the reported cases are evidence of the continuity of cognitive processes from sleep to wakefulness.

Fantini et al. [121] examined the content of dreams and aggressiveness during wakefulness in individuals with RBD, a disorder characterized by loss of muscle atonia during REM sleep and that is commonly accompanied by aggressive bursts during the night (for review, see Frenette) [122]. It is interesting to note that the diagnostic criteria for RBD do not consider the content of dreams; however, it is expected that RBD episodes happen in concomitance to dream activity and that these dreams could be "acted out". Compared with healthy subjects, individuals with RBD reported a higher percentage of dreams with aggressive content, although there was no difference between the groups in Aggression Questionnaire scores. These data indicate that the elevated incidence of aggressive dreams in individuals with RBD is not associated with increased daytime aggression. A more recent analysis have denied the relationship between RBD and aggressive dreams [123] but have been promptly criticized on the literature, due to its dream recall methodology, its reduced sample size, and the fact that 75% of the samples (9 out of 12 patients) were under treatment with clonazepam, which impacts dream-enactment behaviours [124]. The results of Fantini et al. do not support the hypothesis of cognitive continuity during the sleep-wake cycle as the contents of the dreams do not reflect in the behaviour during wakefulness. The differences between these two studies can be partly explained by the conditions of the patients. While in the study by Hempel et al. [120] the subjects were schizophrenic patients with psychotic dream-related aggression, Fantini et al. [121] investigated individuals with RBD.

Some studies have been carried out to assess the characteristics related to dreaming in patients with borderline personality disorder (BPD), a psychiatric condition characterized by aggressiveness and impulsivity [57]. Such patients were examined by Semiz et al. [54] for the occurrence of nightmares as a consequence of acute stress and the presence of dream anxiety, which is a function of personality. This study revealed that patients with BPD presented higher prevalence of nightmares and higher rates of dream anxiety. In addition, the patients experiencing nightmares were found to be in a more serious clinical condition, revealing a close link between the frequency of nightmares and the severity of BPD. However, it must be pointed out that aggressiveness and the surge in the frequency of nightmares are most likely independent events and may both be manifestations of the psychiatric condition.

## Aggression and Sleep in Adults

Recent studies have reinforced the idea that poor sleep quantity and quality might lead into an increased aggressive behaviour in adults [125–128]. The reasons for these effects are still under debate, and diverse possible explanations have been raised in recent literature. Vaughn et al. [128] evaluated and observed a significant relationship between poor sleep and increased reactive violence among African-Americans, suggesting that social factors, such as ethnic discrimination, may play a role on these results. Randler and Volmer also evaluated the relationship between poor sleep and aggression on a sample of young adults, demonstrating that sleep duration is negatively correlated with verbal and physical aggression [127]. They credit part of

these results to social jetlag, a condition characterized by an unpairing of one's physiological sleep rhythm and preferences with the social routine. Kamphuis et al. support the observation that poor sleep lead to increased reactive aggression. According to these authors, this relationship may be mediated by the impaired prefrontal cortical functioning observed in sleep-deprived individuals. Curiously, the only laboratory-controlled sleep-deprived study on this field have demonstrated that a 33-h-long sleep deprivation lowers reactive aggression, in concomitance with a reduction on testosterone level [129]. One might note that this last example made use of an acute controlled sleep deprivation scale, while the others used samples who were chronically sleep deprived, being these differences between acute and chronic sleep deprivations the possible explanation for these different effects.

## Aggression and Sleep in Children

Several studies assess the interaction of sleep and aggressive behaviour in children. It is known that aggressive behaviour and issues related to conduct disorder in children and adolescents may be triggered by various sleep-related factors, like poor sleep hygiene, sleep restriction, restless legs syndrome, and insomnia [30, 130]. Here, we will consider studies examining how general problems and sleep habits are related to behaviour. The relationship between sleep-disordered breathing and aggressiveness is further assessed in a separate section.

The interaction between sleep disorders and aggressiveness was examined in children between 4 and 12 years of age by means of questionnaires completed by the children's parents [131]. Aggressive behaviour was correlated with several conditions relevant to sleep, such as parasomnias, enuresis, daytime fatigue, insomnia, and noisy sleep (which encompass sleep bruxism and sleep-talking). Moreover, aggressiveness in these children proved to be a predicting factor for noisy sleep. Gregory and O'Connor [132] assessed the consequence of early childhood (4 years old) sleep problems on behavioural issues at the beginning of adolescence, between 13 and 15 years of age. The results indicate that the presence of sleep problems during childhood is a predictive factor of aggressive behaviour in adolescence, although childhood aggressiveness did not seem to be a factor predicting sleep problems during adolescence. Interestingly, these data suggest that the relationship observed by Stein et al. [131], who reported that aggression significantly predicted noisy sleep in childhood, is not maintained longitudinally. Gregory et al. [133] carried out a similar study examining the opposite relationship, providing questionnaires to the parents of children and adolescents from 9 to 19 years old and again when they reached 19–32 years old. In that study, sleeping less during childhood was a predictive factor for the development of aggressive symptoms as an adult, corroborating previous reports [132].

The association between sleeping habits and behaviour in preschool children was assessed by Yokomaku et al. [134]. In this study, children who presented bad sleep and social habits, like going out with adults after 9:00 PM two or more times per week, going to bed after 11:00 PM four or more times per week, and getting home after 9:00 PM three or more times a week, when compared to children who did not engage in any of these habits, presented longer night sleep times, shorter naps, and higher aggressive behaviour scores as well as higher anxiety and depression scores. Furthermore, the aggressive behaviour score was strongly correlated with the time at which the individual went to bed and awakened. Likewise, Schlarb et al. demonstrated that eveningness is positively correlated with aggression in both children and adolescent [135].

## Sleep-Disordered Breathing and Aggression

Sleep-disordered breathing (SDB) is a generic nomenclature given to conditions in which snoring and limited airflow are observed, leading to arousals or oxyhaemoglobin desaturations. SDB encompasses three general

categories: obstructive sleep apnoea, central sleep apnoea, and sleep-related hypoventilation syndromes [136, 137]. The relationship between SDB and aggression has been examined by several authors. Herein, this association, as well as the effect of treatment of such disorders on aggressive behaviour, is examined in both children and adults.

## Sleep-Disordered Breathing and Aggressive Behaviour in Children

SDB during childhood is well recognized and has been thoroughly described in the literature. It has been argued that the disorders at this stage of life can be attributed to two main causes: adenotonsillar hypertrophy and reduced oropharyngeal dimensions [138]. Moreover, it is estimated that the prevalence of obstructive sleep apnoea in children ranges from 2% to 3% and reports of primary snoring range from 3% to 12% [139]. Knowing that children may develop SDB and that such disorders lead to comorbidities that may cause complications in adulthood [21], it becomes necessary to examine the effect of those disorders upon the behaviour of children.

Ali et al. [140] analysed the relationship between SDB and behavioural issues in children aged 4–5 years using parental report and overnight sleep monitoring. In this investigation, aggressive behaviour was reported by parents whose children carried a higher risk of developing some respiratory disorder. In a similar study conducted with 3019 children aged 5 years, the presence of SDB, assessed by parental-completed questionnaire, was associated with a twofold increase in aggressive behaviour compared with children without SDB symptoms [141]. A third study encompassing 2474 first graders confirmed snoring influences aggressive behaviour in children regardless of BMI, attesting that paediatric SDB is not explained by obesity as it commonly is among adults [142]. These three studies, taken together with others with smaller samples and conducted, respectively, with questionnaires and polysomnography [143–145], reinforce the existence of an association between aggressiveness and SDB in children.

## Adenotonsillectomy in Children and Its Implications for Aggressiveness

Tonsilar hypertrophy is the main cause of SDB in children [138] and is frequently treated by adenotonsillectomy, which is the main therapeutic strategy for this disorder in children [62, 146]. SDB during childhood may carry several behavioural consequences, including aggressiveness as previously discussed [62, 140, 141]. Therefore, several studies have focused not only on the effects of adenotonsillectomy on the evolution of SDB but also on its impact on SDB-associated behavioural problems.

Stradling et al. [147] were the first to report that children undergoing adenotonsillectomy presented nearly complete remission of their cognitive and behavioural symptoms as well as remission of other parameters directly linked to sleep, like hypoxemia and somnolence. This is supported by similar studies demonstrating a concomitant reduction in restless sleep and aggression following surgery [63, 148, 149]. These studies suggest that the decrease in aggressive behaviour is due to the improvement in sleep parameters following surgery.

Contrary to the aforementioned studies, Constantin et al. [150] retrospectively assessed the sleep and behavioural outcomes of adenotonsillectomy in children and reported that although the surgery improved parental reports of sleep, respiration, and quality of life, it did not promote any improvement in behaviour.

## Sleep-Disordered Breathing and Aggressive Behaviour in Adults

The literature is rich in papers examining SDB and aggressive behaviour in children, but the same cannot be said for adults as few papers have investigated the interaction of these two variables in the adult population. This dearth of existing research can be explained by the far more complex aetiology of SDB in adults than in children. However, there is some evidence that supports the relationship between SDB and aggression. For example, Booth et al. [151] examined a highly aggressive criminal population who had committed some form of sexual offence and who presented a previous diagnosis of obstructive

sleep apnoea. The subjects underwent polysomnography and were subsequently treated with continuous positive air pressure (CPAP), and the Aggression Questionnaire was completed before and after the treatment. Pretreatment aggressive behaviour was strongly correlated with the Epworth Somnolence Scale, but after CPAP treatment, the aggression score fell substantially. These data suggest that in highly aggressive individuals, sleep apnoea may be a determining factor in the manifestation of aggression.

The effects of sleep apnoea on cognition and behaviour as well as the relevance of CPAP treatment for such conditions were previously discussed [25, 152]. Although these reviews clarify fundamental aspects of the relationship between sleep apnoea and behaviour, none of them examine aggressiveness directly, clearly illustrating the shortage of studies and data relevant to this relationship in adults.

## Aggression and Sleep in Psychiatric Disorders

When contemplating the relationship between sleep and aggressive behaviour in psychiatric disorders, one must bear in mind that aggressiveness and violence are not diagnoses but rather behaviours [153]. Thus, very often the aggressive behaviour is present as a manifestation of several psychiatric disorders [154]. Among the psychiatric illnesses related to aggressive behaviour and sleep, the most relevant are the personality disorders. However, one might highlight the association of aggression and sleep in other conditions such as in schizophrenia, drug abuse, and nonspecific mental retardation.

### Personality Disorders

Individuals afflicted with antisocial personality disorder (APD) are marked by patterns of disregard for the rights of others and the law, low or absent empathy, and absence of regret. They may also be impulsive, irresponsible, and aggressive [58, 155]. Borderline personality disorder (BPD) shares some of these characteristics, particularly impulsiveness and aggressiveness [57, 156]. In general, BPD is characterized by a pervasive pattern of instability in emotional regulation, interpersonal relations, self-image, and impulse control.

Several studies demonstrate that individuals with APD and BPD have disrupted sleep patterns. Lindberg et al. [50] examined, among other variables, the quality of subjective sleep in individuals with APD and found that these individuals reported more difficulty falling asleep, more night-time arousals, and higher daytime somnolence compared to control subjects. Similarly, Semiz et al. [53] found that APD patients were afflicted by a higher number of complaints related to sleep quality, measured with the Pittsburgh Sleep Quality Index, and also higher scores of aggressiveness, measured by the Aggression Questionnaire. Significant and positive correlations were found among all of the sleep and aggressiveness parameters. Lindberg et al. [58] also assessed the sleep patterns in 16 individuals afflicted with APD, six of whom had concomitant BPD, and found lower sleep times in stages 2 and 3 and higher sleep times in stage 4 compared to controls. Furthermore, individuals with severe misconduct or intermittent explosive disorder presented lower sleep times in stages 2 and 3 and higher sleep times in stage 4 when compared to lower misconduct individuals or individuals without intermittent explosive disorder. Together with previous evidences [157], these findings suggest that the amount of sleep in stage 4 is related to aggressive behaviour.

Few studies of APD have been conducted in women. In two of them, the similarities with male data led the authors to conclude that the biological correlates of impulsive aggression in antisocial individuals are common to both genders [52, 60].

The sleep pattern of BPD patients has been under investigation for quite some time. In general, this disorder is characterized by shortened REM latency and higher REM density [158, 159]. However, these findings have not yet been associated with impulsivity or aggression, commonly observed in these individuals, although there may be a relationship with dream content (see above for discussion).

### Schizophrenia

Schizophrenic patients may display aggressive acts, associated with a distortion or warping of perception, such as hallucinations; however, it is unclear whether the nature of such acts is impulsive or premeditated [160]. Sleep disturbances are also common in schizophrenic subjects. It is estimated that 30–80% of schizophrenics are affected by some form of sleep disorder [161]. Although both aggressiveness and sleep disorders are important and concomitant characteristics of schizophrenia, few studies have assessed these two variables together. Lindberg et al. [51] described the case of a schizophrenic woman with traits of APD and a history of homicide attempts that underwent treatment with quetiapine and citalopram. In this patient, the expected sleep patterns for schizophrenia [161], including reduced sleep efficiency and total sleep time, were observed, in addition to a high percentage of slow-wave sleep, which is common in APD [58] but contrary to what is expected in schizophrenia. It should be noted that increase in slow-wave sleep is observed in schizophrenic patients under treatment with clozapine and olanzapine specifically, but not with quetiapine [161]. After treatment the patient presented reduction of slow-wave sleep to normal levels, which was attributed to citalopram, as well as improvement in her behaviour and clinical condition [59], suggesting a relationship between sleep patterns and aggression in schizophrenia. However, more studies are needed to explore this question.

### Other Psychiatric Disorders

The literature is rich in studies of drug abuse as it relates to aggression and sleep disorders, particularly in adolescents. Alcohol and other drugs are intimately associated with violence and aggressiveness [162, 163]. With regard to sleep, the presence of disorders like insomnia may be used as risk indicators for drug abuse in adolescents [164, 165]. Fewer studies directly assess the relationship between sleep and aggressiveness. Notably, Haynes et al. [166] demonstrated the existence of a clear inverse relation between improvement in the sleep parameters and aggressiveness in adolescent participants in a drug abuse treatment program, which was made especially evident by an improvement in total sleep time and a reduction of idealization of aggressive acts.

Some studies report cases in which there is an association between aggressiveness and sleep in mentally retarded individuals. Among these is a report of a 31-year-old man with severe mental retardation who was chronically sleep deprived and highly aggressive [45]. This study defines sleep deprivation as sleeping less than 5 h per night. Whether this is a case of sleep deprivation or just a report of a short sleeper can be questioned, as can whether his aggressiveness is due to sleep deprivation or to his psychiatric condition. Piazza et al. [115] described results obtained from the observation of 51 patients with developmental disorders (e.g. Down syndrome, Lesch-Nyhan syndrome, and Sanfilippo syndrome) who engaged in aggressive behaviours, including self-mutilation, destructiveness, and aggression against others. In this population, total sleep time was reduced as a result of a combination of increased sleep latency, more arousals during the night, and late awakening.

## Violent Behaviour During Sleep

Many cases of aggressive acts committed during sleep are described in the literature, spurring discussion about which disorders could elicit such acts. Several are the conditions which might lead to violent behaviours during sleep, among which should be highlighted arousal disorders and RBD, epilepsy (mainly nocturnal frontal lobe epilepsy), and some psychiatric conditions [167].

Broughton et al. [168] described a homicide committed during suspected sleepwalking and discussed possible reasons for it, like epilepsy and RBD. Nofzinger and Wettstein [47] reported a homicide supposedly committed due to confusional arousal caused by severe and chronic obstructive sleep apnoea, while Cartwright [169] described the genealogy of an individual accused of homicide that was attributed to a sleep disorder. This genealogy included a history of sleepwalking, sleep-talking, night terror, enuresis, and

bruxism, revealing the relevance of a family history of sleep disturbances related to aggressive behaviours. These studies indicate that parasomnias, including confusional arousals, night terror, sleepwalking, and RBD, may be the sleep disorders most commonly related to violent behaviour during sleep. Among other sleep disorders that may lead to violent acts, obstructive sleep apnoea and idiopathic hypersomnia must be highlighted [46]. Although the reported prevalence of aggression during sleep is 2%, clinical experience indicates that violence during sleep is more frequent than estimated [170].

Although many case reports exist regarding aggression during sleep, few systematic studies have been conducted in relation to this issue, probably due to the rarity of this phenomenon. Moldofsky et al. [44] assessed 64 patients diagnosed with night terror or sleepwalking. Polysomnographic analysis showed that among such patients, those who were violent toward other individuals had less alpha activity and a lower percentage of sleep in stage 4. The authors concluded that aggression during sleep may be due to two main, but not necessarily concurrent, factors: the presence of a pre-disposing factor, like parasomnia during childhood or a family history of parasomnia, and a triggering stressor, like a disturbance in the sleep rhythm or a psychological stress. Frauscher et al. [171] verified that individuals with RBD had greater amounts of movements during the night, including violent movements that could be dangerous for a partner, when compared to healthy individuals. Reviewing 32 cases of confusional arousals, sleepwalking, and night terror, Pressman [172] concluded that aggressiveness does not occur intentionally and is, in most cases, triggered by proximity and direct physical contact.

Considering the relevance of aggressive behaviour associated to sleep as well as the lack of epidemiological efforts in this field, Ohayon and Schenck [173] conducted a population-based study in order to investigate the prevalence of violent behaviours during sleep. This study, conducted with over 19,000 individuals from six different European countries, revealed that about 1.4–1.7% of the population above 15 years old presents violent behaviours during sleep. Moreover, the most frequent conditions related to these violent acts were dream enactment, sleep walking, and sleep terrors. The results of this broad survey are similar and partially corroborate the previous estimates [170].

## Forensic Implications of Sleep Aggression

Poor sleep is correlated with increased impulsive and aggressive behaviour in forensic populations [126]. Additionally, as mentioned previously, sleep aggression may result in crimes like attempted murder or even murder in fact. However, crimes committed during sleep, and therefore unconsciously, have remarkably led to several debates and discussions [174]. The lack of diagnostic tests and parameters for sleep disorders related to aggressiveness represents a problem, particularly due to the episodic nature of such disorders and to their complete reversibility during wakefulness [169]. In this sense, some authors have proposed criteria to define aggression related to sleep disorders, purporting to offer an underlying basis for juridical decisions regarding the subject. Poyares et al. [153] called attention to the importance of a complete and impartial evaluation of the defendant and of medical testimonials for the defence as well as for the prosecution. Additionally, those authors call attention to the importance of having a detailed medical history as well as clinical and laboratory assessments, including neurological, psychiatric, and polysomnographic assessments.

Specific criteria to identify violent cases triggered by sleep apnoea associated with confusional arousals were proposed by Nofzinger and Wettstein [47]. The authors explain the importance of a medical diagnosis for sleep apnoea syndrome, evaluation of possible psychiatric comorbidities, demonstration of unconscious automatism by polysomnography, and verification of behaviour during wakefulness. Notwithstanding, it must be noted that the absence of such behaviours from polysomnography or the existence of discrete behaviours should

not be taken as proof that these do or do not exist due to the rarity of their occurrence.

General guidelines for the determination of violent acts triggered by sleep disorders were stipulated by Mahowald and Schenck [174]. According to these guidelines, the following criteria must be met before such acts can be deemed associated with sleep:

- Suspicion of a sleep disturbance.
- Short duration of the violent act (minutes).
- Abrupt, impulsive, immediate, and directed behaviour, without apparent premeditation or motivation.
- The victim is someone who was present, possibly the stimulus for the awakening.
- Perplexity, once consciousness is regained, without attempt to escape, conceal, or mask the action.
- Amnesia, although not necessarily complete.
- Specifically for cases of sleep terror, sleepwalking, or sleep drunkenness: the act may occur while attempting to awaken the individual, usually during the beginning of sleep, and can be facilitated by alcohol intake, administration of sedatives, hypnotics, or sleep deprivation.

Although aggression related to sleep is well documented in the medical literature and despite efforts to clarify the definition of a crime committed unconsciously due to a sleep disorder, there is still reluctance and resistance in the juridical system regarding medical opinions and testimonials about the matter. This stems from the belief that knowledge regarding sleep can be based solely on subjective daily experience [46]. As reflex, different verdicts have been issued in very similar cases [169]. However, the opinion of sleep medicine specialists has been requested more often in such cases in recent years [174].

## Conclusions and Perspectives

In general, sleep research is a broad field, and the volume of knowledge is increasing. This is due in part to the social and public health relevance of sleep. Like sleep, aggressive behaviour is also an important factor to be considered in the context of public health. Even so, summarizing the main findings and conceptualizations of this association is complex, as both themes are interrelated in many ways. Moreover, some factors inherent to research on aggressive behaviour are important for the comprehension of the presented data. First, aggressive behaviour and related aspects are reported under different nomenclatures in the literature, like *aberrant behaviour* [114], *aggression* [58], *aggressive behaviour* [175], *aggressiveness* [121], *impulsivity* [176], *problematic behaviour* [134], and *violent behaviour* [172]. Second, aggression and violence are behaviours that can be expressed in specific situations and circumstances but are not diagnoses [46, 153], and this fact makes the subject very broad but nonspecific.

Another interesting point to be noted is that the reviewed studies do not discuss aggression as a behavioural trait or state. However, this discussion is implicit throughout the text, with a close relationship with the bidirectional association between sleep and aggression. Aggressive behaviour could be considered a behavioural trait when it is a pre-observed condition, such as in APD patients. On the other hand, when aggressive behaviour is observed as a function of sleep loss or disruption, it is more likely to be considered as a reversible behavioural state. Nonetheless, in some cases the discrimination of trait or state aggressiveness has limitations. Such is the case of the aggressive behaviour induced by sleep-disordered breathing in children. In this case, this is a chronic condition with long-term effects and is therefore similar to a trait characteristic. However, after adenotonsillectomy, the behaviour tends to improve, revealing aggression to be a state feature. Regarding animal research, since aggression is analysed as an escalated behaviour in most of the cases, the discrimination in trait and state has low significance.

Although the volume of publications about the relationship between sleep and aggression is rising and its relevance is evident, there have been few breakthroughs in this field over the past decade. The main findings date from between the end of the 1960s and the beginning of the 1980s,

when the topic was studied in animals as well as in humans. It was also during that period that some understanding was acquired about the neurobiology of this relationship. Since then, studies have assessed sleep and aggression in several contexts but not evaluated the direct relationship between them. Such is the case of studies that examine the effects of adenotonsillectomy on the behavioural patterns of children with SDB, those examining sleep in individuals whose psychiatric disorders lead to aggressive and impulsive behaviours, and those studies regarding the legal consequences of violent acts committed while asleep. Despite the notable relevance of such studies and their contribution to our understanding of sleep and aggression, much remains to be examined, and such issues are potential themes for future investigations. Figures 20.2 and 20.3 provide a graphical synthesis regarding the proposed association. Below are key areas for future research into the direct relationship between aggression and sleep, raising testable hypothesis for future studies:

- It is not known whether an aggressive response to sleep deprivation, especially in animals, is an adaptive mechanism or a consequence of dysfunction of homeostatic mechanisms. Considering that adaptive mechanism has a great importance for animal research but limited relevance in human context, an evaluation of this would be informative regarding the translational applicability of basic studies on sleep and aggression.
- The neuronal circuitry underlying aggressive behaviour in animals and sleep is somewhat understood, but little is known about how such circuitry is modulated in the case of aggressive behaviour induced by sleep alterations. Studies examining the circuitry during sleep deprivation-induced aggression are critical for understanding the neurobiology underlying this relationship.
- Similarly, the roles of the various neurotransmitters in the relationship of sleep and aggressive behaviour are not well known.
- Sleep, aggression, and hormones are rarely and superficially approached together. In view of the lack of such studies, some effort to relate sleep, aggression, and hormones is necessary.
- Few longitudinal studies have been conducted to assess the relationship between sleep and aggressive behaviour. The studies discussed above allow the conclusion that these issues are associated but do not provide any insight into the mechanisms relating them. Furthermore, it is not known how or why (a) aggressive individuals present sleep alterations or (b) sleep deprivation and sleep disorders lead to aggressive conduct.
- Longitudinal investigations focusing on the ontogeny of the relationship between aggressive behaviour and sleep are promising. These studies could reveal the development of aggressiveness related to sleep from childhood to adult life.

In addition to such basic aspects of the relationship between sleep and aggressive behaviour, other more refined and specific associations between these two themes may also be explored in future studies. Some of the relationships that have as yet to be examined are:

- In animals, little is known about the manipulation of sleep over a specific category of aggressive behaviour, namely, maternal aggression. Despite the current data that points to an increase in maternal aggression due to sleep restriction, this relationship still requires further examination.
- In animals as well as in human research, no study has assessed the effect of sleep or its manipulation on distinct classifications or categories of aggressive behaviour. It is not clear, for example, in which contexts sleep deprivation in animals produces defensive or offensive aggression, as well as whether heightened aggression in sleep-deprived humans is impulsive-reactive-hostile-affective or controlled-proactive-instrumental-predatory.
- The relation between SDB, especially obstructive sleep apnoea, and aggression in adults has not yet been examined in a consistent manner. Despite strong indications that the relation-

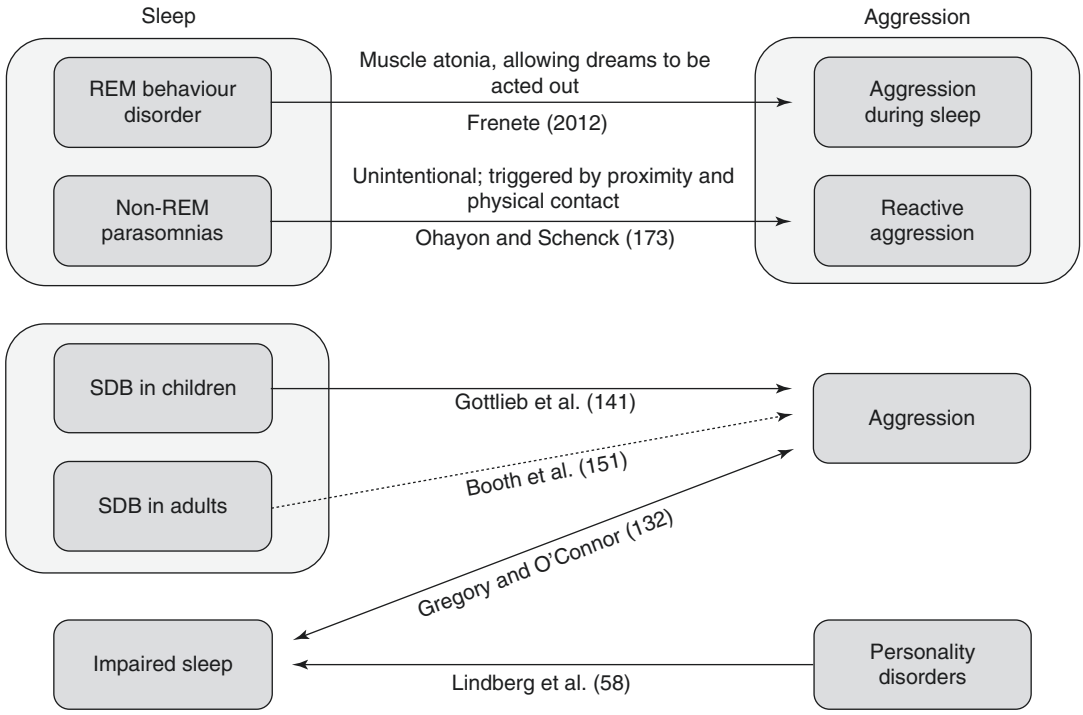


**Fig. 20.3** Relationship between sleep and aggression in humans. The arrows indicate the direction of the association, and the dashed arrow points a weak but plausible relationship. For each case is presented a key reference. Whenever possible, the underlying mechanisms are showed; however, most of the associations are based only in the outcome. REM: rapid eye movements; SDB: sleep-disordered breathing

ship between these two variables does exist, few studies have been conducted, and the existing data are inconclusive. Since obstructive sleep apnoea is very prevalent, the evaluation of its effects on aggressive behaviour is necessary.

In short, the interrelationship of sleep and aggressive behaviour is broad and relevant and has been examined within several contexts, attesting its bidirectionality. Based on the reviewed studies, it becomes plausible to conclude that sleep deprivation induces aggression (e.g. paradoxical sleep deprivation inducing aggression in rats), in several contexts, although more studies are needed. The opposite relationship, aggressive behavioural phenotype inducing changes in sleep parameters, is applicable in a lower extent (e.g. APD patients or rodents submitted to social defeat). However, in these cases the relationship is better established. Despite the need for additional investigations into the subject, this review summarized the knowledge that exists on the relationship between sleep and aggressive behaviour, pointing out its neurobiological relevance.

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# Part III

# Neurosciences, Learning, Teaching and the Role of Social Environment

# Effectiveness of Prosocial Behavior Interventions: A Meta-analysis

21

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Following the current prevailing view in psychology, the intervention programs focused primarily on reducing risk factors associated with internalizing and externalizing problems without paying much attention to the promotion or stimulation of constructive behaviors. Consequently, there are several intervention programs of known effectiveness designed to discourage disruptive behaviors such as aggressive behavior in children and teenagers, which then study their secondary effect on positive behavior, for example, prosociality [1]. However, with the emergence of positive psychology, the development of programs began to directly promote prosocial attitudes or behaviors in children as well as adolescents. With this change in approach in the manner of designing and addressing intervention, the need arises to analyze the efficacy of these intervention programs whose main purpose is to promote prosocial behaviors.

## Prosocial Behaviors

Prosocial behaviors have been defined as voluntary actions aimed at sharing, comforting, and helping others [2–4]. Several research studies have shown that helping behavior arises at an early age, for example, studies performed by Warneken and Tomasello [5] found evidence that infants between 14 and 18 months of age display instrumental helping behaviors. Instrumental helping develops once a child can perceive the needs of others and can spontaneously provide help, for example, in reaching for an object or removing an obstacle without receiving a reward. According to Warneken and Tomasello [5], instrumental helping is the first rudiment of altruistic behavior. Other studies showed that cooperation and sharing behaviors appear around the ages of 24 and 25 months, respectively [6, 7],

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while more elaborate prosocial behaviors such as comforting others first appear around the age of 30 months [8].

Although many studies on prosociality have been conducted, there are less longitudinal studies (performed on the same participants across time) that report the evolution of prosocial behaviors during the different stages of life span. Since previous studies have shown the relationship that exists between the development of moral reasoning and prosocial behavior, the authors were inclined to affirm that prosocial behavior increased with age [9]. However, a recent study conducted on children and adolescents from 10 to 17 years old found that prosocial behavior patterns are relatively stable and identified three distinct prosocial trajectories, high, medium, and low, which remained stable across the ages under study [10]. Hence, one may deduce that having acquired the maximum level of prosocial reasoning does not guarantee the emergence of prosocial behavior, since the latter is also the fruit of a voluntary and intentional decision.

Furthermore, it is encouraging to know that previous research has indicated that prosocial behavior is a relatively supple variable that can be stimulated through appropriate educational actions [e.g., 11, 6]. "The main goals of humane education are to provide children the opportunity to learn and understand another's experience, share their feelings, and to help others. Each of these components is associated with the feeling of having empathy for others" [12 (399)] and, consequently, would lead to the manifestation of greater levels of helping behavior. Prosocial behaviors, such as sharing, comforting, and being available to help others, are behaviors that are highly valued in the society because they contribute to the social well-being and to the construction of a more equitable world, hence the importance of analyzing the efficacy of existing intervention programs given that the critical role of prosocial behaviors on civic and social commitments are well known, as well as in their prevention of crime and of disruptive behaviors.

## Prosocial Behaviors and Aggressive Behaviors

Prosocial and aggressive behaviors are independent behavioral tendencies derived from different dispositions [13]. However, there is substantial literature indicating that prosocial behaviors act as protective factors against aggressive behaviors [14]. Previous research indicates that "while aggressive behaviors are critical due to their negative effects on psychosocial adjustment in the short-, mid- and long-term, the lack of prosocial behavior seems to be critical especially due to its long-term effects" [15 (213)]. For example, longitudinal studies developed by Flynn and collaborators [10 (476)] showed that a medium or high prosocial trajectory was associated with significantly less externalizing behavior than the low trajectory, and being on a high prosocial trajectory was associated with reduced borderline personality features compared with the low prosocial trajectory.

Early intervention is an important element for the promotion of positive behavior and for the prevention of violence and its consequences. Evidence suggests that when earlier interventions are made, better prognoses in development can be expected given the plasticity that children have. However, any intervention program – even though it is not applied during childhood – can be a positive promotion factor for growth.

## The Current Meta-analysis

Many intervention programs with the purpose of mitigating aggressive behaviors in the general population as well as in children or adolescents with serious behavioral problems [16] also show having an effect on the promotion of prosocial behaviors. The interest of this meta-analysis is precisely the possibility of studying whether the inverse effect exists, that is, if existing prosocial intervention programs are successful at efficiently promoting prosocial behaviors, while they mitigate aggressive behaviors. More specifically, this meta-analysis includes an examination of the effectiveness of intervention programs intended for children and adolescents between

the ages of 8 and 18 years old, developed between 2000 and July 2017 inclusive.

## Method

The performance of this meta-analysis followed the same procedures as Ciocanel and collaborators in a recent meta-analysis performed in 2017 [17]. The inclusion criteria for studies in the meta-analysis included the following:

### Population

The selection of the population focused on interventions for children and adolescents ranging between the ages of 8 and 18 for both sexes. The interventions that were intended for relatives or adults and who did not directly act upon the children and adolescents were excluded. Since our attention was focused on the promotion of prosocial behavior on the general public, those populations with specific characteristics such as high levels of aggressiveness, disability, and mental disorders, among others, were excluded.

### Intervention

Those interventions whose main goal was to promote prosocial behaviors in children and adolescents and whose research design included experimental and control groups were selected. Those interventions whose main purpose was inhibiting aggressive behaviors and whose secondary purpose were to promote prosocial behaviors were excluded. The duration of the intervention was not considered an inclusion criterion.

### Outcome and Setting

Any prosocial behavior, such as cooperative, helpful, or comforting behaviors, is measured at the onset and finish of the intervention through self-reporting, third-party reports, or observations. Similarly, as a result, the measurement of aggressive behavior was taken, described as verbal aggression, physical aggression, breaking rules, starting a fight, etc.

All interventions with significant and nonsignificant results in comparison with the control group were included. Interventions that were carried out inside and outside of the school settings were included.

### Design

Those interventions that were chosen had a design that contained a control group allowing the comparison of prosocial and aggressive behavior intervention results. All publications appearing between 2000 and September 2017 were selected, and only those written in English, Spanish, or Portuguese were included. Publications in other languages, such as Chinese, were excluded.

### Search Strategy

An exhaustive review of the literature was performed to collect published and non-published studies which complied with the inclusion criteria, using the following databases: Scielo, NCBI, Science Direct, JSTOR, Dialnet, Networked Digital Library of Theses and Dissertations, Academic Search Premier, ERIC, Directory of Open Access Journals, and EBSCO Host. The search was carried out in September 2017, and studies published in English, Spanish, or Portuguese were selected.

The search keywords used for meeting the objective of the meta-analysis were “prosocial behavior” and its derived terms “prosociality” and “altruism”; and the following terms were utilized in order to comply with the intervention criteria: “intervention,” “outcome,” “program,” and “treatment.”

### Study Selection and Data Extraction

The selection of studies was performed by two independent reviewers and included three selection stages. In the first stage, the title of

the article was considered, and those studies that complied with the prosociality intervention inclusion criteria were chosen. Following the first selection stage, a second stage consisted of reviewing article abstracts and selecting those studies which fulfilled the inclusion criteria relating to population and methodological design. Finally, ten (10) studies were left that fulfilled all of the inclusion criteria, and the data needed to perform the analysis was extracted from them. The information retrieved included: author and year of study, intervention (duration, location), sample characteristics (age group and mean, gender ratio), and methodological design.

### Risk Bias Assessment

The RevMan 5.3 program developed by Cochrane was used to assess the risk of bias in the articles included in the meta-analysis. Two authors independently evaluated every single article included in this review. Whenever there was a disagreement in the classification criteria between low risk, high risk, and unclear risk, the classification was discussed until an agreement was reached.

### Statistical Analyses

The Comprehensive Meta-Analysis Program (version 2) and RevMan 5.3 were used to carry out the meta-analyses. We used the Comprehensive Meta-Analysis Program to calculate forest plot, funnel plot, and heterogeneity, and the RevMan 5.3 was used to calculate risk of bias and to create the CONSORT diagram.

### Effect Size Calculations

For continuous outcomes, we calculated the standardized mean differences and the standard errors. To avoid effect size underestimation, the Hedge's g correction for bias was applied, which is usually recommended for a sample size lower than 20 [18, 19]. None of the studies had dichotomous outcomes. When a study had multiple measures for the same outcome, an overall effect size was calculated by averaging the individual effect sizes.

### Statistical Heterogeneity

Statistical heterogeneity between the studies was assessed using the Q statistics and the $I^2$ statistics. A nonsignificant Q statistics and an $I^2$ statistics smaller than 50 are expected to be found, which indicates the absence of heterogeneity between the studies included in the meta-analysis [20].

### Publication Bias

Finally, the presence of publication bias was assessed using funnel plots and the fail-safe number, which assess the potential impact of unpublished studies on the analysis. A fail-safe number is often considered robust if it is greater than 5n+10, where n is the original number of studies [21].

## Results

Figure 21.1, obtained from the RevMan 5.3 program, summarizes the search and selection procedures of articles included in the meta-analysis. A total of 10.641 articles were identified in the databases described under the Search Strategy section and 1.009 in the web and through a review of the bibliography of other articles. Afterward, 6.108 articles were selected through the reading of titles and abstracts. Of these, 106 were selected for an in-depth review, and following a full text reading, 96 were dismissed. Ten were included in the final meta-analysis (see Fig. 21.1 and Table 21.1).

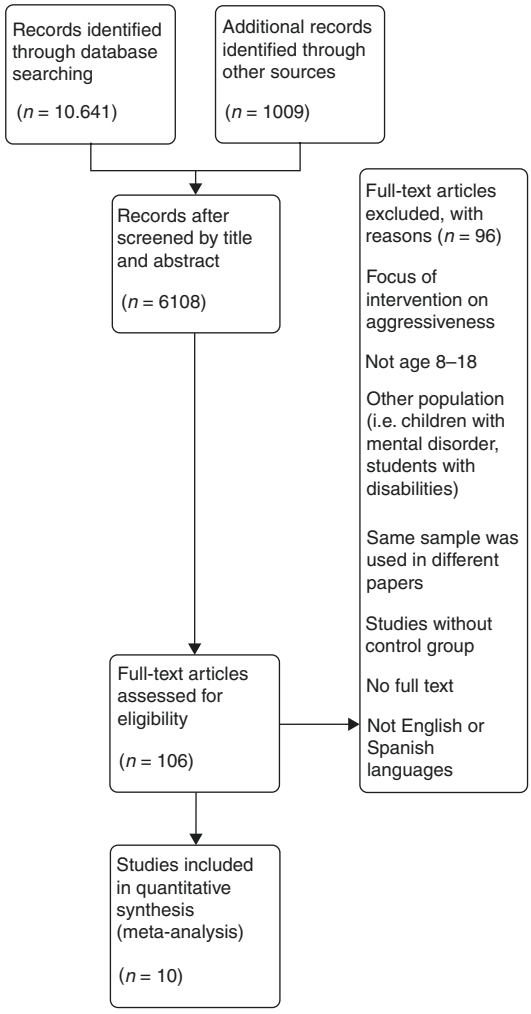



**Fig. 21.1** Obtained from the RevMan 5.3 program, summarizes the search and selection procedures of articles included in the meta-analysis

## Characteristics of Included Studies

### Design

Three of the selected studies were performed in Canada [22, 28], three were in Spain [24, 27, 30], and the rest were carried out in the United States, Lithuania, Italy, and Ireland. Six were published in scientific journals and four were dissertations. Publications from 2000 to 2017 were included, while most publications were dated after 2010 (60%). All of the designs were controlled studies and eight of them were randomized studies. All interventions were performed within the school setting, some during class times and others following the class schedule. Most of the studies collected their information through self-reporting or reports provided by teachers, parents, and classmates. In those cases where studies used were more than one measurement for the evaluation of prosociality or aggressiveness variables, a combination of assessments was used to obtain a closer approximation to the assessment of the true behavior of the child or adolescent. All of the studies except one informed that participants gave informed consent of their parents [27]. Only one of the studies reported follow-up measures [23].

### Participants

A total of 3.020 youth participated in the studies, and 1.483 were subjected to some type of experimental intervention. The age range for the sample was 8–18 years, and there weren't any significant differences regarding gender distribution. Overall participant's families belonged to the working middle class, mainly Caucasian Catholics [23, 24, 29, 30], although some of the studies presented greater cultural diversity [27], and only one of the studies was carried out in a lower-middle class residential area [30].

### Intervention

The interventions were performed with the purpose of promoting prosocial behaviors and were all carried out within a school setting whether it be inside the classroom or in schoolyards. Some of the interventions were carried forth during class schedules, and others were performed after classes. In some cases, the interventions were implemented by researchers, and in other cases, teachers received training so that they may conduct interventions.

**Table 21.1** Characteristics of included studies ($N = 10$)

| 1st author (year) | Program name | Location | Baseline sample (age, % female) | Intervention type (format) | Duration | Setting | Follow-up period | Published in | Reports | IC[a] | Who conducted the intervention | Design |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Binfet (2000) [22] | Moral reasoning group | Vancouver, Canada | Intervention participants: 25. Women: 48%<br>Total of participants 97 (10–13 years M: 11,6 SD: 0,67) Caucasian 57% Asian 26%, Black, Indian 49,4% women | On-site. Weekly discussion meetings | 10 weeks. Weekly 40-min sessions during school hours | Schools | No follow-up | Dissertation | Self-reports. Peer reports. Teacher reports | Yes | Main researcher and graduated alumni | Controlled randomized study |
| Binfet (2000) [22] | Moral Reflection Group | Vancouver, Canada | Intervention participants: 23. Women 43%. Total participants 97 (10–13 years M: 11,6 SD: 0,67). Caucasian 57% Asian 26%, black, Indian. 49,4% women | On-site. Weekly discussion meetings | 10 weeks. Weekly 40-min sessions during school hours | Schools | No follow-up | Dissertation | Self-reports. Peer reports. Teacher reports | Yes | Main researcher and graduated alumni | Controlled randomized study |
| Caprara (2015) [23] | Promoting Prosocial and Emotional Skills to Counteract Externalizing Problems in Adolescence (CEPIDEA) | Genzano, Italy | Intervention participants 151 (M: 12,4 SD: 0,49) women: 48%. Control group participants 140 (M: 12,6; SD: 0,53) women 55,7%. Total participants: 291. 14% of parents were professionals; 25% merchants, 31% qualified workers; 29% nonqualified workers and 1% retired | On-site | 6 months. Lessons on prosocial behaviors once a week (total of 16) | Schools | 18 months | Periodical: Journal of Youth and Adolescence | Peer reports | Yes | Teachers were trained to conduct interventions | Not specified |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Garaigordobil (2008) [24] | Psychological intervention program | Basque Country, Spain | Intervention participants: 54. Total participants 86 (10–11 years) women: 60%. Middle socioeconomic level, 39% of parents had a university education | On-site | During school year. Weekly 2-h play sessions horas during school hours | Schools. In the gymnasium or the activities hall | No follow-up | Periodical: childhood and learning | Self-reports. Parent and teacher reports. Peer reports | Yes | Program implemented by teachers and psychology researchers and students | Controlled randomized study |
| McCarty (2014) [25] | Actively Caring for People (AC4P) | Southwest Virginia, USA | Intervention participants 209. Total participants 403 | On-site | 5 weeks. Weekly 22-min sessions | School | No follow-up | Dissertation | Self-reports | Yes | Coaches (trained university students) | |
| O' Hare (2015) [26] | Mate-Tricks | Dublin, Ireland | Intervention participants 184. Women 46%. Total participants 580 (9–10 years). Women 44% | On-site after school, with sessions for parents, for children, and for parents and children together | During school year. After school hours | School | | Periodical: The Elementary School Journal | Self-reports | Yes | Trained staff | Controlled randomized study |
| Romersi (2011) [27] | Minimal Prosocial Improvement Program (PMIP) | Barcelona, Spain | Intervention participants 128 54,7%. Total participants 198 (14–16 years M:14,16 SD: 0,80). Women 53,5%. Urban area sample | On-site, work sessions | 6 months. 12 sessions of 1 h or an hour and a half approximately every 2 weeks | Schools | No follow-up | Periodical: Annals of Psychology | Peer reports | Not specified | Trained operators | Controlled non-randomized study |

(continued)

**Table 21.1** (continued)

| 1st author (year) | Program name | Location | Baseline sample (age, % female) | Intervention type (format) | Duration | Setting | Follow-up period | Published in | Reports | IC[a] | Who conducted the intervention | Design |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Schonert-Reichl 2012 [28] | Roots of Empathy (ROE) | Vancouver and Toronto (Canada) | Intervention participants 306. Total participants 585. Women: 47%. (8–12 years M: 10, SD 0,87) vast social and cultural diversity of sample | On-site. 26 30–40 min lessons on different subjects | 9 months. 26 30–40 min lessons during class hours | Schools | No follow-up | Periodical: School Mental Health | Teacher and peer reports | Yes | Trained Implementors | Controlled non-randomized study |
| Sukys (2016) [29] | Olympic Education Programme | Lithuania | 381 (M: 17,06 SD:0,96) women: 52%. Total participants 783. Women: 53%. The majority of participants were Caucasian, middle class Catholics | On-site | 3 years. Intervention integrated to school curricular activities: history, physical education, art, etc. | Schools | No follow-up | Periodical: European Journal of Sport Science | Self-reports | Yes | Teachers | Controlled randomized study |
| León Zarceño (2008) [30] | Not specified | Valencia, Spain | 22 (11–13 years M:11,59) 50%. Total participants 41 (10–12 years) 46%. Area with lower-middle class residents with a growing number of immigrants | On-site. During physical education classes | 3 months. During physical education classes | Schools | No follow-up | Dissertation | Self-report | Yes | Physical education teachers trained in intervention | Controlled non-randomized study |

[a]*IC* informed consent

## Bias Risk

Bias risk is summarized in Fig. 21.2. A majority of studies (eight out of the ten included) informed the randomized inclusion of participants to the experimental and control group. With regard to the allocation concealment, six studies informed having used this procedure. One study skewed participants in the experimental group from the intervention program, two of them were not clear as to their procedures, and the remaining seven did not skew participants. In any case, due to the characteristics of these interventions, it is often not viable to follow this procedure. Half of the studies informed that the evaluators had no knowledge about whether the children or adolescents had participated in an experimental or placebo group. One article failed to inform about the existence of lost data, another one is unclear about the treatment that it was given, and the remaining articles inform about lost data and the treatment they were given in terms of the analysis. It seems very unlikely that the authors omitted information on their study results or that they include other types of bias in their reports.

## Heterogeneity

High levels of heterogeneity were found among those studies that analyzed the effectiveness of intervention programs in their promotion of prosociality (Q-value = 32.03, gl 9, $p \leq 0.001$, $I^2 = 71$). The same was found for heterogeneity among studies in which the effectiveness of intervention programs on the inhibition of aggressive behaviors was analyzed (Q-value = 67.03, gl 4, $p \leq 0.001$, $I^2 = 94$).

## Intervention Effect: Prosocial Behavior

Ten (10) studies included in this meta-analysis analyzed the effectiveness of intervention programs on the promotion of prosocial behaviors. As mentioned above, prosocial behaviors were assessed in some studies through self-reporting provided in some cases by participants and, in other cases, by teachers, parents, and/or fellow classmates of children or adolescents. Given that in two of the studies [24, 28] more than one measurement was used to assess the prosociality variables, a combination of assessments was used to obtain a closer approximation to the assessment of the prosocial behavior of the participant. The forest plot results can be seen in Fig. 21.3. Effect sizes were of $g = 0.23$ (95% CI = 0.07, 0.39, Z-value = 2.86, $p \leq 0.01$) favoring the intervention condition using random model and $g = 0.23$ using fix model (95% CI = 0.16, 0.31, Z-value = 6.12, $p \leq 0.001$).

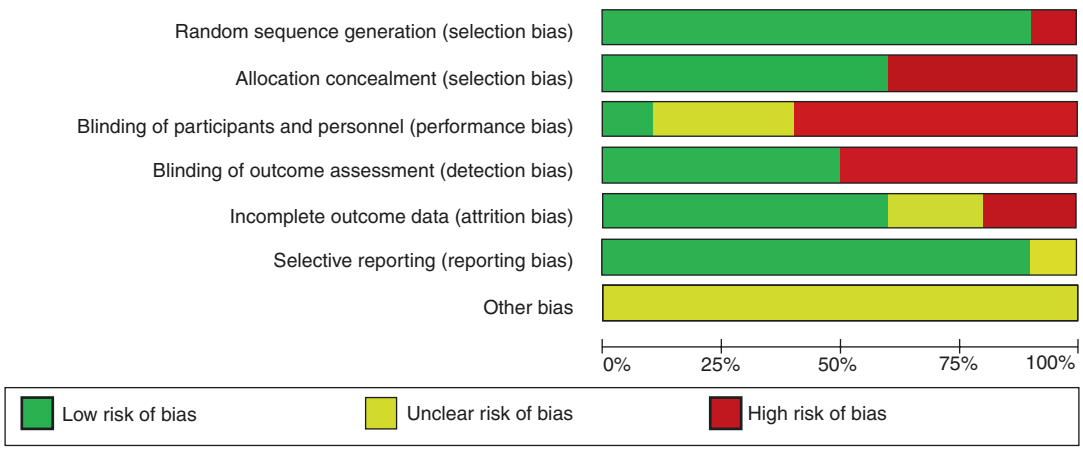
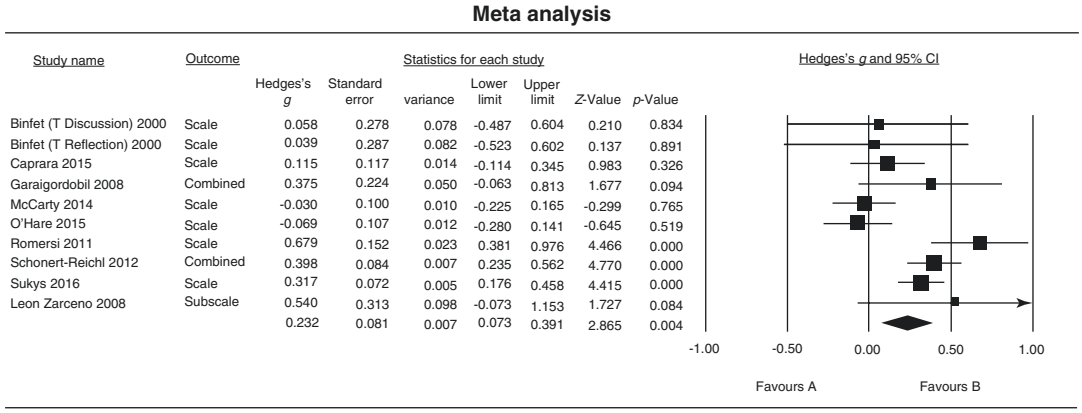
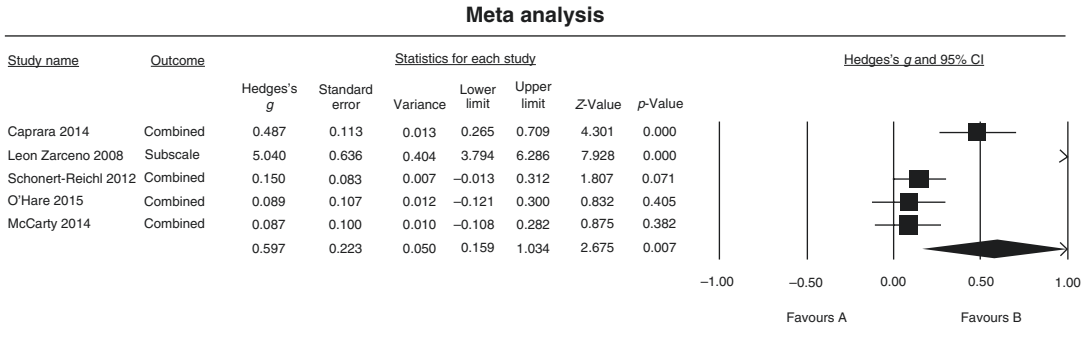



**Fig. 21.2** Risk of bias ratings across included studies




**Note: Favors A = favor control, and Favors B = favor intervention**

**Fig. 21.3** Effect sizes for prosocial behaviors




**Note: Favors A = favor control, and Favors B = favor intervention**

**Fig. 21.4** Effect sizes for aggressiveness

## Intervention Effect: Aggressiveness

Five (5) studies included in this meta-analysis analyzed the effectiveness of their intervention programs in aggressive behavior inhibition. Given that four out of the five studies included [23, 25, 26, 28] used more than one measurement for the assessment of the aggressiveness variable, a combination of assessments were used to obtain a closer approximation to the estimated aggressive behavior of participants. The forest plot results can be seen in Fig. 21.4. Effect sizes were of $g = 0.60$ (95% CI = 0.16, 1.03, Z-value = 2.67, $p \leq 0.001$) favoring the intervention condition using random model and $g = 0.22$ using fix model (95% CI = 0.12, 0.31, Z-value = 4.37, $p \leq 0.001$).

## Publication Bias

Publication bias was not detected, as the funnel plot shapes were symmetrical for all analyses (see Fig. 21.5). Moreover, the fail-safe number was calculated to assess the potential impact of unpublished studies on the analysis. The fail-safe number obtained in this meta-analysis was 70, which indicated the number of studies that would be required to reverse our conclusions regarding intervention. Because it is unlikely that 70 studies

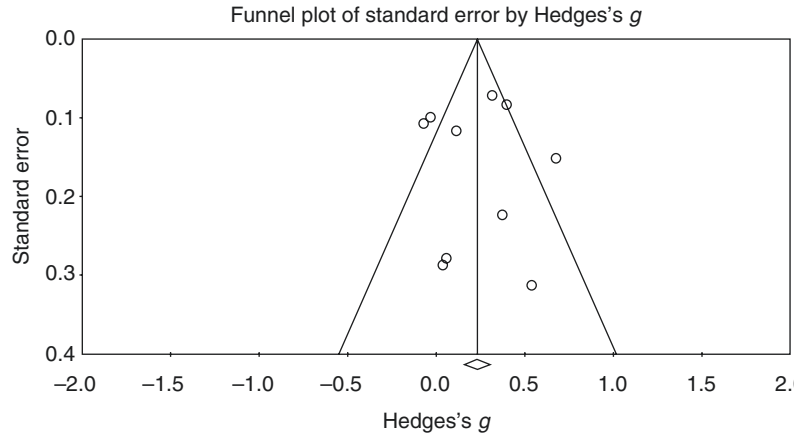



**Fig. 21.5** Funnel plot

would be found with a more extensive literature search, it is estimated that there is no publication bias.

## Discussion

Given the importance that prosocial behaviors have on psychological development and the proper functioning of children and adolescents in the contexts of family, school, and society, it was imperative to study the effectiveness of intervention programs for their promotion. To our knowledge, this is the first meta-analysis focusing on the study of prosociality intervention programs, although there is a previous meta-analysis that examines both published and unpublished randomized controlled trials to report on the effects of positive youth development interventions on multiple outcomes. However, this previous meta-analysis focused on analyzing results such as academic adjustment, sexual health outcomes, problem behavior, psychological adjustment, and behavioral adjustment; under this last category, an intervention program was analyzed for the prevention of behavioral problems which studied the effectiveness of the promotion of prosocial behaviors, but this was not its main objective [17]. This gap in the scientific literature is accompanied by the lack of empirical evidence supporting the effectiveness of applied research for the promotion of prosocial behaviors conducted by psychologists in different areas. At the same time, being able to count on meta-analysis on these topics can contribute to better decision-making regarding the selection of better intervention strategies in the event of wanting to apply some of these programs in our contexts.

Through our work we were able to observe that while certain programs devoted to the promotion of prosociality existed prior to the emergence of positive psychology [31–33], it is starting 2000 that the greatest number of interventions appear with a particular increase in 2010. However, there continue to be relatively few interventions, and it would be advisable to develop new programs or increase the empirical evidence of existing programs. Additionally, another important aspect that needs to be underscored is the fact that prosociality intervention programs are scarce beginning earlier than 8 years of age, and in our review, we were only able to identify the one developed by Piek and collaborators [34], while the majority focuses on the 8- to 18-year-old age range. Likewise, most of them have been conducted within the school context whether it be during the class schedule or outside of it. It is thus convenient to also develop certain programs that allow us to exercise these positive practices in other contexts such as in the family or society in general.

The results obtained from this meta-analysis maintain that intervention programs aimed at promoting prosocial behaviors showed a moderate effectiveness in the promotion of them. These results would be providing empirical evi-

dence on the usefulness and effectiveness of these programs from a positive viewpoint prone to strengthen positive resources. According to our studies, from the intervention programs analyzed here, those that showed greater effectiveness in the promotion of prosocial behaviors were the programs developed by Romersi in 2011, Schonert-Reich and collaborators in 2012, and Sukys in 2016 [27–29]. Additionally, our findings also allow us to confirm that intervention programs focused on the promotion of prosocial behaviors were highly effective in the prevention of aggressive behaviors. This allows us to infer that the strengthening of positive resources is effective in the prevention of behaviors that could be disruptive for children as much as adolescents themselves and for their interpersonal relationships. Of the programs analyzed in this meta-analysis, the programs that showed greater effectiveness in the prevention of aggressiveness were those developed by Caprara and collaborators in 2015 and León Zarceño in 2008 [23, 30].

Nonetheless, it must be highlighted that the levels of heterogeneity found in this meta-analysis were very high both in terms of analyzing the effects of intervention on the prosociality variable and on the aggressiveness variable. This is an important limitation of this study, and therefore the results discussed above must be handled with caution. The high levels of heterogeneity may have a number of causes, one being the fact that we compared different intervention programs that use different strategies for the promotion of prosocial behaviors and for secondly mitigating aggressive-type behaviors. The study developed by Binfet [22] uses indirect intervention strategies, for example, discussion and moral reflection, for promoting prosocial behaviors, since there is previous empirical evidence showing a relationship between these variables. By contrast, for example, Romersi [27] uses direct intervention strategies for prosocial behaviors such as the analysis of movies, the personal development of a plan for prosociality with a registration sheet, etc. Another important source of heterogeneity among studies may be attributable to the assessment instruments utilized for measuring variables, and assessment ranges were very dissimilar among themselves which may contribute to broader confidence intervals producing greater heterogeneity among studies. Another possibility may be due to the extensive age bracket of participants (ranging from 8 to 18 years of age), unfortunately due to the scarcity of intervention programs focusing on prosociality, whereby we were forced to include studies applied to children as well as adolescents without having the possibility of analyzing subgroups according to age as was originally planned.

In order to solve the heterogeneity difficulties addresses above, it is necessary to rely on a greater number of primary investigations allowing the performance of more accurate analyses focusing on different age groups of participants, taking into account the assessment instruments or counting on a more numerous response for these intervention programs on the basis of different samples and in different social and cultural contexts.

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# Ethical Position, Empathy and Prosocial Behaviour Model: Its Contribution to Prevention and Psychotherapeutic Approaches of Antisocial Disorders

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## Introduction

In the theoretical framework of the so-called postmodernity, the ethics of moral principles has been weakened, prioritizing the relative circumstances and situations and becoming the human being in the measure of all things, thus increasing individualism. Relativism is one of the most popular and most reviled philosophical doctrines of our time. Defenders see it as a harbinger of tolerance and the only ethical and epistemic stance worthy of the open-minded and tolerant. Detractors dismiss it for its alleged incoherence and uncritical intellectual permissiveness [1].

This ethical position has a great impact on adolescents and young people, who constitute a very permeable population to the philosophical positions prevailing in society, since they are in a stage of the life cycle in which the moral perspectives are getting consolidated.

The human beings organize their behaviour in terms of their beliefs, values, ethical positions and previous experiences.

Ethical positions can influence social and moral behaviour, particularly prosociality and penalization of acts, being empathy an important mediating variable.

The idea that empathy is a major determinant of prosocial behaviour has been widely

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accepted among psychologists, such as Martin Hoffman [2, 3] and Nancy Eisenberg [4–6]. The experience of empathy has been shown to motivate prosocial behaviour, for example, volunteering, donating to charities, sharing with peers and helping and comforting others. Empathy has become very important, both as an individual developmental variable and its relationship with other variables such as sociomoral development and prosociality. Besides, empathy inhibits aggression and antisocial behaviour.

This article aims to present an interaction model, taking ethical position and empathy as predictors of prosocial behaviour and penalization of acts as faults and crimes (moral judgement).

## Ethical Position

Barry R. Schlenker and Donelson Forsyth [7] examined the philosophical positions on the nature of ethics, and they considered that individual differences in ethical ideology are believed to play a key role in moral judgement and ethical decision-making.

Ethics position theory (EPT) maintains that individuals' personal moral philosophies influence their judgements, actions and emotions in ethically intense situations. This theory, when describing moral viewpoints, stresses two moral ideological dimensions: Idealism (concern for benign outcomes, good consequences) and Relativism (scepticism regarding the existence of inviolate moral principles). Forsyth [8] suggests that individual differences in Idealism and Relativism influence moral judgements.

Idealism refers to one's concern for minimizing negative consequences and maximizing good consequences, particularly for others. Idealists assume that desirable consequences can always be obtained; a right action is always possible. Less idealistic or non-idealistic individuals admit that undesirable consequences will often be mixed in with desired ones, so they are pragmatists.

Idealists assume that we should avoid harming others, while pragmatists assume that harm will sometimes be necessary to do good.

Pragmatism is a teleological position that proposes that the ultimate judgement of the morality of an action, or set of actions, depends upon the consequences produced by it. One is ethically bound to act in a way that has good consequences.

Idealists, like Immanuel Kant, argued that a moral principle cannot allow any exceptions, regardless of its consequences. Although a lie may have positive consequences, a lie is a lie, so it is always immoral. He gives emphasis on maintaining consistency with moral principles to obtain the desired goals.

Immanuel Kant condemned a lie told even with the best of intentions, whereas Jeremy Bentham (a pragmatic philosopher) favoured the telling of untruths so long as they benefited the greatest number of people.

Individuals believe that moral rules are universal or relative. Relativism describes one's emphasis on moral rules and principles when making decisions about right and wrong. Relativists reject the possibility of relying on universal moral norms to draw conclusions from moral judgements, whereas others (non-relativists) believe in making use of moral absolutes when making judgements. Relativists question the value of universal moral principles. Non-relativists appeal to natural law or rationality to determine moral judgements. Acts must be judged as moral or immoral through their comparison with universal rules that are absolute and rules that stand for themselves, regardless of any relationship or comparison with concrete things. The absolute is the unconditioned, independent, disconnected, what is in itself, what is not mediated by anything and the immutable. The relative characterizes the phenomenon in its relations and links with other phenomena, depending on other phenomena.

The non-relativistic point of view (Absolutism) is that at least some truths or values in the relevant domain apply to all times, places or social and cultural frameworks. These truths and values are universal and not bound by historical or social conditions.

Furthermore, these ethical positions which have been discussed focused on whether moral reasoning is driven by intuitive affective processes or by conscious reasoning. The Kantian approach postulates that deliberate conscious reasoning processes generally precede emotions. Lawrence Kohlberg [9, 10], who is a rationalist, asserts a sequential and hierarchical development and articulation of moral reasoning extending from childhood into adulthood; his findings show culturally universal stages of moral development rather than relative values. Kohlberg [11] argued that in all cultures, adults will be closer than children to a post-conventional morality based on harm, rights and justice.

On the contrary, Jonathan David Haidt makes an important distinction between reasoning, which is a conscious activity in which conclusions are derived through several steps, and intuition, also a cognitive process that is characterized "as the sudden appearance in consciousness of a moral judgement, including an affective valence (good-bad, like-dislike), without any conscious awareness of having gone through steps of searching, weighing evidence, or inferring a conclusion" [12] (p. 818). Whereas reasoning is largely conscious, intuition is based on automatic and unconscious processes that is why affective evaluations play an important role in moral intuitions. Moral intuition is primary, and reasoning is secondary.

Haidt suggests that cultural norms and culturally shaped emotions have a substantial impact on the domain of morality and the process of moral judgement. The domain of morality appears to vary cross-culturally. Nonetheless, Haidt thinks that it is possible to integrate cognitive developmental findings with research on culture and emotions [13].

Elliot Turiel [14] states that neither individuals nor cultures have monolithic, homogeneous world-views.

Other researchers argue that some moral rules may be components of a universal moral grammar [15, 16]. Hauser is a professor of Psychology, Human Evolutionary Biology and Organismic and Evolutionary Biology at Harvard University. He argues that millions of years of natural selection have moulded a universal moral grammar within our brains that enables us to make rapid decisions about ethical dilemmas. He thinks that there might be something like a universal moral grammar, a set of principles that every human is born with. It is an analogic thought based on Noam Chomsky, who proposed that all humans are equipped with a universal linguistic grammar, a set of instinctive rules that underlie all languages. There is a set of universal principles that dictate how we think about the nature of harming and helping others, but each culture has some freedom (not unlimited) to dictate who is harmed and who is helped.

Forsyth considers that Relativism is a sceptical position that emerged from anthropological findings of drastic moral code differences between societies. According to this position, all moral standards are relative to the society in which they occur, so one cannot determine what is ultimately right or wrong. The best thing one can do is to show that an action, or set of actions, is consistent or not with the predominant patterns within a particular society. Some authors suggest that David Hume is the first cultural relativist. For example, Blanshard states that "Hume held that to approve of conduct is to have a certain feeling about it, a feeling caused by its perceived tendency to increase the happiness of people with whom we can sympathize; and to pronounce it right is to say that in our society people generally feel that way about it" [17] (p. 5).

The ethics position theory only argues that individual differences in morality are, in part, based on Relativism and Idealism. Many investigators have contrasted moralities based on rules with moralities based on consequences.

Later Forsyth's research shows that individuals who differ in Relativism and Idealism divaricate when making moral judgements [18], evaluating contemporary moral issues [8], attributing responsibility after wrongdoing [19] and judging the ethics of psychological research [7, 20].

Recent studies investigated the effect of ethical ideologies on moral judgement, attitudes and behaviour. For example, Abhishek Shukla and Rajeev Srivastava [21] consider that the relation-

ship between ethical ideology and job stress appears to be complex. Their study is based on the model presented by Forsyth, showing two dimensions (Idealism and Relativism) that play an important role in ethical evaluation and behaviour. Based on a survey of 561 employees of hotel industry in India, ethical ideologies were found to be negatively associated with job stress. The data were analysed using Pearson correlations and multiple regressions, and the results showed that Relativism is negatively correlated with job stress. Further, it has been established that Idealism and Relativism interact in such a way that there is a negative relationship between Idealism and job stress when Relativism is low and a positive relationship when Relativism is high. These findings imply that ethical ideology adversely influences job stress in the organization.

Grieve and Mahar [22] explored the effects of ethical position on emotional manipulation (emotional manipulation is defined as the capability of individuals to manipulate the emotions of others within a self-serving framework) and psychopathy in adolescents. Psychopathy has also been shown to be associated with manipulative behaviour [23].

In this research ten items evaluate the tendency to use emotional manipulation; a sample item is: *I know how to play two people off against each other*.

Grieve and Mahar said that psychopathy was originally viewed as a homogenous construct, but recent approaches suggest it can be differentiated into two related factors: primary and secondary [24, 25]. Primary psychopathy is characterized by malevolent, manipulative, callous, deceptive and remorseless behaviour, with lack or reduced affectivity. Secondary psychopathy is characterized by impulsivity, anxiety and antisocial behaviour. In this research psychopathy was measured using Levenson et al.'s Self-Report Psychopathy Scale [25]. Pearson coefficients show that Idealism is negatively correlated with primary and secondary psychopathy and also with emotional manipulation [22].

To evaluate the relationship between moral attitudes and ethical position, a study [8] was conducted with the Moral Attitudes Survey [26], which contrasts individuals who support an ethics of responsibility with individuals who support an ethics of personal conscience. Regarding the relationship between this instrument and the Ethical Position Questionnaire (EPQ) of Donelson Forsyth, it was found a significant negative correlation between the Moral Attitudes Survey score and Relativism. In other words, an ethics of responsibility is opposed to Relativism.

Recent research has shown that increased moral Relativism and the decline of Absolutism (non-Relativism) relax good morals and create readiness for immoral behaviour [27].

Furthermore, other research has empirically demonstrated that moral realism (contrary to Relativism) is positively associated with increased donations to good causes, which may be considered prosocial behaviour [28].

Studies on ethical position and welfare have recently been conducted, finding that variations in personal ethics are associated with variations in well-being, increasing or decreasing it. In particular, high level of Idealism is associated with initiative of personal growth, presence of meaning of life, hope, happiness and self-realization. On the contrary, high level of Relativism is associated with a low meaning of life [29].

These studies show us the importance of ethical position to a model that takes into account all the variables that influence prosocial attitudes and behaviour and the judgement of antisocial acts.

## Empathy

Edward Bradford Titchener [30] translated the German term *einfülung* as empathy, meaning to feel inside something or someone. Theodor Lipps [31] took this concept from aesthetics and developed it in the field of psychology. He defines empathy as the tendency to feel within what is perceived or imagined, recognizing the existence of the other. Thus, empathy began to be studied in the psychology of aesthetic experience and has been studied from the beginning of the twentieth century [32, 33].

Today, empathy has acquired great importance as an individual variable of development and also in its relation to other variables such as sociomoral development and prosociality among others [34–37].

Empathy is also defined as the ability to understand other's perspective or feelings and affections putting oneself into their place [38]. One of the most used definition is "emotional reaction elicited and congruent with the other's emotional state which is identical, or very similar, to what the other person is feeling or has expectations to feel" [39] (p. 260).

Martin Hoffman [2] thinks that empathy is the spark of human concern for others and the glue or adhesive that makes social life possible. While he considers this may be fragile, it is what has kept social life throughout evolution and can continue as long as there are human beings.

On the other hand, Eisenberg and Strayer [34] assure that empathy implies sharing the emotion that is perceived in the other, that is to say, to feel with the other.

The approach to empathy has two different ways [2, 40]: one emphasizes the importance of cognition in the empathic processes by addressing empathy as cognitive awareness of the internal states of other people, that is to say, their thoughts, feelings, perceptions, intentions, etc., and the second way has stressed the affective aspect, understanding empathy as an emotional vicarious response to the perceived emotional experience of others.

While affective empathy seems to be a simple construct (feeling what the other feels), when affective empathy is studied, the construct gets even more complex. It is more useful to define empathy to speak not in terms of outcomes but in terms of the processes underlying the relationship between those of the observer and the observed feelings. Given affective empathy, the key requirement of an empathic response is the implication of the psychological processes that make a person have more congruent feelings with the situation observed than with the situation itself. It should be noted that empathic processes frequently produce the same sensation in the observer as in the observed, but not necessarily; so, for example, empathy can be felt when someone is attacked and when the victim is not feeling anger but sadness or disappointment [2].

Another distinction that can be made in the study of empathy is situational and dispositional empathy. Situational empathy is understood as the empathy experienced by a person before a given situation or event, that is to say, the one that arises before certain stimuli. Dispositional empathy, on the other hand, is a personality tendency to be more disposed to empathy [41].

The dispositional empathy is of great importance for moral development, especially of the prosocial and helping behaviour, because there are studies that confirm that people with high levels of dispositional empathy tend to show more situational empathy and more disposition to aid and prosociality [42].

Nancy Eisenberg and Paul Miller [4] examined the validity of the assumption that empathic responding is an important source of prosocial (including altruistic) behaviour.

Richaud and Mesurado [43] evaluated the predictive power of positive emotions and empathy on prosocial behaviour and the inhibiting power of positive emotions and empathy on aggressive behaviour in a sample of 221 boys and girls aged between 10 and 13 years old. They found that in both, boys and girls, empathy and positive emotions are involved in prosocial behaviour, although in boys, empathy has a greater predictive power than positive emotions on prosocial behaviour. Both empathy and positive emotions are only inhibitors of aggressive behaviour in women, which cannot be observed in the male sample.

In addition, Mesurado and Richaud [44] conducted a study with 422 university students of both sexes between 18 and 25 years old. They found that parental challenger and parental support have an important influence on positive behaviour, such as prosocial behaviour addressed to friends and relatives. The brief version of the Parental Challenge Questionnaire was used to measure parental challenge. This scale was developed by Dailey and includes ten items measured on seven-point Likert-type scales, for example, "My mother/father asked me what I learned from my failures".

In the context of parent-child interaction, a challenge is characterized by Daley as a factor that provides "opportunities for stimulation and growth: pushing or testing the child's existing abilities and skills that may result in building or strengthening cognitive, behaviour, social, or affective knowledge or skills" [45] (pp. 644–645).

The results provide empirical support for this definition because the combination of parental support and parental challenge has an important influence on positive cognitive and affective mental state (prosocial flow) and an influence on positive behaviour, such as prosocial behaviour towards friends and family, but no influence on behaviour towards strangers [44].

In the same study, a positive direct effect of empathy on prosocial behaviour, addressed to friends, relatives and strangers, is observed.

Malgorzata Gambin and Carla Sharp [46] consider that impaired empathy is associated with a variety of psychiatric conditions, although little is known about the differential relations between certain forms of psychopathology and cognitive and affective empathy in male and female adolescents. Their study examines the relations between externalizing and internalizing disorders and cognitive and affective empathy, respectively, while controlling for covariance among different forms of psychopathology, separately, in girls and boys. A total of 507 inpatient adolescents (319 girls and 188 boys) in the age range of 12–17 years old completed the Basic Empathy Scale that measures affective and cognitive empathy. The Youth Self-Report Form and Child Behavior Checklist were used to assess the severity of psychopathological symptoms. Their results demonstrated that affective empathy was positively related to internalizing problems observed by parents and youths and self-reported attention deficit hyperactivity disorder (ADHD) symptoms in both girls and boys. Internalizing symptoms (anxiety and affective problems) were shown to be associated with higher level of affective empathy in girls and boys, and the correlations were stronger and more significant in girls than in boys.

Several studies revealed that girls are characterized by higher levels of empathy and internalizing disorders and lower level of externalizing disorders than boys. They consider that it is very important to explore relationships between empathy and psychopathology separately in females and males.

Many studies investigated gender differences in relation to empathy and conduct disorders, which demonstrated that deficits in empathy are present in both girls and boys with conduct disorders and that impaired empathy is observed only in boys, but not in girls with aggressive behaviour [47, 48].

Depression seems to be associated with impaired empathy at an affective level. Specifically, depressed individuals report high levels of empathic stress in response to the suffering of others. Depressed women seem more impaired in empathic accuracy than depressed men [49].

An empathic response has affective and cognitive processes. Affective empathy is defined as the degree to which someone feels the feelings of another person. This experience or recognition may have positive or negative consequences. On the one hand, experiencing the feelings of others may elicit compassion. Compassion motivates people to approach others and provide support, the other-oriented response as empathic concern. With the Interpersonal Reactivity Index (IRI), a multidimensional self-report measure of trait empathy developed by Davis [50], high empathic concern scores have been associated with unselfishness, understanding, prosociality and being sensitive during social interaction. This suggests that other-oriented responses to the feelings of others may lead to positive outcomes.

Recently, new scales to measure empathy have been developed, such as the New Spanish Empathy Questionnaire for Children and Early Adolescents [51] based on Decety and Jackson's model [52] and Gerdes and Segal's contributions [53]. It measures the following dimensions: emotional contagion, self-other awareness, perspective-taking, emotional regulation and empathic action.

This questionnaire is very important for research and clinical work because it is a brief instrument that can evaluate empathy, a key psychological issue for social relationship

development, quality of life and psychological well-being in children and adolescents.

In this study, 479 schoolchildren boys and girls (mean age 10.77, SD = 1.16) were evaluated. It was observed that all scales of the new instrument of empathy had positive correlations with prosocial behaviour and negative correlations with physical and verbal aggression [51]. This is further evidence of the importance of empathy for the reduction of aggressive behaviour and social maladaptation.

This study has important implications for research and clinical practice. Given its simplicity and brevity, this new self-report scale may work well as a screening method to evaluate the key psychological issues underlying different child behaviours that predict the success or failure of social relationships, individual quality of life and mental well-being [51].

## Prosociality

The term prosociality, in the current meaning of the scientific work of psychological discipline, was coined by Wispé [54] as an antonym of antisocial behaviour. This term was consolidated in later studies like those of Staub [55], Mussen and Eisenberg [56].

The study of prosociality has made great progress in recent years, as nowadays it has been given much importance to the development of a healthy personality oriented to a positive interpersonal and social relationship. Research on this variable has increased in the last decades [57–62].

Prosociality is understood as the behaviour tending to help or benefit other people, regardless of the intention that is pursued with this help. Prosocial behaviour is the result of multiple individual and situational factors including parental variables and empathic traits [59].

Closely related to prosociality is altruism, understood as an unconditioned love for the neighbour belonging to the feelings sphere and the motives and values of the person to do good of the other, even sacrificing one's own, and different from prosociality understood as the tendency to give way to actions that are characterized by the biased effect it produces in the other, pertaining to the habits sphere, practices and the usual modality of social interaction [63].

According to the empathy-altruism hypothesis by Daniel Batson [64], the decision of helping or not depends primarily on whether you feel empathy for the person and secondarily on the cost and rewards (social exchange concerns).

Some authors consider that altruism consists in helping others mainly by a dispositional orientation to others or moral reasons without regard to external rewards or punishments [65]. On the other hand, prosocial behaviour could have external rewards or motivations. According to the social-exchange theory, people help others because they want to gain goods from the one being helped. People try to calculate rewards and costs of helping others, and so they aim at maximizing rewards and minimizing costs [66]. Thus, all altruistic behaviour would be prosocial, but not all prosocial behaviour would necessarily be altruistic.

Roche Olivar [67, 68] expresses that true prosocial behaviour refers to the absence of extrinsic or material reward in helping other people or groups. Thus, he defines prosociality as the behaviour that, without the search for external, extrinsic or material rewards, favours other people or groups or social goals, objectively positive, and increases the probability of generating positive reciprocity of quality and solidarity in interpersonal or social relationships, safeguarding the identity, creativity and initiative of the individuals or groups involved [68].

The prosocial behaviour characteristics are as follows:

- Physical support: Non-verbal behaviour that provides assistance to other people to fulfil a certain objective and has their approval
- Physical service: Behaviour that eliminates the need for recipients to intervene physically in the performance of a task or tasks and concludes with their approval or satisfaction
- Giving: Delivering objects, food or possessions to others by losing their property or use
- Verbal help: Explanations, verbal instruction and sharing ideas or life experiences, which

are useful and desirable for other people or groups in achieving a goal
- Verbal comfort: Verbal expressions to reduce sadness or distress in people and improve their mood
- Confirmation and positive appraisal of the other: Verbal expressions to confirm the value of others or increase their self-esteem, even in the presence of others (positively interpret the behaviour of others, apologize, intercede through words of sympathy or praise)
- Deep listening: Meta-verbal behaviour and attitudes of attention that express patient acceptance but actively oriented to the contents expressed by the interlocutor in a conversation
- Empathy: Verbal behaviour that, starting from a voluntary emptying of our own contents, expresses cognitive understanding of the thoughts of the interlocutor or emotion of being experiencing similar feelings to his
- Solidarity: Physical or verbal behaviour that expresses voluntary acceptance of sharing the particularly distressing consequences of unfortunate conditions, statuses, situations or fortune of other people, groups or countries
- Positive presence and unity: Personal presence that expresses attitudes of psychological proximity, attention, deep listening, empathy, availability for service, help and solidarity with other people and contributes to the psychological climate of well-being, peace, concord, reciprocity and unity in a group or meeting of two or more people [68]

The disadvantages or limits of prosociality, according to this author, are that prosocial behaviour is not ordered in a way that preserves or safeguards the identity, creativity and initiative of the people or groups involved. It may generate negative and undesirable consequences such as decreased self-esteem of the receiver, inferiority feelings, dependence learning and increased self-esteem of the giver through the increase of dominion over the receiver.

However, through their prosocial behaviour, the givers improve their self-esteem, their conscience and the perception of their abilities, although this is not the objective that motivates prosocial behaviour [68].

Wendt, Bartoli and Arteche [69] said that researchers have repeatedly neglected the contribution of traits such as narcissism and impulsivity to the development of psychopathy, realms that are equally important in determining potential prospects of future psychopaths. Their research has shown that early personality features (narcissism) and behavioural features (impulsivity) make important contributions to child behavioural presentation. These variables predicted concurrent prosocial and antisocial behaviour in schoolchildren. The exploration of narcissism and impulsivity not only gives a more robust picture – as explained by a significant increase in the variance explained – but also implications in terms of intervention designs aiming to prevent conduct problems (CP) and promote prosocial behaviour among at-risk populations. Narcissism is also "a statistically significant predictor of pro and antisocial behavior, although less strong than impulsivity. Here, implications for clinical treatment might include transferring excessive focus from the individual (i.e., avoidance of fostering egocentricity features) and stressing perspective-taking abilities and empathy" [69] (p. 269). Similar results with adolescents were found by Muñoz Centifanti, Kimonis and Aucoin [70].

## Penalization of Acts as Faults and Crimes. Moral Judgement and Moral Transgression

In order to determine whether an act is morally right or morally wrong, every person makes a value judgement to adjudicate the moral character of that action. Those acts called human are plausible of judgement because the subject has a certain degree of freedom and conscience.

Depending on the ethical position that the subject adopts, taking into account the level of Relativism and Idealism, it is estimated that penalization as crimes or faults may vary.

The topic of penalization of acts as faults and crimes (moral transgression) has been studied in Argentina by Horacio Rimoldi and Alfredo

López Alonso [71]. They have worked on the estimation of the penalization of simple and conditional judgements. Simple judgements are subjective estimations of some attributions of psychological significance (such as the degree of penalization), evaluated in a stimulus (fault or crime), without the latter being surrounded by any other contextual element of psychological stimulation. An example of an item of simple judgement may be to "steal a book". On the other hand, the conditional judgement adds a circumstantial element to the context of the stimulus, ceasing to be neutral. An example of a conditional judgement is how we penalize robbing if a person has robbed in previous opportunities or committed other serious crimes [71–73].

Studies on judges have been carried out using the estimation of faults or crimes with simple and conditional judgements [72]. These studies have evaluated the value of justice and judges' objectivity, observing the influence of the antecedents in crimes judged. These subjects were also studied in a non-legal population (students of various careers, workers, housewives, etc.). In these studies, a greater penalization was observed in the female population, with women being less tolerant than men, as they obtained higher scores in the penometric scale. It was observed that the non-legal population penalized more the damage done to the crime victim than to the property protected by law. Thus, for example, the theft of a van is more punishable if that vehicle is used as the only means of work, penalizing less harshly if the van belongs to a person from the upper class [74].

More recently, studies were carried out on university students who were separated into those with high Relativism and those with low one, and then they were compared. Significant differences were found in the following faults and crimes: premarital relations, abortion, school truancy, forcing a woman into prostitution, bigamy, suicide attempt and prostitution. The subjects with low Relativism penalized the mentioned items higher. On the other hand, robberies and homicides were penalized similarly in those with high or low Relativism. In the same study, it was observed that the mean of penalization was higher in non-relativists [75].

In the other dimension presented by Donelson Forsyth [8], the more idealistic subjects penalized highly faults and crimes [75]. It was only in the variables related to robberies that idealists and pragmatists have similar penalization. At the same time, idealists tend to penalize faults lower (e.g. insulting a teacher, school truancy, disturbing neighbours); but they also strongly penalize suicide attempts, drug administration and prostitution.

Evaluating the correlations between the penalizations of acts and Relativism, it was found that almost all correlations are negative, that is to say that to greater Relativism less penalty to faults and crimes [75].

Rodriguez [76] observed that the five acts most penalized as faults and crimes were a thief killing a person to rob him, carrying out an abortion, robbing a church, consuming cocaine and robbing an art museum. It is striking to think that the most penalized faults or crimes are related to the attack to human life.

Regarding the consumption of cocaine and cannabis, cocaine consumption is one of the most penalized acts, whereas smoking cannabis is in the 13th rank of all faults and crimes. This fact coincides with the empirical research carried out in our country by the Argentine Social Debt Observatory [77], which has shown that occasional consumption of cannabis in adolescents is much higher than that of cocaine (23.7% of cannabis versus 7% of cocaine). This fact shows the naturalization that has been made of the consumption of cannabis among adolescents, something that has not happened with other drugs like cocaine or heroin.

## An Important Previous Contribution to a Prosociality Model

Caprara et al. [78] presented a model in the same direction than our proposal. It is an important contribution to the construction of an integral model. They consider that their posited conceptual model accounted for a significant portion of variance in prosociality and provides guidance to interventions aimed at promoting prosociality.

They examined the double mediation by values and self-efficacy beliefs of the relation between trait agreeableness and individual differences in prosociality.

One important goal in this study was to ascertain whether agreeableness, self-transcendence values and empathic self-efficacy beliefs represent stronger predictors of prosociality thans other do like Big Five traits, other values or other self-efficacy beliefs, respectively. They examined (a) the prediction of prosociality from the three target predictors (agreeableness, self-transcendence values, and empathic self-efficacy beliefs), (b) whether agreeableness predicted prosociality when controlling for the other four traits simultaneously (i.e. extraversion, conscientiousness, emotional stability and openness to experience), (c) whether self-transcendence predicted prosociality once variance predicted by any of the three remaining broad categories of values was taken into account (i.e. openness to change, self-enhancement and conservation values) and (d) whether empathic self-efficacy beliefs accounted for a significant proportion of variance once variance due to social self-efficacy beliefs was controlled.

## A Proposal and a Contribution to an Integral Model of Prosociality

Currently, it is necessary to construct, complete and evaluate theoretical models that can integrate beliefs, values, ethical positions, emotions and empathy for the understanding of prosocial and antisocial behaviour, which incorporate the cognitive, affective and behavioural aspects. In this way, the following proposed model has ethical position as independent variable, with the mediation of empathy and prosocial behaviour and penalization of acts as independent variables [76, 78].

The empirical study on ethical positions and prosociality in Argentinian adolescents and young people has shown evidence that subjects with a non-relativistic ethical position have higher levels of prosociality [76]. Table 22.1 reports the result of ANOVA to evaluate the difference in prosocial behaviour according to relativistic and non-relativistic ethical positions. There are statistically significant differences, with the non-relativistic subjects obtaining greater average in prosocial behaviour. Table 22.2 shows the result of MANOVA to evaluate the difference in prosocial tenden-

**Table 22.1** Means and standard deviations of prosocial behaviour according to ethical position

| | Relativists ($n$ = 116) | | Absolutists ($n$ = 125) | | $F$ | $p$ | $Eta^2$ | |
|---|---|---|---|---|---|---|---|---|
| | $M$ | SD | $M$ | SD | | | | Observed power |
| Prosocial behaviour | 3.35 | 0.51 | 3.71 | 0.57 | 25.9 | 0.000 | 0.098 | 0.999 |

**Table 22.2** Means and standard deviations of prosocial tendencies according to ethical position

| | Relativists ($n$ = 116) | | Absolutists ($n$ = 125) | | $F$ | $p$ | $Eta^2$ | |
|---|---|---|---|---|---|---|---|---|
| Prosocial tendencies | $M$ | SD | $M$ | SD | | | | Observed power |
| Public | 1.87 | 0.79 | 1.98 | 0.79 | 1.13 | 0.288 | 0.005 | 0.186 |
| Altruist | 3.99 | 0.72 | 4.10 | 0.73 | 1.37 | 0.242 | 0.005 | 0.215 |
| Anonymous | 2.52 | 0.90 | 2.94 | 0.82 | 14.20 | 0.000 | 0.056 | 0.963 |
| Responsive | 3.32 | 0.59 | 3.57 | 0.58 | 11.23 | 0.001 | 0.045 | 0.916 |

$F_{\text{Hotelling}}$ (4, 236) = 5.75 $p$ = 0.000 $eta^2$ = 0.089 observed power 0.999

**Table 22.3** Means and standard deviations of empathy according to ethical position

| | Relativists ($n$ = 116) | | Absolutists ($n$ = 125) | | $F$ | $p$ | $Eta^2$ | |
|---|---|---|---|---|---|---|---|---|
| | $M$ | SD | $M$ | SD | | | | Observed power |
| Empathy | 3.70 | 0.44 | 3.85 | 0.48 | 6.84 | 0.009 | 0.028 | 0.740 |

**Table 22.4** Means and standard deviations of penalization of acts according to ethical position

| | Relativists ($n$ = 116) | | Absolutists ($n$ = 125) | | $F$ | $p$ | $Eta^2$ | |
|---|---|---|---|---|---|---|---|---|
| | $M$ | DS | $M$ | DS | | | | Observed power |
| Penalization of acts | 2.62 | 0.52 | 3.01 | 0.61 | 28.42 | 0.000 | 0.106 | 1.000 |

cies according to relativistic and non-relativistic ethical positions. The trace of Hotelling indicates statistically significant differences. The F univariate shows that the subjects with a non-relativistic ethical position have higher averages in prosocial sensitive and anonymous tendencies.

Empirical study on ethical positions and empathy in Argentinian adolescents and young people has shown evidence that subjects with a non-relativistic ethical stance has a higher level of empathy [76]. In Table 22.3 we can see the result of ANOVA that evaluate the difference in empathy according to relativistic and non-relativistic ethical positions. There is a statistically significant difference with non-relativists obtaining a greater mean in empathy. It is important to mention that the empathy scale used in this study is based on Mehrabian and Epstein [40] empathy and disposition measures.

The empirical study on ethical positions and empathy in Argentinian adolescents and young people has shown evidence that subjects with a non-relativistic ethical position has a higher penalization level of acts as faults or crimes [76]. In Table 22.4 we can observe the result of ANOVA to evaluate the difference in penalty according to relativistic and non-relativistic ethical position. There are statistically significant differences, obtaining non-relativists greater mean in penalty.

## A Structural Equation Model of Ethical Position, Empathy, Prosocial Behaviour and Penalization of Acts

A current empirical study with a sample of 515 Argentinian adolescents and young people between 17 and 20 years old has shown a significant positive correlation between a non-relativistic ethical position and prosocial behaviour, empathy and penalization of acts. Besides, it has shown a significant negative correlation of the Relativism with prosocial behaviour and penalization [79]. This study proposes a prediction model of the prosocial behaviour and the penalization of acts as faults or crimes, both being concrete variables of human morality. In Fig. 22.1 it can be seen that the model explains 40% of the variance of prosocial behaviour and 12% of the variance of penalization of acts. In the study, it can be observed a direct negative effect of Relativism on the penalization of acts. At the same time the penalization of acts gets a direct positive effect from non-Relativism (Absolutism) and empathy. On the other hand, prosocial behaviour receives a direct effect from empathy.

The proposed model takes into account what N. Eisenberg [80] expressed in his classic article on prosociality, in which she states that moral principles and other cognitive regulators of empathy level, along with low impulsivity, allow effective and sustained prosocial behaviour.

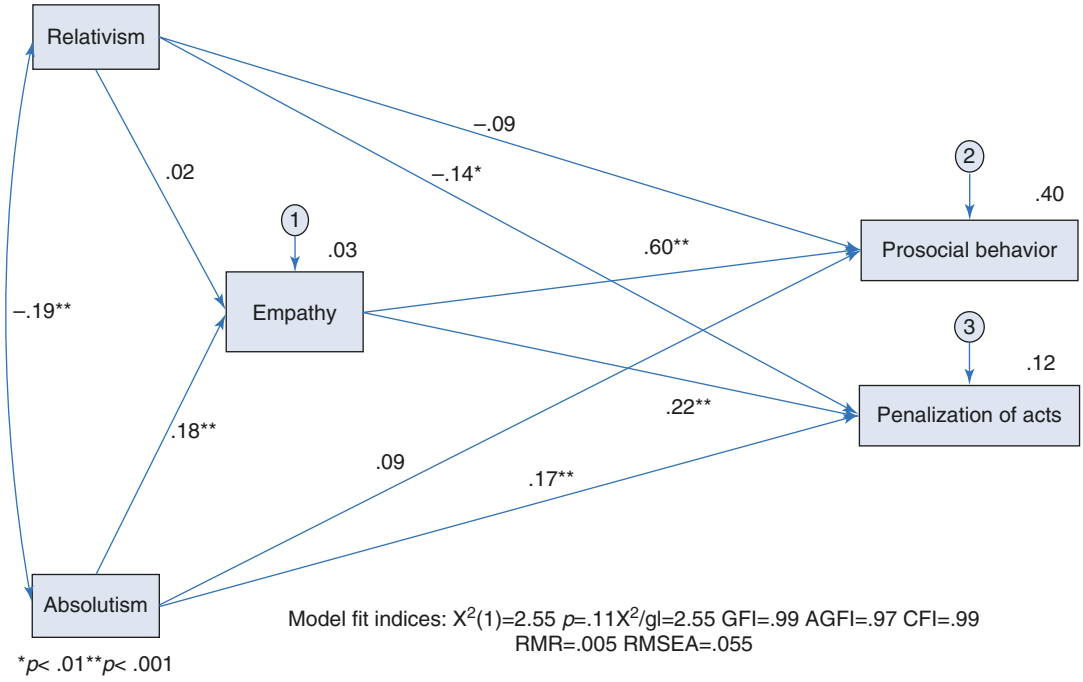


**Fig. 22.1** A structural equation model of ethical position, empathy, prosocial behaviour and penalization of acts

There is evidence that prosociality is related to the emphasis individuals place on moral foundations. Morality, especially in non-relativist subjects, fosters self-control and self-regulation, which allows individuals to simultaneously strive for high moral standards and moral behaviour, maintain high levels of well-being and prosociality, and can avoid antisocial actions.

To live in society with other humans requires adherence to certain rules and the control of individuals' desires for immediate gratification.

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# 23

# Bridging Cognitive, Affective, and Social Neuroscience with Education

María Cristina Richaud, Vanessa Arán Filippetti, and Belén Mesurado

In recent years there has been an important growth of neurosciences that has contributed generating new knowledge that can help us to understand teaching and learning under different perspectives. If learning is a core concept in education, then some discoveries in neuroscience can help us to better understand our student's learning processes and therefore teach them in a more appropriate, effective, and enjoyable way [1].

The new field of "educational neuroscience" or "neuroeducation" studies some of the basic learning processes such as reading, writing, and mathematics but also analyzes "learning to learn," including the study of cognitive and emotional processes and the cognitive and metacognitive processes that enhance learning. Neuroeducation is understood as the development of the neuro-mind throughout the education process, not a mere hybrid of neurosciences and educational sciences but rather a novel original composition [2]. Advances in the neurosciences have confirmed theoretical positions advanced by developmental psychology for years, such as the importance of early experience in development. The novelty is the convergence of evidence stemming from diverse scientific fields of knowledge. Information about learning and development has converged to provide a more complete framework on how intellectual development takes place [3].

The clarification of some of the learning mechanisms by neuroscience has been improved with the appearance of noninvasive neuroimaging technologies which have allowed researchers to observe human learning processes directly, at least from a mechanistic point of view [3]. Current sophisticated neuroimaging techniques constitute a real contribution to the education field [4–10] since functional neuroimaging techniques allow the identification of brain areas that activate during different learning tasks. For example, in the area of reading, several studies that have used these brain recording techniques in adults – functional magnetic resonance imaging (fMRI), positron emission tomography (PET) – have revealed the involvement of left hemisphere perisylvian areas in the reading process, including the extrastriate visual cortex, inferior parietal regions, superior temporal gyrus, and inferior frontal cortex, with variations in particular tasks used; visual word form processing would involve occipital regions, while spelling (orthographic) processes would involve inferior frontal and parietal areas and inferior temporal ones [7, 11]. With respect to writing, it has been demonstrated that the generative writing of single

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words would activate the left posterior inferior temporal cortex and the left inferior and dorsolateral prefrontal cortex [12]. Additionally, fMRI studies performed on children have revealed that the neural integration of letters and speech sounds in the planum temporal/Heschl's sulcus and the neural response to letters in the fusiform gyrus accounted for a high percentage of the variance (40%) of reading achievement. Neural integration of letters and speech sounds associated with the planum temporale region and superior temporal sulcus is reduced in dyslexic children [13].

In the Brain Waves Module 2 [14], several key ideas and educational opportunities from neuroscience are proposed: (a) nature and nurture affect the learning brain, (b) the brain is plastic, (c) the brain's response to reward is influenced by expectations and uncertainty, (d) the brain has mechanisms for self-regulation, (e) education is a powerful form of cognitive improvement, (f) there are individual differences in the learning ability with a basis in the brain, and (g) neuroscience informs adaptive learning technology.

Neuroscience has provided evidence regarding the importance of the environment on the development of the brain and has helped us understand that individual genetic predispositions can be shaped through education and nurturing. For example, it has been demonstrated through computer modeling that small variations in initial human processing that might be genetically governed obtain broad cognitive differences following human experience [5]. Experiences that are often repeated – whether they be positive or negative – have a significant impact on how the brain structures itself. The strengthening of synaptic connections occurs through functional validation, in such a way that brain connections adapt to environmental requirements [15]. The genetic makeup of our brain only partly determines what we know and how we behave; an important part depends on environmental factors that determine what we experience. Education is one of the most important environmental factors [14]. Learning changes the physical structure of the brain. Those structural changes alter the functional structure of the brain; in other words, the learning process organizes and reorganizes the brain.

The functional organization of the brain depends on and benefits positively from human experience [16]. The brain is molded by genes, development, and experience but also plays an important role in molding its own experiences and cultural environment [17]. Development is not simply a biologically caused process, but it is also an active process that obtains essential information from experience [3].

The brain has an extraordinary adaptability or "neuroplasticity" which is due to the aforementioned process by which neural connections are strengthened when they are simultaneously and repeatedly activated. This is known as experience-dependent plasticity and is present throughout life [4, 18, 19]. Neuroplasticity allows the brain to adapt to environmental requirements and to store learning results in the form of memories, which allows preparing for future events based on experience. Opposite to plasticity is the learning of counterproductive habits that are difficult to change [20].

However, brain development is not linear; there are sensitive periods or windows of opportunity, with greater neuroplasticity in specific brain regions in which certain types of knowledge and skills are more easily learned, extending beyond childhood and adolescence [21, 22]. For example, the results obtained after 1-year intervention on the cognitive and socio-emotional abilities of socially vulnerable children, when intervention started at age 11, indicate that although progress was made, it was significantly weaker than when the intervention started at age 6 [23, 24].

With respect to gender, the overall pattern of neural development is similar between genders, but the rate of brain maturation is different, with girls attaining complete maturation slightly before boys [25]. Brain plasticity continues throughout life as proved by certain activities that demand the acquisition of specific skills [26]. At the same time, it has been found that many skills need continuous training in order to maintain the changes in the brain. To illustrate this point, in the intervention on socially vulnerable children, an interruption in the intervention for a while triggered learning setbacks [24]. Similarly,

changes in the adult brain of individuals who have acquired special skills such as music [27] and dancing [28] have also been shown. This illustrates the abovementioned experience-dependent plasticity.

However, neuroplasticity has limits and individual differences. It would seem that there are limits on how internal predispositions and external stimuli can affect learning [14]. There is evidence that after brain injury certain functions respond better to rehabilitation than others and some cannot be relearned at all [29]. There are many different factors that play a role in the recovery and compensation of brain functions, and both pharmacological treatments and training plans have been studied as potential means of extending plasticity into adulthood [30]. Furthermore, neuroscientists have studied the relationship between reward and learning in the context of reinforcement learning [14]. Evidence exists that the individual's reward system allows us to learn which actions have the most valuable outcome and that just reducing prediction errors can itself be rewarding. The brain's response to prediction error also supports other types of learning such as the ability to recall information [31]. Research also demonstrates that the level of uncertainty about the reward one might receive contributes in a significant way to the dimension of the neural response it generates [32]. These findings challenge the notions of a simple relationship between reward and motivation in school and appear to suggest new ways for using rewards more effectively in support of learning [14, 31].

Recent studies have shown that the ability to inhibit inappropriate behavior develops relatively slowly during childhood but continues to increase during adolescence and early adulthood [33]. This is probably due to the fact that the regions of the brain involved in inhibition, particularly the prefrontal cortex, continue changing as much in terms of structure as in function during adolescence and early 20s [34]. Furthermore, there are large individual differences in our ability to exert self-control, which persist across our life span.

The frontal and prefrontal areas of our brain are responsible for our monitoring and control abilities, as well as specific functions related to the control of certain behaviors, such as choosing a behavior option for specific social or physical situations [35, 36].

The brain's frontal and prefrontal regions have proven to be important for keeping executive mental functions directed toward specific objectives and are also known to play a role in thought elaboration. They are involved in many of the brain's functions that are associated with above-average intelligence, such as abilities for making predictions, making future plans, and considering the consequences of motor actions even prior to their realization. Said behaviors or executive functions favor strategic planning, impulse control, organized searching, and flexibility of thought and action [37]. In this regard, we have analyzed the relationship between executive functions and reflexivity-impulsivity, the importance of executive functions and self-regulation on learning and performance indicating context, genetic and epigenetic factors, and interventions effects and have developed an intervention program to reduce cognitive impulsivity and increase inhibitory control, reflexivity, and planning [38–43]. Since it has been found that self-reported ability to exert self-control is an important predictor of academic success, it would seem valuable to gain an understanding of the neural basis of self-control and its structuring through appropriate methods [14].

There are individual differences in the ability to learn with a basis in the brain. Current work in neuroscience is oriented toward identifying the brain basis of learning difficulties. Even in the case of those with severe learning difficulties, having an improved understanding of the specific cognitive and neurological correlates of the disorder may be exploited to render education more effective [44].

A large part of neuroscientific research has focused on more specific learning difficulties, such as the development of dyslexia and of dyscalculia. Research has identified underlying cognitive that can be assessed with experimental tests and serves to explain other difficulties associated with poor achievement [14].

Although research studies have shown that there are brain correlates or markers for learning difficulties, these markers are subtle and complex. It is still not possible to predict or assess an individual's specific disability from a brain scan [25]. This is because even in a diagnosis category such as the development of dyslexia, there exist substantial anatomical variations from one individual to another. The study of dyslexia using a combination of behavioral and neuroimaging methods indicates that it is possible to identify neurocognitive impediments to learn and suggests appropriate teaching methods. Other learning difficulties can benefit from the same type of approach for discovering underlying neural systems [14]. Functional neuroimaging study results show that dyslexic children and adults have abnormal patterns of activation in areas of the brain involved in language and reading [45, 46]. With improved behavioral testing methods, informed through findings in neuroscience and genetics, improving the current approach to diagnosis for all neurodevelopmental disorders such as ADHD would become possible [47].

## Neuroscience and Learning Technology

Neuroscientific findings can often identify a specific locus for a particular learning impediment. While they may not be able to determine the exact way of intervening, they may suggest the nature of a concept or skill that needs to be worked on and the type of cognitive activity that needs to be strengthened. Learning technologies can play a complementary role to that of the teacher so as to rehearse specific learning activities. For example, research has identified poor comprehension of "number sense" as an underlying cause of dyscalculia [48, 49]. Computer games have been designed for students to practice number comprehension, adapting to the child's skill level. Adaptive programs emulate a teacher who constantly adapts to the student's comprehension level. Therefore, they allow much more practice than is usually possible through individual teaching [50].

## Some Studies on the Relationship Between Executive Functions and Academic Performance in Writing, Reading, and Mathematics

In the recent years, the study of executive functions (EF) in the academic setting has received special attention, given that these processes favor cognitive, behavioral, and emotional self-regulation and are related to the academic achievement of children. Research in the field of neuropsychology has demonstrated that the EF play a central role in the development of pre-academic skills [51] as much as in learning and academic performance in schoolchildren [52–54]. In this regard, in a series of studies recently performed on children and adolescents, we found that executive functions are key predictors of writing [55] and reading comprehension [40] and achievement in mathematics [56].

Firstly, by examining the relationship between the EF and performance in writing tasks, we found that these cognitive processes significantly contribute to writing, even after controlling age, verbal intelligence, and reading comprehension. Specifically, we found that working memory (WM) and spontaneous flexibility account for unique percentage variance in the composition of written texts, whereas the spontaneous flexibility, WM, and inhibition explained a percentage of variation in the composition of expository texts [55]. With regard to the relationship between EF and reading comprehension, our findings suggest that WM and spontaneous cognitive flexibility (i.e., verbal fluency) would be the major executive processes explaining, to an extent, the individual performance variations in reading comprehension tasks. Specifically, according to our findings, the central WM executive component and semantic verbal fluidity would be the main executive processes involved in the reading comprehension of both children and adolescents [40]. Finally, while examining the relationship between EF and different math skills (i.e., number production, mental calculus, and arithmetical problems), we found that the WM would be involved in numerical and mental calculus production, while

cognitive flexibility would selectively be associated with arithmetic problem-solving. Furthermore, we found that in the presence of EF, the intelligence coefficient (IC) would not directly have an influence over the performance of the analyzed mathematic domains [56]. These findings indicate the relevance of using different measurements to assess each EF domain at the moment of analyzing its relationship with academic skills, insomuch as there may exist selective associations in accordance with the nature of each EF (e.g., verbal vs. no verbal) and of the academic tasks analyzed.

Overall, our results suggest that individual achievement variations could be explained due to the individual differences in executive functioning. Hence the importance of including contributions made by the field of neuropsychology to the field of education, especially those referred to cognitive and socio-affective processes which intervene in academic performance and favor self-regulated learning.

## Affective and Social Neuroscience and Education

The role that emotions play in education is crucial [57–59]. Modern advances in functional neuroimaging techniques demonstrate that emotions enhance learning to the extent in which they intensify neural activity and reinforce synaptic connections. For this reason, when addressing the education of students with autonomy and decision-making abilities, we must not forget that in rational decision-making, emotions are essential and help understand certain behaviors that are difficult to achieve through other perspectives [2]. We therefore believe that emotions and motivation largely direct the human attention system, which decides what information will be stored in neural circuits and, therefore, learned [6, 7].

For years emphasis was placed on cognitive neuroscience findings to try to explain the processes that are at the basis of learning, which include reasoning, decision-making, and processes related to language, reading, and mathematics. However, recent advances in the neuroscience of emotions highlight the connections between cognitive and emotional functions, in particular, those between decision-making, social functioning, and moral reasoning and bring a promising future to breakthroughs in understanding the role of emotions in decision-making, the relationship between learning and emotion, how culture shapes learning, and lastly human moral and ethical development [60].

Education often fails to consider that high-level cognitive skills taught at school do not work as disembodied rational systems somehow influenced by but separated from emotion and the body.

There is evidence that the interrelated development between emotion and cognition is dependent on emergency, maturity, and complex neural circuit interconnections in multiple areas of the brain, including the prefrontal cortex, the limbic cortex, the amygdala, the hypothalamus, and the brain stem [61]. The circuits associated with emotion regulation are highly interactive with those that are associated with executive functions (such as planning, judgment, and decision-making), which are intimately involved in the development of problem-solving skills during the preschool years [62]. In terms of the basic functioning of the brain, emotions hold executive functions when they are well regulated, but when poorly controlled, they interfere with attention and decision-making [63–67].

> … the original purpose for which our brains evolved was to manage our physiology, to optimize our survival, and to allow us to flourish. When one considers that this purpose inherently involves monitoring and altering the state of the body and mind in increasingly complex ways, one can appreciate that emotions, which play out in the body and mind, are profoundly intertwined with thought. And after all, this should not be surprising. Complex brains could not have evolved separately from the organisms they were meant to regulate. [60]

Furthermore, as the brain turns more complex, including social interactions and relationships becomes necessary. This has various important implications for research at the nexus of education and neuroscience. It signals new directions for understanding the interface between biology,

learning, and culture [68–70]. Evidence stemming from psychophysiological studies and from individuals with brain damage or who are normal have allowed finding specific neural mechanisms underlying the functioning of emotional signaling in normal and abnormal decision-making [71–73]. Emotional processes underlie our apparent rational decision-making and learning in the real world. Furthermore, this relationship underscores the importance of perceiving and incorporating social feedback in learning [60].

Immordino-Yang and Damasio [60] formulated two important hypotheses: (1) emotion plays a fundamental role in the skills and knowledge acquired at school so that they may be transferred to new situations and to real life, and (2) the social influences of culture can be fused into learning, thought, and behavior through emotion.

There is evidence [74] that neurological systems supporting decision-making are generally the same systems that support social and moral behavior. Without adequate access to emotional, social, and moral feedback, learning cannot effectively function in the real world. The most recognized aspects of cognition in education are deeply affected by emotion and indeed are included in the emotional process.

Immordino-Yang and Damasio [60] state that the teaching of children often focuses on logical reasoning skills and factual learning, which constitute major indicators of academic success. In reality, however, neither learning nor memory happens in a purely rational domain, divorced from emotion, although much of our knowledge appears in a moderately rational unemotional form. Similarly, when students are taught to minimize the emotional aspects of their academic curriculum and to function primarily in the rational domain, teachers are encouraging students to develop a type of knowledge which cannot be transferred to real-life situations. As shown in patients with acquired brain damage, knowledge and reasoning that are divorced from emotion and learning lack meaning and motivation and are of little use in the real world. The more educators become aware of the nature that exists between emotion and cognition, the more capable they will be of including this relationship in the design of learning environments.

Day and Leitch [75] propose that feelings and emotions have a vital role in learning development, since it is through our subjective emotional world that we develop personal construct and meaning of outside reality and we give meaning to our relationships and our eventual place in the world. This clearly relates to our personal motivation and ability to pay attention [75, 76]. LeDoux [76] states that the emotional brain may act as an intermediary between the thinking brain and the outside world; there would be an interplay between thought and feeling and between feeling and memory. When feelings are ignored, they can act unnoticed and consequently do not recognize positive or negative impacts. When there is an overflow in our emotional brain, our working brain may have very little capacity for attention in order to keep in mind the facts required to finish a task, acquire a concept, or make an intelligent decision. Finally, it is stressed that powerful emotions – anxiety, love, anger, and pleasure – can create neural static in the prefrontal cortex, which can sabotage the capacity for attention in working memory.

## Critical Perspectives on the Application of Neuroscience to Educational Practice

Despite the numerous contributions of neuroscience toward explaining the processes involved in learning, many scientists remain skeptical as to the viability of applying these findings to the classroom. Nunley [77], for example, asserts that education should wait for neuroscientists to explain how this new research on the brain may be applied to the classroom. Wolf [78] stresses this cautious attitude regarding neuroscience research and questions whether this is a new trend or if we are truly on the brink of discovering a teaching and learning theory which is scientifically sound. Likewise, Madigan [79] states that knowing how the brain works could help us to understand how people learn but cautions on the danger of extrapolating certain

findings to curricular specifications without real research to support it.

Willingham [80] establishes three problems that he considers significantly reduce the potential of neuroscience contributions for education: (1) artificial sciences such as education pursue objectives for which the natural sciences like neuroscience do not contribute information. Natural sciences such as neuroscience are descriptive; their objective is to discover the principles that govern neural structure and function. Artificial sciences are normative. Their goal is the creation of an artifact which serves a specific purpose within a given environment. The artifact created in education is a set of pedagogical strategies and materials. When educators design a pedagogical strategy, they must know how humans learn, become motivated, understand language, and regulate emotion, among other things. In this case neuroscience may provide critical information. Nevertheless, education goals oftentimes include features for which the natural sciences have no answers for, for example, developing a sense of esthetics in preschool children. In these cases, neuroscience may never provide a prescriptive solution. Willingham [80] calls this the "goals problem."

The second problem set forth by Willingham [80] is that of levels of analysis. The highest level of analysis in neuroscience refers to the mapping of the brain structure and cognitive functions (e.g., memory, attention) or the interaction of functions (e.g., the impact of emotion on learning). Neuroscientists study these cognitive functions in isolation for the sake of simplicity. They do not study the entire nervous system with all of its possible component interactions. The information that education researchers borrow from neuroscience refer to an isolated cognitive process, but the interaction with other systems is part of the educational context. This constitutes the "vertical problem."

The third problem posed by Willingham [80] is finding a way for translating the contents of one field into the other. Education theory and empirical data are behavioral. Neuroscientific theory and data take many forms because the nervous system has many characteristics. electrical, chemical, spatial, temporal, etc. This is called the "horizontal problem."

For Willingham [80], neuroscientific data can be used with behavioral data when there is a theory and body of data at the behavioral level. According to Willingham [80], the only way there can be a fruitful relationship between neuroscience and education is if its expectations are realistic. Educators should not expect neuroscience (1) to be prescriptive, (2) to establish educational objectives, which by their characteristics are incompatible with neuroscientific analysis, and (3) can serve to answer questions at a finer level of analysis, such as how people read or learn. However, these data are only useful in the context of a well-developed behavioral theory.

From a current perspective that favors integration and dialogue between education and neuroscience research, Ansari and Coch [81] assert that the emerging field of education, brain, and mind should be characterized by multiple methodologies and levels of analysis in diverse contexts, whether in teaching or in research. They maintain that only through an awareness and comprehension of the differences and similarities in both traditional fields of research, both in education and cognitive neuroscience, will it be possible to achieve a common basis necessary to an integrated science of education, brain, mind, and learning [2].

## Discussion and Conclusions

The incorporation of neuroscience into the field of education has been quite fruitful for understanding which are the cerebral processes and cognitive resources involved in learning and explaining what cognitive and metacognitive strategies improve academic performance. Knowledge about how cognitive and socio-affective functions affect the performance of different academic skills (e.g., reading, writing, and mathematics) as well as the regions of the brain implicated in different learning deficits (e.g., dyslexia) has optimized learning disability diagnosis. At the same time, early diagnosis of weaknesses presented by a child in diverse

cognitive and socio-affective aspects that play an important role in self-regulation contributes to the appropriate management of the child's academic difficulties and to the design of techniques in neuroscience that seek alternative methods to enhance learning.

Our findings related to the influence of executive functions on the performance of diverse academic skills emphasize the importance of developing and implementing curricular changes that accompany and stimulate the development of executive functions or their effective use in pursuit of favoring the use of metacognitive strategies to achieve self-regulated learning (learn to learn). In this regard, several studies performed in the school environment have shown significant improvements in executive functioning and self-regulation following the implementation of cognitive training programs that were adapted to the curricula [38, 82, 83] they promote, as well as the employment of cognitive and metacognitive strategies. Therefore, the incorporation of cognitive and metacognitive strategies into curricular content, as well as the implementation of curricular adjustments oriented at modifying the structure of academic tasks for children with executive difficulties, would constitute effective academic strategies for preventing academic difficulties and for optimizing learning in school.

While the contributions of neuroscience can underpin measures centered on the educational system and teaching methods by contemplating cognitive and socio-affective processes that are involved in the learning process, we believe that the study of learning difficulties must be addressed from a multifocal perspective, which considers the child's living environment as well as the school and the parent's educational level, among other factors. For example, it has been demonstrated that coming from a socially vulnerable family, as well as attending a school with a low socioeconomic profile, negatively correlates with the cognitive performance of students [43, 84]. For this reason, it must not be overlooked that the problem of improving school performance is complex and its solution probably requires a multidimensional approach [40] which not only takes into account contributions from the neurosciences but also regards educational psychology as well as the effects of the social environment on the child.

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# New Insights on the Treatment of Emotional Problems

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## Introduction

Continuously we are hearing that new paradigms are coming to psychiatry or at least to mental health. The concept of emotion and what to do with them is fluid, changing. From the evolutionary perspective, every emotion has a surviving function. At the same time, we know that the term "emotion" is just a human construct to describe a set of behaviors, sensations, faces, and biochemical reactions. If we follow these principles, can we consider anxiety as a *disorder* as we talk of pneumonia as such? Is there a bacterium or pathogenic process behind anxiety? Or is it just something normal? Can't it twist our life in such a way that it may become unbearable? At the same time, we know that there is quite a lot of consensus about how the chronic exposure to an emotion or at least to "stress" may lead to a neural, cellular, and molecular restructuration of the brain architecture. Mental health caregivers should consider all these findings to give patients the most holistic treatment. In this chapter, we are going to talk about the emerging scientific therapies derived from the cognitive-behavioral tradition, the new paradigm in which they are based, and how to combine this knowledge with the biological treatments in a thoughtful way.

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## To Suffer or Not to Suffer: That Is the Question

Suffering is part of life. It has always been said in different cultures, philosophies, religions, and so on. Every man who has achieved something important in life has suffered. We just need to read a biography of Julius Caesar, Alexandro Magno, Jesus, Gandhi, or even Paul McCartney to realize that if you want to follow great ideals or projects, there will be obstacles. But you don't need to have something so extraordinary as this people if you want to suffer. There will also be problems if you really want to be a loving father or mother, a present friend, or vegetarian. There is no scape. Every worth living life implies difficulties, and most of



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them are inside ourselves. Whatever you do, if it is worthy, there will be not only external problems but also thoughts or feelings, and many of them are unwanted. A *caregiving* mother feels intense anxiety when his child is crying with fever, a *good friend* feels sadness when his fellow has lost his job, and a girl feels jealousy when her beloved boyfriend is watching another woman. What's more, if the same mother has the thought that her child might be sick, she may feel that same anxiety. If the good friend has the thought of an unemployed friend, he may feel the same sadness, and if the girl has the thought that his boyfriend is a Don Juan, she may feel that same jealousness.

As you might be thinking, a good amount of our suffering is *behind the skin* and is *just* a feeling or a thought. And it is very useful to be *aware* of this fact. Can these internal phenomena stop us? Can they determine our life and freedom? If you are a clinician and you are reading these lines, you will certainly answer "Yes." If patients could be aware of these experiences and choose having some other, we might not have a job. It is that simple. Consciousness of the phenomena reduces problems and leads to have a distance with what is happening and that distance gives the chance to do something different than what the feeling or the thought is dictating. Not everybody has that awareness, but luckily it can be trained, by practicing mindfulness, for example.

But, many times, before giving some medication, do we take all this into account? Is it necessary or useful to avoid suffering in any way? The anxiety will make the mother run to the hospital. If emotions have a function, why should we try to control it? How many attempts have our patients done to control their internal experience without success or making things worse? It is called the "control paradox": you don't want it, and then you have it. Many studies have demonstrated this principle [1–5]. Are we going to be part of this control attempt? Why? When? How can we treat people who suffer if we don't understand suffering? It seems, at today's state of art, that suffering, all of it, is wrong and has to be cured or even eliminated.

Steven Hayes, one of the developers of the acceptance and commitment therapy (ACT), uses the term "*experiential avoidance*" to describe a well-known phenomenon that "occurs when a person is unwilling to remain in contact with particular private experiences (e.g., bodily sensations, emotions, thoughts, memories, behavioral predispositions) and takes steps to alter the form or frequency of these events and the contexts that occasion them." This process is recognized as a central psychopathologic problem by many psychotherapy schools [6].

On the other side, we know that emotions can be tricky. If you have worked with patients diagnosed with borderline personality disorder, you would probably have noticed that many of the behavioral problems, suicide principally, occur during the pick of an intense emotion. From the dialectic behavioral therapy (DBT from now onward) perspective, suicide ideation and behaviors have the function of giving relief; they stop the supposedly unbearable emotion. If patients have no other means of soothing their selves, suicide or self-harm is an option [7].

## New Paradigms

Let's go a bit deeper in the philosophic problem. Thomas Kuhn and Stephen Pepper are well known for their studies of philosophical paradigms. From Khun's perspective, there are different moments in the *evolution* of them. There is a "normal" period in which every scientist thinks that all the reality is explained by his paradigm assumptions, until something happens, a phenomenon can't be understood or explained, and everything blows up. That's the moment where a new paradigm arises [8]. Sometimes we need to wait until all the members of the old paradigm die, and then the new one comes. We believe that something is happening right now. In the first place, some traditional schools of psychodynamic psychotherapy were the gold standard, if you allow me to do such an anachronism, but after its lack of efficacy, scientifics tend to look for something more objective, such as behavior.

Behaviorism was something surprisingly new, but alone was not enough, so the pendulum returned inside the head with cognitivism. Again, it was a new step, an improvement, but again, it was not enough. A good amount of patients were still suffering without appropriate answers to their problems.

Hayes describes three waves of evolution of evidence-based therapies [9]. The first one consists on the behaviorism: the study of the laws of learning and the behavioral analysis. The model is based on procedures rigorously tested and based on well-established principles. Techniques such as the progressive desensitization were developed during this moment. It had some weak points. There was a tendency to minimize deep matters frequently associated to psychology, such as emotions of thoughts, to target observable and simple problems. These theories also generated weak postulates about language and cognition.

The necessity of having tools to directly deal with cognition led to the cognitive therapy, based on the notion that behavioral and emotional events are strongly influenced by cognition. Here the goal is the modification of what the patient is thinking so as to help him change emotions or behaviors. This is the second wave.

This approach started to be questioned in 1996, when Jacobson et al. published an article that demonstrated that the complete cognitive-behavioral treatment for depression was as effective as behavioral interventions alone [10]. Besides, other studies started to show that the "change" might not be caused by neither the reduction of suffering nor by cognitive restructuring but by a change in the relation with the content of experience and a stronger compromise with the process of living. These findings were replicated by different authors in different places of the world [11]. On the other hand, it has also been shown that positive outcomes in CBT-oriented treatments took place before implementing key aspects of the technique [12]. What is more, neither the degree by which fear is reduced nor the ending fear level predict therapeutic outcome [13]. That's how the third wave emerged. Now the goal is to change the relation between private or environmental events and the response of people to them. Finally, these approaches seriously address issues such as spirituality, values, and self [9].

Of course, in the middle of this war was also medicine, developing barbiturics, benzodiazepines, antidepressants, and so on. Great business. The problem is that despite all this, a great number of patients are still "no responders" to treatment, psychotherapeutic or pharmacological. We still don't know exactly how much standard cognitive-behavioral therapy works and why [14–16]. So, what's the problem? Are we trying not so hard? Do we need to give them more therapy or medication? More medication? Really? The US population takes a lot of psychiatric pills. Do they need more?

Allen Frances, chairman of the taskforce that developed DSM IV, says: "We are becoming a society of pill poppers. One out of every five U.S. adults uses at least one drug for a psychiatric problem; 11 percent of all adults took an antidepressant in 2010; nearly 4 percent of our children are on a stimulant and 4 percent of our teenagers are taking an antidepressant; 25 percent of nursing home residents are given antipsychotics. In Canada between 2005 and 2009, the use of psychostimulants went up by 36 percent, and SSRIs by 44 percent…." Psychiatric meds are now the star revenue producers for the drug companies—in 2011, over $18 billion for antipsychotics (an amazing 6 percent of all drug sales), $11 billion on antidepressants, and nearly $8 billion for ADHD drugs. Expenditure on antipsychotics has tripled, and antidepressant use nearly quadrupled from 1988 to 2008" [17].

At the same time, the prestige of psychiatry is going down by the minute. Psychiatrists are seen as guys who give you pills; if you are really bad, go to the psychiatrist to get pilled. We (I am a psychiatrist) are also demonized for being classifiers of people, even the judges of normal or abnormal behaviors. In the past, we were very closed to police.

I believe we are not so fool; we are just having the problem that Thomas Khun described long ago. We are still in a paradigm which is not enough, which is trying to put people in a box too small for them, and it is about to explode.

Pepper postulates different ways of observing the world and different *paradigms* or *hypothesis about the world*: mechanicism, formism, organicism, and contextualism [18, 19]. According to Hayes, scientific psychology is biased by observing behavior in a mechanistic way: we will understand the problem if we understand the machine, the relation between its parts, and the predictable result of the forces. This view makes us study the intraorganismic relations of the subjects, the interaction, for instance, between a trait and a behavior. For example, Hayes cites the work of Bandura, who demonstrated that our own perception of our efficacy for doing a task is related with the realization or not of the job. This theory can predict precisely if somebody is going to do something, but it is not telling us how to make changes in this person [19].

We are not pretending to say that these mechanistic theories failed, it seems that the information they provide corresponds to reality, but it does not seem to be that useful. Correlating intraorganismic variables does not say much about neither how the environment affects a behavior nor what we can really do to change them. In physics, knowing how the parts of a machine interact leads us to useful information because we can then manipulate those parts. The problem with intraorganismic events in this model is that their parts are not so easily manipulable. It's not really clear how a therapy can change a thought; it's not clear if it can be done at all. It seems that we always think the same way in certain situations. Besides, it's also not very clear if we can change emotions that easily.

These variables seem to be manipulable if we manipulate environmental events which affect these organisms. Hayes and cols suggest studying behavior as an "act in a context with a function" as the context is the environment in which behavior occurs. Only the contextual variables can be modified, and not the behavior itself (it is important to know that these authors also subscribe to the "radical behaviorism," in which everything that a dead cannot do is behavior, even thoughts or emotions, and all of them are sensible to the effects of contingencies around them). From this perspective, the validity of a model is given by its ability of contributing to the achievement of a previous goal. That's why this proposal is known as "functional contextualism." It has the focus on the utilitarist function of a certain context [9, 19, 20]. We believe that this is something new.

Of course, in this model, there are not correct or incorrect objectives; they are arbitrary. In this paradigm, what works is what helps clients have the life that he freely has chosen to live. Besides, this paradigm provides a theoretical and philosophic frame in which research can correlate context and behavior. Paraphrasing Hayes, in this approach, people is encouraged to stay with the experience of what works or does not work, being it an emotion, a thought, or whatever.

Hayes [20] describes four possible contexts that facilitate the experiential avoidance described above:

(a) The context of literal meaning: an emotion can be evoked by the fact of the death of a beloved one or just by the thought of that. We tend to get confused between what we think and reality itself; we can sometimes take thoughts as facts. For instance, someone may suffer because in his mind appears the word "looser," and he believes it. This is a context were words are literally believed.
(b) The context of evaluation is based on conventional verbal agreements about what is bad and good. When combined with literal meaning, evaluations present themselves not as actions but as actions of the world: we say "that is bad," not "that is, and I evaluate it as bad."
(c) The context of reason-giving is established by the tendency of the verbal community to support actions if a sufficiently good explanation is given. Someone might say that he or she doesn't want to invite someone to dinner because that person is a bad example for the children, but that is not necessary the cause. Many times, there is an emotion and not a reason behind the behavior, for instance, disgust. The real cause of the denial is that he or she feels disgust when they are in front of the "bad example." Nevertheless, we tend to feel

satisfied with those "explanations." Reasons have automatically learned functions. In this case, the reason is negatively reinforced by the relief of the disgust, but these persons might be doing something against their values when discriminating this guy.

(d) The context of emotional control. It is very common to hear from almost everybody that they do therapy because they want to feel good. This context can also be called feel-goodism. It consists on applying problem solving strategies useful in the outside world to internal experiences. Emotion is the problem. The target in this case is to stop feeling anxiety, sadness, or whatever. The feeling must leave. Today, culture (in general terms) is a context in which suffering is a problem.

According to these assumptions, the new contextual approaches tend to help patients to:

1. Recognize their own patterns of behavior by doing function analysis of their behavioral problems.
2. Practice mindfulness to notice thoughts and emotions and live the present moment.
3. Accept reality and emotions, focusing on the fact that many emotions are part of living a meaningful life (this is also a sophisticated way of doing exposure, not only for exposure itself but also to have freedom to get closer to value living with flexibility, sometimes even with the emotion).
4. Define or clarify their own values, as new rules freely accepted which now will give sense to the inevitable suffering of life.
5. Defuse from the content of the mind and from the arbitrary rules and contexts that take our freedom away [6, 7, 16, 21].

## Emotions: What They Are and What to Do

After all what was written above, we will now focus specifically on emotions, considering that this chapter is about *treatment* of emotions. We think that every clinician should meditate about all this information before prescribing any therapeutic procedure. Of course, the topic is long and complicated. We will try to cite the authors we believe are the most important.

Humans have the ability of observing their own internal events and behavior and then naming them. Sometimes it is useful and sometimes it's a mess. Which is the difference between sadness and melancholy? We can discuss for hours.

Joseph Ledoux, an authority on the matter, wrote articles clarifying many things. Basically he gave shape to his idea after a lot of research about what emotions and feelings are, starting from Darwin. He concluded that the most effective approach for studying them was focusing on emotions in terms of brain circuits that contribute to behaviors related to survival functions. The feelings are what we say about the activation of this circuit in ourselves or in others, so it is something subjective and very difficult to measure. Of course, it is even more difficult to talk about feelings in animals [22, 23].

Dialectic behavioral therapy (DBT) is one of the therapies with the stronger evidence for efficacy in treating borderline personality disorder [24]. From the perspective of this approach, emotion dysregulation is one of the core problems of this population. The treatment consists on teaching skills of mindfulness, interpersonal effectiveness, distress tolerance, and of course emotional regulation.

Interestingly, Marsha Linehan, the developer of this therapy, says that "much of the emotional distress is the result of a secondary response (shame, anxiety or rage) to primary emotions. Often the primary emotions are adaptive and appropriate to the context. The reduction of this secondary distress requires exposure to the primary emotion in a nonjudgmental atmosphere" [21]. It seems that in many times emotion "per se" is not the problem but the secondary emotions that arise when we don't know how to manage or even if we try to control them when we are not supposed to.

Like DBT, the Unified Protocol [25, 26] addresses deficits in emotion regulation that underlie emotional disorders by (1) increasing

present focused emotion awareness, (2) increasing cognitive flexibility, (3) identifying and preventing patterns of emotion avoidance and maladaptive emotion-driven behaviors, (4) increasing awareness and tolerance of emotion-related physical sensations, and (5) utilizing emotion-focused exposure procedures.

Basically, in the emotion regulation module of DBT [21], patients are taught to:

1. *Understand and Name Emotions*

A lot of time is taken to consider what is happening inside the skin and how to name it. It is also very important to know which the common triggers of every emotion are and which the typical phenomenology that comes afterward is. In this way, patients know what is happening to them, why, and what to do next.

2. *Changing Unwanted Emotions*

Patients are not taught that emotions are good or bad; they just have a function, and sometimes they lose that function if they are not in the appropriate context. Emotions can be triggered by interpretations or by events. That is why the first step is to check the facts to see if the response is justified or not.

According to Linehan, "DBT assumes that most people feel painful emotions for good reasons…Thus, an important way to control emotions is to control the events that set off emotions." There is a problem outside yourself that you need to solve to get peace.

Finally, Linehan teaches to do opposite action. She usually says that emotions *love their selves*. If you follow the impulse of action, the emotion will grow; if you act in an opposite way of the impulse, the emotion is reduced. Therapist must be careful when teaching this to patients, because many times, as we say before, the impulse of the emotion is justified and useful for the survival of the individual. In the case of fear or anxiety, opposite action is an equivalent term for exposure.

3. *Reduce Emotional Vulnerability: Building Mastery, Cope Ahead, and Taking Care of the Body*

In here patient is taught to accumulate positive emotions in the short run (by actively scheduling daily positive experiences, such as doing sports or going to visit somebody you love) and to start planning a "life worth living" in the long term. This is the main objective of all the therapy, and this idea is emphasized every minute during all the treatment. In here, DBT is very similar to ACT because values and goals are discussed and planned.

Building Mastery is a chapter also seen in other treatments for depression, and it consists on building a sense of self-efficacy by engaging in self-goal-directed activities.

Cope ahead is an ability designed by Linehan after she herself developed a phobia to tunnels. At first, she tried to overcome it just by doing exposure, but she realized that it was not enough; anxiety was still too high, so she tried to anticipate to the worst possible outcome by planning what to do if it really happens. After doing so, her anxiety response started to go down. Concretely, she practiced in her imagination what to do if the tunnel falls.

The ability to take care of the body is a way to emphasize the importance of fundamental things such as eating, sleeping, going to the doctor when necessary, avoiding using drugs, practicing sports, and so on. Many times, patients forget about this, or, what is worse, they do not even notice how their body need to be comfort.

4. *Managing Extreme Emotions*

DBT is sometimes called the "ice cube therapy" because the ability of managing extreme emotions by grabbing some ice is well known. What is very important here is to teach the patient that many of their most problematic behaviors, such as cutting their selves or even being suicidal, are an ineffective way to manage emotions. After cutting or consuming drugs, for instance, emotions usually go down and people feel relieved. The problem of this behavior is in the

long run, because it is proved that this behaviors increase the probability of committing suicide.

In this module, patients are taught to recognize their breakdown point: the moment in which emotions are so intense that they cannot use sophisticated skills and their life is in danger, so they need to control them. This is done in different ways, but in summary, what patients should do is to strongly stimulate a sense to change the physiology of the arousal. The typical thing trained in here is to grab ice, enter a cold shower, bite pepper, hear loud music (which of course must be opposite to the emotion), smell strong odors, practicing intense exercise, and so on.

Frequently, the problem in here is with psychiatrists, who usually do not know how the treatment works and prescribe pills to take in this very moment. The typical drugs used in here are benzodiazepines (BDZs). This is usually tricky, because these drugs are very addictive, and they block the possibility of learning an ability. The patient usually interprets that the medication was what helped instead. What's more, they are not as effective; usually they need between 1 and 2 h to start to work [27], depending on the literature you consult, when the abilities are almost immediate. In many cases, the benzodiazepines become a reassurement behavior leading to maintain the problem in the long run or interfere in the process of emotion exposure [28, 29].

## The Misuse of Benzodiazepines

Nowadays the misuse of benzodiazepines is still being a worldwide problem. There are strict indications for benzodiazepines depending on the problem. These indications consider the half-life of the drug, the potency, the onset of action, the illness, the characteristics of the patient, etc. It is well known that the use of these drugs shouldn't be longer than 4 weeks [30]. Psychological dependence has never been seen in patients treated for less than 2 weeks; nevertheless half of patients that were in daily treatment for more than 4 months became dependent [30]. Although benzodiazepines have disadvantages, these are useful while the physician waits to the effect of the cognitive-behavioral therapy (CBT) or/and the non-BDZ drug, when anxiety is incapacitating [31]. In these cases, BDZs with slower onset and longer half-life may be the correct option to prevent abuse [30].

These are the indications of BDZ, according to the consulted literature [30–34]:

- *Insomnia*: as first-line therapy, we recommend cognitive-behavioral therapy, sleep restriction, and stimulus control. However, BDZ is useful as adjunctive agents in the short term. We clarified that BDZ should not be used as a monotherapy, and also it is preferable to use them only for 2 weeks and no further than 1 month.
- *Generalized anxiety disorder (GAD)*: BDZ is only used symptomatically; therefore, these drugs must not be first-line treatment. First-line treatment should be selective serotonin reuptake inhibitors (SSRIs) or serotonin and noradrenaline reuptake inhibitors (SNRIs) and combined with CBT. The use of BDZ is in discussion because it can interfere with CBT and disturb learning. BDZ can be used but with worst outcomes.
- *Panic disorder*: the APA (American Psychiatric Association) guideline for the treatment of panic disorder and the NICE (National Institute for Care and Health Excellence) guideline on the treatment of panic disorder and GAD do not recommend the use of BDZ in this clinical context.
- *Social anxiety disorder*: the first-line treatment is SSRIs or SNRIs or/and CBT. BDZ is not indicated and may interfere in long-term therapy. In this case, the combination of a non-BDZ drug and CBT had not shown a synergism.
- *Depression*: BDZ are commonly used to treat the anxiety associated with depression. These drugs should be used but just in the short term to help people who doesn't sleep or are extremely agitated. For example for insomnia a Z-drug can be used and for jitteriness pregabalin, and many other examples can be described. CBT and many others psychotherapies have strong evidence for treating depression, but psychotherapy needs a basis of mood

stability to be performed, so BDZ can be used to help people who doesn't sleep or are extremely agitated.

- *Other anxiety disorders*: BDZ can be used as complementary treatment and with the same criteria as above, in post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). The role of pharmacotherapy is still a matter of discussion in PTSD. There is evidence that indicates that these drugs should be avoided in this clinical context, principally because of their ability for generating dependence and because they block the effectiveness of exposure therapies [28, 35–39].

Of course, BDZs can be used in many other situations, for example, in maniac episodes, akathisia, acute catatonia, psychomotor agitation syndrome, and many nonpsychiatric disorders.

## Chronic Exposure to Stress Leads to Neural Damage and Psychiatric Morbidity

This section has the aim of summarizing the evidence that shows that it is not recommendable to be with high levels of emotions during prolonged periods. Considering the previous cite of Ledoux, we will consider "stress" just as another way to say "emotion."

Actual evidence suggests that the quality of the experiences during youth might have an effect in the adulthood, probably by programming the sensibility of the hypothalamic-pituitary-adrenal axis (HPA axis). Basic research has shown that early exposure of the brain to elevated levels of corticoids might have long-lasting effects on important processes such as memory, metabolism, and cardiovascular functioning. There is strong research that correlates the relationship between corticoids, memory alterations, and, clinically, PTSD (post-traumatic stress disorder). Cortisol levels are usually elevated before and during the circumstances that led to the traumatic experiences [40].

"Stress" activates the hypothalamic-pituitary-adrenal axis (HPA axis) leading to a complex response mediated by corticosteroids and catecholamines, between others. The relationship of stress and anxiety has been extensively described. Corticotropin-releasing hormone (CRH), the putative mediator of the stress response, has been involved in anxiety in rats in the plus maze test [41]. Furthermore, other peptides linked to stress response, like angiotensin, have been related to anxiety levels [42, 43]. Glucocorticoids receptors are expressed through all the brain, acting as transcription factors that regulate the expression of different genes [44]. There is scientific evidence that indicates, in experimental and human models, that during different periods of development, stress plays an important role. During the prenatal period, maternal stress is associated with low weight birth and an increase of the basal activity of the HPA axis during different periods of preadolescence [45–47]. These kids had shown later behavioral and cognitive alterations such as attention deficits, sleep disturbances, depression, and anxiety disorders [48]. It has also been shown that low birth weight combined with low maternal care is associated with a smaller hippocampus volume [49].

Adolescents who grew up in poorer economic conditions have elevated basal levels of glucocorticoids [50], as those whose mothers were depressed during the early postnatal period [51]. These situations predict an elevated risk of developing depression around 16 years [51]. Adolescents exposed to continuous and early adversity showed abnormalities in the gray matter volume, the neuronal integrity of the prefrontal cortex, and a diminished size of anterior cingulate cortex. Prefrontal cortex is particularly vulnerable to stress during this period of life [52].

Many studies in adults reveal that the acute elevation of glucocorticoids reinforces the memories associated with emotional information but interferes with the recovery of neutral information [53]. Low self-steam, a strong predictor of elevation of stress reactivity in humans, is associated with a diminished hippocampal volume [54]. Studies in adults who were abused during childhood also reveal alterations of the activity of the HPA axis [55]. Furthermore, the diminution of volume and function of hippocampus are

characteristics described in depression and PTSD [56, 57].

These and other results, in human and animal or experimental models, have led to postulate the neurotoxic theory, announced for the very first time in 1986 [58], according to which the prolonged exposure to glucocorticoids makes neurons less able to resist insults. This theory claims that the smaller hippocampus is the result of years or decades of PTSD, depressive symptoms, or chronic stress. In contrast with this hypothesis, there has also been formulated vulnerability theory, which suggests that the reduction of the hippocampus is not a consequence of chronic exposure to stressors but a preexistent risk factor genetically induced [59, 60]. Other authors suggest that these postulates are not necessarily conflicting. They can be complementary if taken into account from a neurodevelopmental perspective [44].

Reversible atrophy has been demonstrated in hippocampus and amygdala [44, 61–64], regions responsible of emotional learning and stress response. These structures are involved in the consolidation of memory, particularly when tasks related to contextual or special components are done. The increase of systemic glucocorticoids reinforces the formation of memories for events that trigger emotions [65]. After an excessive exposure to these hormones, the formation or consolidation of declarative memories diminishes, a fact that is interpreted as a way that the nervous system has for selecting information emotionally stimulant. Working memory, commonly associated to the medial prefrontal cortex, is also affected by elevated levels of corticosteroids. In this context, it seems that these hormones play an important role in the management of adverse experiences, allowing and reinforcing the impression that events produce [40].

Of course, the effect of stress at a molecular level has also been thoroughly studied [66–69], but we believe that summarizing all the information around this topic goes beyond the goal of the article.

People diagnosed with borderline personality disorder (BPD) and/or PTSD have elevated levels of physical abuse during childhood or adolescence than subjects without those diagnoses [70]. Besides, the severity of the BPD psychopathology is associated with the severity of the sexual abuse. Taking all this into account, many clinicians suggest that BPD is a type of PTSD [24].

Functional and structural neuroimaging reveals the misfunction of neural networks that mediate different aspects of the bipolar disorder (BPD). There are alterations in fronto-limbic pathways such as the anterior cingulate cortex (ACC), prefrontal cortex, and orbitofrontal and dorsolateral hippocampus and amygdala. Besides, this population has a greater sensibility in the HPA axis [24].

## Conclusion

We believe that we, as clinicians, need to achieve a dialectic balance. On the one side, we can't just sit and wait. There is a neurochemical syndrome behind all that must be reverted, with or without drugs. On the other side, if every time a patient is dealing with an unwanted emotion we jump to give him or her the BDZ or any other drug, what message are we giving? What are we shaping on them? Moreover, if they feel that *we* are anxious to stop their suffering, what are they learning?

Up to this certain point, the reader might think that some of the information written is contradictory. Do we accept or do we change emotions? Quoting Marsha Linehan, "most approaches to mental health treatment focus on changing distressing events and circumstances. They have paid little attention to accepting, finding meaning for, and tolerating distress."

What is obvious is that if you die, you cannot do anything else, at least in this world, so there is a hierarchy: first survive, and then we will see. Secondly, prolonged exposure to stress hormones has deleterious effects on the brain.

After that is solved, we can think about more sophisticated skills, but we believe that above all, the message should be that suffering is part of life and part of having a *worth living* one, so it cannot be avoided. What we can avoid is to suffer uselessly, without a meaning. Taking all this into account, the clinician should meditate which is the step to take in each case. It is a complex clinical decision.

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# The Intelligence of Emotions: A Path to Discover

25

Gilberto A. Gamboa-Bernal

## Emotional Intelligence

Daniel Goleman was a science journalist for *The New York Times* and a scholar at Harvard University who worked on meditation as a resource against stress based on observations made in both India and Sri Lanka.

In 1990, Dr. Goleman began writing about a concept, the concept of emotional intelligence (EI), which he had read about in a scientific paper published a year earlier, written by psychologists John Mayer and Peter Salovey [1]: a type of synthesis that unified some scientific advances in the neurosciences in its relationship with psychology, mainly in investigations of how the brain regulates emotions. Another remote antecedent is the concept of "multiple intelligences" coined by Howard Gardner in 1983 [2].

In 1995, Goleman published his first book on the subject [3], and since then, he has written almost two dozen books, with some variants of EI application: leadership, social skills, academic performance, effective work, ecology, etc.

In these books, he states that EI is both the capacity of the human being to involve the emotions in rational processes as the utilization of the emotions and the *emotional knowledge* to improve thought [4].

The theory begins from the observation of the different capacities that people have to sophisticatedly process the information needed to react according to its emotional dimension; moreover, it is also the tendency to use that information as a guideline in decision-making and behavior in general [5].

Some authors and researchers argue that EI is a set of mental capacities; others only consider EI to be an eclectic conglomeration of positive traits, susceptible of being acquired and developed mainly for the benefit of work activities [6].

The great profusion of material written on EI, mainly of dissemination, has alerted scientists who do not observe a strong theoretical basis for the new concept, whereas its applications have been cyclical following certain characteristics associated with what is popular at the time [7]. An example of this is the application of EI in personnel selection processes, in which candidates are measured according to this psychological theory.

However, criticism of EI goes beyond categorizing it as a new fad in psychology, as yet another consumption product. There are also authors who argue that the epistemological status of EI is very precarious, even nonexistent, because it is not a different form of intelligence and cannot be compared with either real intelligence or rationality [8]. This argument does not exclude that there is a real relationship between reason and emotion, but that does not mean that they are the same.

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The controversy extends not only to the conceptualization of EI but also to the manner in which it is measured. Several instruments have even been designed [9]: the EQ-I of Reuven Bar-On; the MSCEIT of Mayer, Salovey, and Caruso; the ECI of Goleman, Boyatzis, and Hay-McBer; the EQ Map of Q-Metrics; and the EIQ of Higgs and Dulewicz, among others.

Some applications of EI have also been questioned, such as its predictive utility for life skills and its significant results in vital performance, because it has not been observed that this utility exceeds the exercise of cognitive abilities or performance supported by a suitable personality [10].

What EI science says is almost always limited only to the scope of its applications in the workplace and oriented toward success; however, outside of the work environment, it is more difficult to find substantial scientific literature that convincingly justifies the utility of EI [11] because it is viewed more as a theoretical construct rather than as a description of an anthropological reality [12].

An association between EI and the ability to react to stress has also been described, but the results are not conclusive: it can be said that EI is potentially useful for reducing stress for some people, but it has been shown to be not relevant and superfluous for others [13].

In its short history, EI, cataloged by some as a science, has been the object of research whose results are dissimilar because they have generated multiple controversies and only some agreements. The main areas in which research has been conducted are the conceptualization of EI, its applications, and the instruments for measuring it [14].

The rise of the literature on EI has been decreasing in the last decade, but its applications in different scenarios, particularly labor, have increased because they imply more positive attitudes, greater adaptability, better progress in interpersonal and group relations, and a more pronounced propensity toward positive values [15].

This trend toward EI applications has led to the successful association of new initiatives that are gaining momentum at the dawn of the twenty-first century, in which services and companies whose mission and vision have gravitated toward it have multiplied exponentially. An example of this association is that which is presented with coaching in any of its modalities [16]: personal, group, business, organizational, educational, etc.

A simple and quick realization that associations of this nature are focused from a mercantile rather than scientific rationality is shown when in a general search engine, using the words "relationship between coaching and emotional intelligence," more than 3,200,000 results are obtained; in contrast, scientific articles with these terms only report less than 60,000 results. In a specialized engine, such as Scopus, only 23 results are obtained.

Hyper-tech environments in particular and in environments in which human beings interact in general show that human relationships need not be stripped of small key characteristics: kindness, decency, empathy, and respect for privacy. These qualities are not the property of a few but the possibility of all; however, their absence necessarily implies personal and collective impoverishment. Jeff Bezos, the founder and CEO of Amazon, is very aware of what his grandfather, Lawrence Preston, taught him when he was a child regarding an essential maxim in human relationships: "one day, you will understand that it is harder to be nice than to be intelligent [17]." This is another field of application of EI on a large scale: human relationships [18].

In summary, it is possible to affirm that EI is only a popular concept in the literature of personal improvement and organizational performance and that it can be better characterized as a skill that serves to explain and eventually improve human behavior and performance [19]. This approach, proposed from the beginning by Mayer, Salovey, and collaborators, consists of abilities for the perception, assimilation, understanding, and handling of the emotions [20].

By relating these abilities to general cognitive ability and personality in its dimensions of openness to experience, extraversion, neuroticism, conscientiousness, and agreeability, it can be affirmed that EI is a construct that has very

limited performance with regard to aiding in the comprehension of being human [21].

For all of the above, rather than talking about a true emotional intelligence, one should recognize only the role that human intelligence plays in the exercise of emotions, in the sense of guiding these special abilities that are part of the personality and that modulate interactions with others and with the environment.

## A Psychological Perspective

The psychological perspective of emotions can have at least a dual approach: that of clinical psychology and that of social psychology. Clinical psychology is more concerned with the subjective and psychic aspects of emotions than with the physiological phenomena involved in them. Social psychology is concerned not so much with particular subjective facts as with phenomena of the expression and communication of emotions.

To some extent, this helps avoid a dualistic approach when discussing emotions in psychology. However, it also does not contribute to a real appreciation of the emotional phenomenon by focusing only on one facet, be it organic or subjective.

This *real appreciation* is what, in the first instance, interests psychology and is what the following pages are dedicated to, noting in part the social perspective.

At present, there is a type of paradox with emotions: on one hand, they are deprived of importance in their social dimension, verifying a depersonalization of them and a diminution of their intensity, to the configuration of what could be a post-emotional society [22]. On the other hand, in the individual sphere, there is a tendency to be carried away by emotions as a further manifestation of the hypertrophy of autonomy: the authentic way would be to act not as *one thinks* but to act as *one feels*, part of the modern ideal of authenticity [23], in which the emotional-I is the one that sets the rules of what is right and wrong [24].

Another manifestation of this modern ideal of authenticity is defended by the extropians or posthumanists [25]: for them, emotions are key to making ethical assessments, which naturally would not depend on the objectivity of what is done but also on the emotional variability of the one who acts, who surpasses, and who replaces – according to them – human nature [26].

However, the subjectivity of the appreciation necessarily leads to an indispensable exercise of introspection to access it [27], which allows one to recognize what one feels, how one feels, and how one reacts to what one felt. Access to the personal inner world is, however, not enough; to know emotions in detail, it is imperative to capture the ability that one has to exteriorize the answers or, at least, to register the secondary alterations, even if they do not externalize [28].

The method of entering the emotional world through introspection was strongly questioned by behavioral psychology, which only observed that in humans, inputs and outputs of their experiences and other elements of their subjective world could be recorded but were inaccessible to people other than the subject who felt them [29].

In this manner, the emotional processes remained hidden from the external observer, who could not access them even though the subject attempted to communicate with words or writing (verbal) or with gestures and the use of body language (nonverbal).

However, this is only a relative obstacle, given that the capacity of the human being to *read* both verbal and nonverbal language is very large and allows him or her to grasp, with great precision, the emotional state of his or her peers. From the scientific perspective, however, the validity of such an observation is considered weak, and qualitative methods do not have the same recognition as quantitative methods.

Nevertheless, in the qualitative field, a careful, well-done observation supported by a good research protocol and with a reliable sample and statistical methods is a great complement to understanding, as much as it is possible, the emotional world, on par with the introspection performed by the observed subject.

In clinical psychology, this type of approach to subjectivity has increasingly more space: observation combined with introspection [30]. If

to this is added the possibility of making physiological measurements of emotional manifestations, then one can count on good material, which allows some aspects of the emotional world to be more fully explained [31].

However, the advances of neurology and neuropsychology in the knowledge of the central nervous system provide more data for the full understanding of the emotional phenomenon, in which not only cognition or psychological experience suffices to explain it, given that any stimulus that has the rational subject is necessarily accompanied by an organic reaction that makes it almost impossible to be perceived [32]. For this reason, in psychology, theses that raise the mind-body dualism, as well as its applications, are defended increasingly less frequently.

In the observation of emotional states, the expression that they have in the body plays an important role, particularly facial expressions, tone of the voice, gestures, the position and movement of the hands or feet, etc. [33]. Through the more or less attentive examination of a subject, one can gather, with a good possibility of success, what the emotional state is at a given time.

Even facial expressions do not necessarily have to be captured by the observer. However, from them, the observer can deduce, without prompting, the emotional state from which they originate.

These vestiges of the emotional state in body expression may or may not be conscious and may even contradict what is verbally expressed, but they always reflect changes, which denote what may be occurring within the person.

Body language often contains more truth than is expressed verbally because we humans have the potentiality and the tendency to want to cover up the emotional dimension [34]. In these cases, however, body expressions almost always reveal the true states of the soul, and it is not possible to deceive a perceptive or attentive observer.

However, there is still more: body language frequently goes far beyond the verbalizing capacity of emotional states, and people may not be able to express in words what emotion they are experiencing, or the emotion may also confuse them. Instead, body expressions are very genuine and generally do not allow misunderstandings in their interpretation. This situation provides the observer's appreciation – more if he or she is qualified and trained – much more weight to inquire about the emotional life of a person than the same verbal expression would provide [35].

This confusion of emotional states reveals the difficulty with which the human being identifies them in the first person, but it can also be due to the excessive load of the environment that, in the present moment, causes people to move through a medium in which the primordial thing is the image, the speed, the information in real time, etc., elements that prevent a considered reflection on their own experience.

Another psychological characteristic of emotional expressions is that people generally tend to relate them in an interpretive rather than descriptive manner: it seems that it is easier to offer a hermeneutic than to make a narrative; the former implies an exercise that lends itself more to a depersonalization of emotion, whereas the latter implies a more precise knowledge of what is meant [36].

All of these emotional responses are preceded, accompanied, or followed by physiological changes, many of which can be verified; other changes, mainly neurological, are more complicated to identify, although more modern scanners, such as color positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), can help observe what happens in the brain when an emotion occurs. However, the synaptic and neurotransmitter level is still almost completely inaccessible.

All of this suggests that there are at least three ways of manifesting an emotional state: a verbal or expressive form, a mental or subjective form, and an organic or physiological form.

From the psychological perspective, one can ask about the manner in which these three ways of expressing an emotional state are related because this interaction can be parallel, interconnected, or dissociated.

A century ago, the answers to the manner in which these relations can be given would be marked by dualism, as noted above. Now,

psychology prefers to give a broader answer in which it is clear that emotional phenomena are the patrimony of the personal being and his or her autobiography and not of one of his or her parts or functions [37]. This response implies that in the human being, there is continuous feedback that makes it possible for what is known, what is felt, what is thought, etc., to have physiological repercussions and vice versa: an organic situation can generate a more or less recognizable emotional phenomenon.

It should not be forgotten that emotional responses to stimuli do not necessarily reach the conscious level because of the neurological interconnections involved in these responses: on one hand, the amygdalin system in the middle brain, which does not necessarily have a connection with gray matter, and on the other hand, the limbic area with the hippocampus involved, which indeed has a connection with gray matter [38].

However, the psychological perspective also shows that the emotional reactions are not the same with the same stimuli and that in the same person, such reactions may differ from identical stimuli but at different times or circumstances.

Another characteristic of emotions is that they are almost never experienced in isolation and as pure but that there is typically a mixture of emotions, although one predominates over the others; nor can it be ensured that human beings can remain in emotional neutrality but that such phenomena occur in everyday life, change, modify, or disappear with random and cyclical periodicity that depends on each individual being: emotional reactions cannot be standardized.

Internal and external stimuli, the sensations, have the capacity to produce emotions but without any order or without being in concert, which causes great fluctuations that do not allow univocal or uniform patterns of response to be observed or to even be interpreted by knowledge [39]. "Moods," "mood swings," and "emotional responses" have a very distinctive stamp that indicates a deep personal root and are above learned, evolutionary, or automatic reactions.

Perhaps this is the reason why it does not make much sense to attempt a classification of the emotions, as intended in section 1 of the first chapter of this first part. However, it is easy to recognize five emotions that can be described as basic: joy, sadness, fear, anger, and love [40].

These emotions, although different, have a series of characteristics that they all share, given that they imply a mental and physical state that encompasses the entire organism. These characteristics are:

They share a primitive biological meaning, of an evolutionary character, for the survival of the individual or of the species.
They are important for ontogenetic development, that is, for the development of the segregated individual of the species.
Vestiges of them are observed from the first months of extrauterine life.
Each has facial expressions that are recognizable by any member of the species, that is, they are universal and common, regardless of culture, gender, or race.
They are presented in different degrees that depend both on the biography of the subject and on the circumstances, that is, there is a graduality that is affected by the personal history and the contexts in which they occur [41].

In addition to the emotions that can be called basic, in human beings, there are also much more elaborate and complex emotions that have been recognized; these emotions can be called mixed or superior. Within this second form would be emotions such as admiration, respect, envy, ambition, and bewilderment, among others [42].

The constellation of emotions in the human being is extremely broad and is multiplied by personal and individual variability; as noted above, the number of emotions is potentially infinite. For this reason, it is possible to affirm that from the psychological perspective, each human action has at its origin a more or less relevant emotional component that modulates that action and imprints a personal component that facilitates its recognition or ascription to a certain subject.

Temporality in emotions is also important. Although their short duration is generally admitted, humans have longer experiences than reflexes

of initial stimulation. This is how one speaks of emotional states or states of mind that prolong an initial emotion over time [43].

For the human being, the perception of time is not identical in each subject because there is a time that can be measured (*kronos*) and there is a time that is lived (*kairós*) [44]. In general, they are not synchronous, depending on several factors, and one of them is the emotion. Emotion can change the psychological perception of time by making it be perceived as more or less short or prolonged by the subjective resonance that emotion imprints on the person [45].

Time also influences emotion when it is involved in an ethical decision process: time alters cognitive and emotional control such that ethical assessments tend to have more deontological content when there is less time to reason them [46].

These phenomena are directly related to the duration and the intensity of the emotion as well as the complexity of the emotion itself and its possibility of expression, giving a great amount of possible combinations, which makes it superfluous to note them and to describe them: its variability almost tends toward infinity.

In summary, it can be said that from the psychological perspective, emotions are at the base of the human act, not so much as its engine, given that it is the will that reigns in what the intelligence shows, but, rather, as the regulator of the action or as the element that *embodies* it.

Dismissing emotional phenomena brings with it a partial view of human behavior, which does not allow it to be appreciated in its real dimension and meaning. Through emotional life, we recognize ourselves as being different from others, with particular and personal characteristics.

However, it is also true that these same emotional phenomena have a social projection, in the sense that they can be differentiating elements of the family, work, and cultural nuclei in general. The mimetic character of the human being enables this effect of emotions, when transmitted from parents to children, among friends, colleagues, neighbors, or fellow countrymen, among others [47].

## The Modern Neurobiology of Emotions

The leap that has occurred in the study of emotions, owing to the new tools for investigating the brain and its functioning, is appreciable. In recent decades, imaging equipment has been designed and operated to assess, in real time, the functioning of the central nervous system. These devices have also been very important for the diagnosis and prognosis of neurological and mental diseases that could not be accessed due to physical impossibility.

Research in these fields has progressed at a vertiginous speed, and with it, a new method of evaluating not only the emotional and cognitive dimension of the human being but also many other functions that, until now, remained in the penumbra of related speculation has appeared, for example, with perceptive experience [48] such as the recognition of conceptual objects, social cognition, language, and the remarkable human capacity to remember the past and imagine the future, etc.

The observations of the neurophysiologists of the last century have been verified in some cases; in others, they have created controversy, or they have been complemented owing to the use of these new tools [49].

In the field in question, progress has also been significant, particularly in demonstrating that both emotions and cognitions are closely and deeply interrelated in brain tissue and that other structures are engaged in this synchronous functioning, apart from those previously described.

The development of bioinformatics and computational theory has also played an integrative role between emotion and cognition, although this impact has not been as great or widespread as initially thought, among other reasons, because attempting to explain brain functioning only in computational terms implies a reductionist mechanistic loss that does not necessarily correspond to what occurs in reality. In this regard, efforts in the field of psychiatry have been made [50], but the results have not been sufficiently satisfactory.

Where the results of neurobiology have been more fruitful is in the field of etiology of some diseases and psychiatric conditions; in the observation of the effect of stress, anxiety, and other types of emotions on cognitive processes such as selective attention, cognitive control, memory, etc.; and in the opposite phenomena: the participation of the circuits involved in working memory, attention, and executive control in the regulation of the emotions [51]. In addition, the neural bases of some mental disorders have also been found, owing to research in neurobiology [52].

In the same line are investigations that have been conducted in the context of addictions, in which neurochemical circuits related to the emotions have been studied to observe altered emotional states in the course of detoxification processes [53].

On the other hand, neurobiology has demonstrated the anatomical and physiological substrates of emotions and the mechanisms necessary for life in relation to neurons as well as the locations of the cortex and subcortical nuclei [54].

The plasticity of the human brain has also been at the center of several neurobiological investigations that have only corroborated that characteristic since the earliest childhood. In the development of the neurological circuits of emotion and the regulation of stable emotions, the importance of the presence and performance of parents in front of their young children has been described: the imprint of this action is verified in deep neural effects. These changes allow the formation of what some authors call a "neuro-environmental loop," whereby the child acquires the emotional competence necessary to make contact with the external environment and determines his/her mental health in the long term [55].

To date, however, neuroimaging studies are not sufficient to fully explain the intricate functioning of the central nervous system [56], starting with their technical limitations, resolution problems, image artifacts, and inaccuracies in neuroanatomical labeling [57], and, above all, because of the complexity of brain activity.

Some fields have directly benefited from the use of neuroimaging; for example, the use of fMRI has been very important in documenting the effect of negative emotions [58] or the specialization of the different parts of the amygdala in the response to emotional stimuli, studying the connectivity within it [59].

Neuroimaging has also contributed to the understanding of the pathophysiology of some psychiatric diseases, particularly when the regions such as the amygdala, insula, anterior cingulate cortex, hippocampus, and ventromedial prefrontal cortex have been found to be involved in several emotions such as fear and sense of security [60].

Another application of neuroimaging has served to establish the precise relationship between sleep and emotional and social behavior, affective cerebral homeostasis, and emotional and psychiatric problems that cause hypnopathies [61].

Similarly, the interdisciplinary dialogue between the different approaches of the emotional dimension has been facilitated on more certain bases, which support or weaken theoretical positions that in this field have remained almost unchanged over the years. These new forms of knowledge provide insights that complement clinical psychology and philosophy to elucidate what the emotional phenomenon consists of, how it occurs, and what role it plays in human development [62].

## Conclusions

Advances in neurobiology, which have even become a true subspecialty, have contributed to the study and greater knowledge of human emotional experience, in the same manner in which neurological imaging has allowed the exploration of such phenomena and has been able to document the neural areas involved in them.

The interest in recent decades in the connection between emotions and cognitive processes is striking; it cannot be denied that the advance has been great, but there is still a long way to go.

Although the influence of emotions on cognition has been documented, particularly in the processes of selective attention, working

memory, and cognitive control, it can be said that even with the means of neurobiology and imaging that are now available, a clear difference between the emotional brain and the cognitive brain has not yet been established, perhaps because it does not exist, continuing a diffuse conception of emotional and cognitive articulation that cannot but depend on the context in which the human being lives.

Other fields of research are pending, such as the influence of long-term emotions on cognitive processes, perhaps mediated by neurochemical changes, other laboratory tests that more reliably measure the cerebral activity captured by functional neuroimaging, etc. These investigations will serve, among other things, to advance the etiopathogenesis and therapy of some psychiatric diseases in which both emotion and cognition are substantially compromised.

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# Part IV

# Explaining Human Pathological Behaviors. From Brain Disorders to Psychopathology

# Mild Cognitive Impairment: Diagnosis and Treatment

26

Rose Emily Nina-Estrella

## Introduction

The diagnostic of mild cognitive impairment (MCI) is relatively new. If we go back in history, Alois Alzheimer observed a patient at the Frankfurt Asylum named Mrs. Auguste D. This 51-year-old woman suffered from a loss of short-term memory, among other behavioral symptoms that puzzled Dr. Alzheimer [1]. After 5 years, in April 1906, the patient died, and Dr. Alzheimer sent her brain and her medical records to Munich, where he was working in the lab of Dr. Emil Kraepelin. By staining sections of her brain in the laboratory, he was able to identify amyloid plaques and neurofibrillary tangles [1]. The important seminar given by Dr. Alzheimer on November 3, 1906, was the first time that the pathology and the clinical symptoms of the disorder were presented together. The nosological entity was termed presenile dementia. Alzheimer published his findings in 1907 [2]. Curiously this patient was 51-year-old. Alzheimer never imagined that this new concept MCI would be associated with the dementia he described.

There are many definitions proposed to describe the intermediate stage between healthy aging with slight cognitive changes and dementia [3–6]. Some terms have been used to characterize the cognitive decline associated with aging, including benign senescent forgetfulness, age-associated memory impairment, and age-associated cognitive decline [7–9]. Other terms also have been described, but are not synonyms, including isolated memory impairment, incipient dementia, and dementia prodrome [10].

The history of the term MCI started in the late 1980s by Reisberg and colleagues to characterize subjects who were at this intermediate stage; the identification of these subjects was based on the Global Deterioration Scale, when criteria for Stage 3 were fulfilled [8]. Petersen et al. in 1999 further developed the concept by proposing criteria based on an observational study of aging [5]. These first clinical criteria for MCI were proposed by this group of investigators from the Mayo Clinic in the late 1990s [5].

An international consensus conference of MCI was held in 2003; the discussion was about the first Key Symposium on MCI led to the formulation of revised core criteria for this condition [11]. The expanded Mayo Clinic criteria for MCI were not totally focused on memory impairment alone but were broadened to include impairment in other areas of cognitive functioning [11].

Recently, the National Institute on Aging and the Alzheimer's Association (NIA-AA) charged a work group with the task of re-discussing MCI criteria along with the AD spectrum [12]. The NIA-AA proposed criteria for the specific

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definition of MCI due to AD, but the core clinical criteria overlap with those proposed by the 2003 MCI Key Symposium.

In 2007, APA formed the *DSM-5* Task Force to begin revising the manual as well as 13 work groups focusing on various disorder areas. *DSM-5* was published in 2013. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, released in 2013, replaces the term dementia with major neurocognitive disorder and mild neurocognitive disorder. The new terms focus on a decline, rather than a deficit, in function [13]. The condition of MCI is termed mild neurocognitive disorder (NCD) [14]. Mild NCD recognizes subtle features of cognitive impairment that are distinct from aging but do not represent dementia. Also it concerns the initial phases of cognitive disorders and precedes major NCD which is analogous to the previous diagnosis of dementia. The criteria for mild NCD closely resemble the expanded core MCI criteria including the following features:

A. Clinical concern raised by the patient or an informant or observations made by the clinician
B. Cognitive impairment in one or more cognitive domains preferably relative to appropriate normative data for that individual
C. Preservation of functional independence and no dementia [14]

These criteria are the same described MCI criteria. The DSM-5 approach involves the characterization of the syndrome, mild or major NCD, and then a subsequent task of determining its etiology, such as AD, frontotemporal degeneration, Lewy body disorders, or vascular cognitive impairment. This suggests that biomarkers are likely to be incorporated into the decision process, but most are not validated at present for use in routine clinical practice and remain in areas of major research interest [15].

Finally, the term mild cognitive impairment (MCI) represents an intermediate stage between normal aging and the development of pathologic aging and dementia, but not everyone with mild cognitive impairment will suffer dementia. MCI does not meet the criteria for dementia. In those cases associated to dementia, MCI will be in anteroom. One common classification of MCI distinguishes between amnestic and non-amnestic forms.

## Etiology

The etiology of MCI and its clinical manifestations are heterogeneous. As previously described, the classification of MCI is classified into one of two categories: amnestic MCI (a-MCI) if performance on neuropsychological tests of episodic memory was poor and and non-amnestic MCI (na-MCI) in the case of poor performance on neuropsychological tests covering cognitive domains other than memory, such as executive functions and language or visuospatial abilities. The impairment could be described to one cognitive domain (MCI-single domain) or to multiple domains (MCI-multiple domains). A patient could be classified in one of four possible clinical subtypes: (a) a-MCI-single domain, (b) a-MCI-multiple domain, (c) na-MCI-single domain, and (d) na-MCI-multiple domain. For the total clinical view, it needs to integrate information coming from the anamnesis, laboratory tests, and neuroimaging, when available, to guide the clinician in formulating hypotheses regarding the progression of the cognitive impairment syndromes. Specifically, the central idea was that, through the combination of clinical subtypes and putative etiologies, it could be possible to predict the type of dementia that MCI patients would develop [11].

The amnestic MCI, in which memory impairment predominates, is often a precursor of clinical Alzheimer disease (AD). Given that amnestic MCI often results from Alzheimer disease (AD) pathology, it is not surprising that most patients with amnestic MCI progress to clinical AD within 6 years [16].

The non-amnestic forms of MCI are characterized by a variety of cognitive impairments, the most common of which is probably impaired executive function. Non-amnestic forms of MCI are associated to cerebrovascular disease, Lewy body dementia, Parkinson disease, frontotempo-

ral dementias, atypical Alzheimer disease, or no specific underlying pathology. And also mood disorders, medical illness, and medications may affect cognition in such a way that a patient will meet criteria for MCI (usually non-amnestic MCI). Many such patients have normal neuropsychological test results when reevaluated a year later [16].

The pathophysiology of MCI is multifactorial. In cases of amnestic MCI, they result from pathologic changes of AD that have not yet become severe enough to cause clinical dementia [17]. Non-amnestic MCI may be associated with cerebrovascular disease, frontotemporal dementias (as a precursor), or no specific pathology [17].

## Epidemiology

The prevalence of mild cognitive impairment (MCI) ranges from 12% to 18% in persons older than 60 years, which appears in many international studies [18–21].

The MCI increases with age. Many studies indicate that the risk of Alzheimer disease (AD) is significantly higher in women than in men. Nothing is known about cultural and racial factors influencing the clinical manifestations of MCI [16].

The onset of MCI could vary. There are many examples from studies which describe MCI in different ages. For example, middle-aged subjects diagnosed with MCI are most likely to have a single etiological entity such as early-onset AD. In younger populations, conditions such as HIV/AIDS, traumatic brain injury, and psychiatric disorders can be relatively more common.

When MCI is detected in persons of 70 years of age and above – and even more so in those of 80 years and above – a degenerative or a mixed etiology is more likely to be inferred. Most of the epidemiological studies focused on older populations have reported a preponderance of AD-type clinical characterization, and neuropathological data have shown that mixed AD/vascular features are more common than pure AD characteristics [22, 23].

In younger people, the MCI has lower risk of incident of dementia which is easier to discard the diagnosis and treat in the clinical setting. In very old populations, MCI may be due to several causes including systemic disorders, brain tumors, subdural hematoma, multiple morbidities, medications, psychiatric disorders, and terminal decline [16].

This means that the MCI includes a list of possible causes, preferably age-related, that should be excluded when the research aim is to estimate the likelihood of progression of MCI to AD or other dementias. However, for clinical purposes, the inclusion of these forms in the MCI definition is essential and very relevant to the identification of those forms of MCI in the general population that can be successfully treated [16].

## Diagnosis

A patient with mild cognitive impairment usually presents a subjective description of memory loss. These are the most common symptom, understanding that amnestic MCI is the most common type considering the age.

However, some authorities affirm that the most common form of MCI affects multiple spheres of cognition. Less common presentations of MCI include language disturbance (e.g., difficulty in finding words), attention deficit (e.g., difficulty in following or focusing on conversations), and deterioration in visuospatial skills (e.g., disorientation in familiar surroundings in the absence of motor and sensory conditions that would account for the complaint). All these symptoms could appear or not in many cases [16].

In summary, the symptoms of mild cognitive impairment (MCI) are often vague and include the following: memory loss, language disturbance (e.g., difficulty in finding words), attention deficit (e.g., difficulty in following or focusing on conversations), and deterioration in visuospatial skills (e.g., disorientation in familiar surroundings in the absence of motor and sensory conditions that would account for the complaint) [16].

In a normal person, the memory functions that decrease with age include the following:

A. Working memory – Holding and manipulating information in the mind, as when reorganizing a short list of words into alphabetical order [24], and verbal and visuospatial working speed, memory, and learning, with visuospatial cognition more affected by aging than verbal cognition [25]
B. Episodic memory Mild cognitive impairment (MCI): – Personal events and experiences [24]
C. Processing speed [26]
D. Prospective memory – The ability to remember performing an action in the future (e.g., remembering to fulfill an appointment or take a medication) [24]
E. Ability to remember new text information, to make inferences about new text information, to access prior knowledge in long-term memory, and to integrate prior knowledge with new text information [27]
F. Recollection [28]

In any case, the defining element of MCI, as postulated by Petersen, is a slowly progressive cognitive impairment that is not attributable to motor or sensory deficits and to which other areas of involvement may eventually be added, before social or occupational impairment supervenes (because this occurrence marks the onset of dementia) [29].

It is very important to make the differences between patients with a memory function decreasing with age and the mild cognitive impairment. To demonstrate we are in the presence of a MCI, we need to do some screening with laboratory, neuropsychological tests, and neuroimaging.

Because a variety of conditions may result in a complaint of cognitive impairment, an individualized workup for such conditions and a consensus on a therapeutic approach should be done.

In the clinical setting, we will do the screening for MCI by order. The overall assesment of the patient should be included: a complete clinical history, a physical examination, observation of possible causes like comorbid conditions and the presence of sensorymotor deficits. The mental status examination is also important for documenting the degree of cognitive dysfunction.

There is no feature of the general physical examination that is characteristic of MCI. But the physical examination should be performed as part of the general evaluation in an effort to determine whether any condition is capable of causing MCI (e.g., thyroid disease, cobalamin deficiency, or venereal disease). It must be searched if there are present sensory and motor deficits that could explain or compound the symptoms.

There is no specific laboratory test for MCI. So it is important to discard conditions like thyroid disease, lipids, diabetes type 2, and others which the physician considered.

With the neuroimaging searches for biologic markers of MCI that may help distinguish among the many conditions that lead from MCI to a dementia. Never forget that the amnestic mild cognitive impairment (MCI) is an early symptomatic but predementia phase of AD. The diagnosis of AD also needs laboratory tests and biomarkers, imaging, and neuropsychological tests. Alzheimer disease (AD) is a clinical diagnosis. Used imaging studies are computed tomography [CT], magnetic resonance imaging [MRI], and, in selected cases, single-photon emission CT [SPECT] or positron emission tomography [PET] [30].

Neuroimaging with its various structural and functional modalities has provided evidence of neurobiological changes across the trajectory of normal aging – MCI – dementia, and AD in particular [31]. Structural MRI studies have identified the key areas of atrophy: the medial temporal lobe, reflecting entorhinal and hippocampal volume loss, and the posterior cingulate [32]. Furthermore, longitudinal studies have shown that acceleration of the annual rate of hippocampal atrophy as well as rates of cortical atrophy and ventricular expansion is good predictor of AD progression in MCI subjects [33, 34]. However, a recent review of previous studies on the progression toward AD in MCI subjects revealed accuracy figures between 56% and 82% [35].

Fluoro-deoxy-D-glucose positron emission tomography ((18) F-2-fluoro-2-deoxy-D-glucose, FDG-PET) studies have demonstrated substantial impairment in temporoparietal and posterior cingulate association cortices in MCI subjects who progress rapidly to dementia and AD in particular [36]. Using amyloid-labeling ligands, such as the most popular C-11 Pittsburgh compound B, PET enables molecular imaging of regional cerebral patterns of amyloid pathology and has shown increased Aβ burden in progressive MCI, particularly in the lateral frontal cortex, posterior cingulate cortex, and regions of the medial and lateral parietal lobe and the lateral temporal lobe [37, 38].

Both MRI and FDG-PET are alternative markers of neuronal degeneration in a model of temporal evolution of disease-specific pathology proposed by Jack et al. [39, 40]. According to this hypothesis, amyloid biomarkers show abnormalities earlier than markers for neuronal degeneration, possibly 10–20 years before first symptom occurrence.

The cerebral spinal fluid (CSF) is a new biomarker. But routine measurement of cerebral spinal fluid (CSF) tau and amyloid is not recommended except in research settings. Lumbar puncture for measurement of tau and amyloid may become part of the diagnostic workup when effective therapies that slow the rate of progression of AD are developed, particularly if the therapies are specific for AD and carry significant morbidity [30]. It is observed in the CSF levels of tau and phosphorylated tau that are often elevated in AD, whereas amyloid levels are usually low. The reason for this is not known, but perhaps amyloid levels are low because the amyloid is deposited in the brain rather than the CSF. By measuring both proteins, sensitivity and specificity of at least 80–90% can be achieved [30].

In comparative studies in which different biomarkers were combined in a prediction model of MCI, the FDG-PET together with episodic memory test was a strong predictor of the clinical transition to AD, whereas CSF biomarkers primarily reflected rate of longitudinal cognitive decline independent of disease severity [41, 42]. In logistic regression models combining clinical information with MRI imaging, CSF proteins, and FDG-PET, the latter added the most prognostic information [43].

Finally, the neuropsychological tests are very important in the MCI. Some of the neuropsychological test in the assessment of AD is the Mini-Mental State Examination (MMSE), which in MCI scores 26. It is often used to assess cognitive status. Health providers are increasingly using an alternate mental status test, the Montreal Cognitive Assessment (MoCA) to screen for cognitive impairment [44, 45]. It also can be used in mild cognitive impairment.

The Alzheimer's Association released guidelines, including an algorithm, to help clinicians in the primary care setting detecting cognitive impairment and determining whether referral or further testing is needed. The following three cognitive assessment tools are recommended [8]: General Practitioner Assessment of Cognition (GPCOG), Mini-Cog, and Memory Impairment Screen (MIS). Additionally, the Alzheimer's Association recommends the following three cognitive assessment tools for use with the patient's spouse, family, or friends [7, 8]: Informant General Practitioner Assessment of Cognition (Informant GPCOG), AD 8-Question Screen (AD8), and Short Informant Questionnaire on Cognitive Decline in the Elderly (short IQCODE).

A new neuropsychological test named MBI checklist (MBI-C), presented by Zahinoor Ismail (University of Calgary), was explained in an interview with *Medscape Medical News*. Dr. Ismail presented his research at the Alzheimer's Association International Conference (AAIC) 2016. This new concept of the mild behavioral impairment (MBI) may be the first sign of mild cognitive impairment (MCI) or dementia (researchers from Canada propose) [46].

MBI is defined as a syndrome of neuropsychiatric symptoms (NPS) that start later in life and are sustained for at least 6 months. Evidence shows that older adults with normal cognition and neuropsychiatric symptoms are more likely to become cognitively impaired and develop MCI than are people without neuropsychiatric

symptoms. The symptoms of MBI, which are included in a proposed MBI checklist (MBI-C), focus on five domains, namely, changes in apathy/drive/motivation, mood/affect/anxiety, impulse control/agitation/reward, social appropriateness, and thoughts/perception [46].

Questions on the MBI-C were designed specifically to address a younger predementia population. The emphasis is on the fact that the emergence of NPS represents a significant change from prior behavior and is present for at least 6 months [46].

The idea is that the scale may prove to be usable searching cases in which biomarker and neuroimaging studies try to detect predementia clinical states but also in epidemiological studies of community samples. Additionally, it may be usable in clinical sample observational studies. The purpose is to help assessing the impact of NPS in older adults. Validation studies of the MBI-C are underway [46].

## Differential Diagnosis

The mild cognitive impairment should have many differential diagnoses. These are the most common disorders: Alzheimer disease (AD), cerebrovascular disease, Parkinson disease, frontotemporal degenerations, thyroid disease, HIV infection, depression, endocrine and metabolic disorders, adverse central nervous system effects of drugs and toxicants, cerebral infection, traumatic brain injury, cognitive adverse effects of sleep disorders, cobalamin deficiency, and chronic psychological stress.

## Treatment

There is not pharmacological treatment recommended for mild cognitive impairment. Cholinesterase inhibitors have not been found to delay the onset of Alzheimer disease (AD) or dementia in individuals with MCI [47]. It has been reported that donepezil may delay the progression to AD in MCI patients with depression without affecting their symptoms of depression [48]. His finding led to suggest that cognitive interventions may have a positive effect [48]. However, a recent systematic review, including nine randomized clinical trials (RCTs) and a total of 5149 persons with MCI, reported essentially no effect of cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) on cognitive test scores or on the progression to dementia within 3 years [49].

The findings of one study of vitamin E and donepezil suggested a positive effect of donepezil up to 12 months and up to 36 months in *ApoE4* carriers, but overall the rate of progression to Alzheimer disease after 3 years was not lower among patients treated with donepezil than among those given placebo [50]. Also, a systematic review on the efficacy of vitamin E for the treatment of MCI, including three RCTs and a total of 1167 participants with MCI, reported no substantial evidence that vitamin E is of benefit in the treatment of MCI [51]. One of the studies included in the review actually found that, even in subjects for whom vitamin E was effective in lowering oxidative stress markers, there was no significant difference in the percentage change in Mini-Mental State Examination core between those with MCI and control subjects [52].

Considering the negative results of multiple RCTs using cholinesterase inhibitors and the lack of RCTs using memantine in MCI, there is no support from regulatory or clinical practice guidelines for the use of cholinesterase inhibitors or memantine in MCI. There is a common practice of prescribing these drugs to subjects with MCI in some parts of the world. There is a need of more studies to prove what is useful for the patient with MCI.

There are other evidences of non-pharmacologicals interventions such as cognitive training and physical exercise, activities that may be neuroprotective or compensatory. A recent review showed how several studies demonstrated the efficacy of cognitive training in MCI measured as improved performances in tests of global cognitive functioning, memory, and metamemory [48, 53]. Different recommendations are important in the prevention and recovery of MCI, for example, diet, physical exercise, vitamins,

minerals, aerobics exercises, cognitive training, social interactions, and others.

The diet is very important. Roberts et al. found that the risk of developing MCI is lower in individuals who consume a Mediterranean diet, which is high in vegetables and unsaturated fats [54].

New studies suggest that practicing mindfulness may reduce anxiety levels and slow cognitive decline in patients with mild cognitive impairment (MCI). The studies, presented at the recent Alzheimer's Association International Conference (AAIC 2017), are preliminary but encouraging. Kheng Siang Ted Ng (National University of Singapore) presented the study sustaining that it is a novel, low-cost, and self-directed mindfulness intervention that may improve cognitive functions and ameliorate biomarker alterations in elderly with MCI. He suggested that the lowering of CRP levels indicated that mindfulness could be slowing a neuroinflammatory component of dementia in that CRP modulates vascular pathology and could cause hypoperfusion of the brain, leading to increased white matter lesions and silent infarctions [55].

It has been also proposed that the use of acupuncture alone or with medication may improve cognitive and memory function in patients with amnestic mild cognitive impairment (MCI). A meta-analysis of five randomized controlled trials (RCTs) and more than 500 patients with MCI and memory deficits showed that those who received acupuncture for 2–3 months had a significantly higher clinical efficacy rate than those who received the oral calcium channel blocker nimodipine. The acupuncture group also had greater improvements on a picture recognition test and on the Mini-Mental State Examination (MMSE). In addition, the participants who had acupuncture plus nimodipine showed significantly better scores on the MMSE compared with those taking nimodipine by itself. However, Min Deng (Wuhan University) proposed that a cautious position must be present considering the low methodological quality of included trials in preliminary reports. More detailed and refined studies are needed [56].

**Conclusion**

The mild cognitive impairment (MCI) is by definition the intermediate stage between normal functioning and possible dementia. The MCI does not meet the criteria of dementia. There are two subtypes of MCI, amnestic and non-amnestic. The amnestic progresses to Alzheimer disease (AD). The non-amnestic has different causes to be considered in the diagnosis. Even there are no specific biomarkers and treatment for MCI, it is mandatory to continue studying more than ever the discoveries of possible new methods for diagnosis and treatment. But in the meanwhile, prevention with a Mediterranean diet, physical and cognitive training, and other healthy resources will help to improve the mild cognitive impairment.

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# 27

# The Value of Neurocognitive Assessment for Diagnosis and Treatment in Schizophrenic Spectrum Disorders

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## Utility of the Concept "Spectrum" in Clinical Care and Research

The schizophrenic spectrum encompasses a set of disorders including, in schematic terms, delusions, hallucinations, disorganized speech and thought, abnormal psychomotor behavior, cognitive impairment, and, sometimes, depression- or manic-like symptoms. Each of them can be present with different duration and intensity. The list includes, as states American Psychiatric Association (2013), a wide range of clinical pictures: schizotypal personality disorder, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, and schizophrenia [1]. It has been highlighted that categorical classifications are descriptive and atheoretical [2].

Guimón (2002) made a critical review regarding the limits of the concept of spectrum in schizophrenia [3]. He warned that the use of numerous subclasses could be a stumbling block for the clinical care and that it is pragmatically expected that more limited classifications will be applied in that area. However, he stressed that the notion of spectrum seems to have been fruitful for research, contributing to a gradual use of dimensional models through the systematic application of factorial analysis. It must be remarked that, since evidences have been accumulated regarding the schizophrenia as a brain illness, categorical diagnosis must precede dimensional approaches.

In spite of the above, this modality is not exempt of limitations. First, Guimón pointed out that most of the findings come from non-pathological populations – or without an informed diagnosis – and are extrapolated to the psychiatric population. Secondly, each trait may also belong to different spectra of the schizophrenic, which makes it difficult to discriminate properly. Thirdly – and this also includes our perspective – it may lead to an overestimation of the statistical criteria for differential diagnosis and an undervaluation of other facets of the disease, linked with greater specificity to the concrete experience of the patient. In summary, although the spectrum concept has elicited important advances in the investigation of schizophrenia, it is worth considering some particular precautions in the design of clinical procedures and defines the number of pragmatically applicable categories in that field.

## Consideration of the Deficit in Different Explanatory Models of Schizophrenia

The relevance attributed to neurocognitive alterations has not been homogenous at all times nor under the predominance of different explanatory models of schizophrenia.

At the end of the nineteenth century, a clinical method developed in Germany opened the game to the modern conceptualization of the disease. Kahlbaum, its creator, described catatonia following these guidelines, then Hecker detailed hebephrenia, and Kraepelin pointed out dementia praecox [4]. The detailed study made by Kraepelin [5] defined early dementia as a set of states that alter the volition and the emotional sphere of the individual, recognizing the loss of unity between intellectual, affective, and volitional capacities. At the heart of his theory lies – as the name warns – the evolution of deficits toward states of mental weakness or dementia. Bleuler [6] considered that it was not a pathology necessarily characterized by precocity of dementia. He proposed the establishment of the term representing a divided mind, placing as fundamental symptoms the deficit in associative and affective areas, the ambivalence, and the autism [7]. Thus, he postulated criteria for performing a state diagnosis, without having to wait – as Kraepelin proposed – to further evolution [8]. It is noteworthy that both the German and Swiss psychiatrists recognized the existence of attentional alterations, but they understood them as consequences of the primary biological damage.

It has been remarked that Kurt Schneider [9], following the phenomenological line of Jaspers [10], reversed the Bleulerian hierarchy of fundamental and accessory symptoms. Although it was later refuted that delirious production and hallucinatory phenomena conformed the pathognomonic

set of the disease, its division between first order (delirious perceptions, sound thinking, delusions of influence) and second order (perplexity, transformations of affective tone, emotional flattening) seems to have had a practical effect until the late 1970s. However, research tasks between the 1970s and 1990s were separately driven toward positive and negative symptoms, attempting to establish subtypes of schizophrenia. Crow made interesting contributions in this way, proposing type I and II syndromes, which have a close relationship with positive and negative symptoms, respectively [11]. After that, research was focused on comparing neurocognitive performance among people with schizophrenia and healthy controls. In the 1980s, evidence was needed to specify which functions were commonly affected, as well as to generalize the results to other spectrum disorders. By the 1990s, the accumulation of findings made it possible to accurately recognize the alterations of each cognitive function, and scientists began analyzing its links with disease and treatment variables [12].

Nowadays, and before the advance of the neurosciences, the anatomofunctional bases that underpin the majority of the alterations have been established [13–15]. Even in a context led by neuroimaging techniques, the classic neuropsychological assessments maintain their importance. Numerous authors argue that functional markers related to cognitive performance would be the most relevant to establish an evolutionary prognosis of the disease, since they are shared by different subgroups of the spectrum [16]. In line with this postulate, the present work aims to synthesize the characteristic set of cognitive alterations of the schizophrenic spectrum, to list the instruments usually used in its investigation and to formulate some observations regarding the clinical advantages of evaluating and intervening at this level.

## Cognitive Alterations in SSD

In this section we present a brief review of the common cognitive alterations in the SSD. Although our selection is not exhaustive, certain criteria have motivated its detailed analysis: (1) perceptual-integrative abnormalities seem to be linked to less effective interpretation of contextual information [17]. (2) Cognitive flexibility and vigilance were included because of the special depth of their impairment [9, 18], and (3) working memory is especially relevant for its mediating role and for the cascade effect that, and as detailed below, could provoke over other capabilities.

In each of the sections, the anatomical and physiological correlates that underlie the alterations are indicated. In essence, most of the deficits seem to be associated with hypoactivity of the prefrontal cortex and its projection to the thalamus and cerebellum, as well as to a reduced activity of the cingulate gyrus [19], alterations related to the nucleus accumbens septi (NAS) [20, 21], and morphological anomalies in the visual cortex [22]. The theories regarding the genesis of these structural dysfunctions are not homogeneous. On one hand, it has been postulated that they derive from a genotypic variation that remains phenotypically latent until adolescence and involves a failure in neuronal pruning [23]. On the other hand, it has been proposed that they result from a neurochemical disorder that leads to the later development of neurotoxicity [24]. In line with this latter perspective, the most studied neurotransmitters have been dopamine, serotonin, and glutamate, and it has been proposed a glutamate hypoactivity leading to dopaminergic hyperactivity and GABA hypoactivity [20, 25, 26].

On the other hand, it is important to point out that the numerous cognitive deficits linked to schizophrenia only correspond to one facet of the disease and do not exhaust the diagnosis, since they are also characteristic of other neurological and psychiatric disorders [27]. Finally, few constructs seem to be related to functional limitations like reduced social skills, low work or school performance, and low interpersonal integration. These include learning ability, working memory, attention, motor functioning, and verbal fluency. Some of the difficulties mentioned also predict problems to benefit from the therapeutic proposals [28]. Another construct that seeks to

encompass social performance is social cognition. Poor social functioning is one of the most disabling dimensions of schizophrenia, and under this concept, they are currently being developed to generate improvements in this aspect [29].

## Perceptual-Integrative Anomalies

During the early conceptualization of schizophrenia, perceptual alterations were not considered as a primary symptom but were thought as a consequence of a delusional interpretation of normal perception [30, 31]. It was from the pioneering work of Conrad [26, 32] that the phenomenon of abnormal perception began to be analyzed in relation to other symptoms of schizophrenia-adopting Gestalt theory as a [33]. This theory was not restricted here to a mere explanation of perceptual grouping [26, 31, 34–38].

In 1980 Place and Gilmore used an experimental perceptual grouping test. It consisted in tachitoscopically presented stimulus, with and without noise elements. They concluded that the organization or "perceptual grouping" was altered in schizophrenics. They sustained that failed the organization of visual information in processing at an early stage [34]. These findings were matter of discussion. Other group confirmed them [35]. However, a third researcher informed that these disorders are relative and non-absolute [38]. In any case, a perceptual problem was postulated.

Starting from the phenomenological approach of Conrad suggesting a gestaltic-related role at the basis of delusion, we assayed an experimental approach. We evaluated performance using the Bender Gestalt Test in acute and chronic schizophrenics comparing with age-paired controls [33]. As expected, we obtained clear findings with it. Three groups were incorporated: healthy controls, acute drug-naive schizophrenic patients in their first psychotic episode, and chronic schizophrenics. Acute schizophrenic patients significantly differed from controls in perseveration. Chronic schizophrenics differed in perseveration and subtle motricity disorders. Chronic patients presented higher values of shape distortion, rotation, and subtle motricity disorders. When all the errors were subtracted from a global score of 100 points, there was a significant decrease in the score obtained in both acute and chronic schizophrenic patients. Furthermore, execution time was significantly delayed in both schizophrenic groups. It may be considered as a compensatory factor, since the execution time was doubled. We may conclude that it was found significant score differences and a significant increase in time execution of the task. This last parameter may be considered as a compensatory activity destined to improve a task executed with relevant difficulties. We postulated that these results obtained in schizophrenic patients may be due to a failure to ability to apprehend objective structure of perception.

Moreover, the application of visual tracking methodologies has been useful in the study of perceptual functioning in schizophrenia [39, 40]. In 1973, Holzman, Proctor, and Hughes observed abnormalities in the patterns of continuous visual follow-up tasks. Recent studies have broadened the perspective, showing that schizophrenic patients adopt suboptimal visual exploration strategies [41] and analyze social context more slowly to attribute intention [17]. Additionally, they collect the wrong information while exploring a face so they can't understand the emotion that it expresses [42]. These conditions are apparently linked to a more general alteration of sensory integration [43]. It is also thought that such dysfunctions are linked to attentional deficits, although it would not be a simple causal relationship [26, 31]. It is reasonable to assume that visual follow-up tasks demand a greater burden of voluntary control [44]. It should be noted that not only attention would be involved but also poor performances in visual tracking and working memory [45].

## Attention

Deficits have been found in sustained attention on schizophrenic patients ("surveillance"), which is related to their daily difficulty in maintaining attention in activities [46, 47]. Similar results have been reported in direct relatives [48, 49] and

in patients with schizotypal personality disorder [50]. On the other hand, it was found a low performance in selective attention tasks, related to alterations and hypoactivity of the anterior cingulate gyrus [51]. There is a strong consensus that psychometric monitoring and selectivity tests, such as the continuous performance task (CPT) and the Stroop Test (ST), are reliable and inexpensive alternatives for assessing the attentional deficit characteristic of schizophrenia [52].

On the other hand, reaction time seems to be a central variable, taking into consideration that schizophrenic spectrum patients usually take longer to respond to the stimulus. It can be presumed that this condition is linked both to slow response selection and to some deficiencies in manual motor speed [53]. However, Luck and Gold [54] have pointed out the need to accurately characterize the attentional aspect to be assessed with each task, since if attention is considered as a single construct and its close linkages to the operational memory are not taken into account, the results could be interpreted erroneously or exaggeratedly.

### Memory

Being proved that it does not derive of the lack of attentional filtering of stimuli [55], the working memory deficit seems to determinate in some way most memory impairments (short and long term) in schizophrenia [9, 56]. These limitations were evidenced by visual tracking techniques in reading tests [57]. Failures appear to be associated with a decreased blood flow to the right dorsolateral prefrontal cortex [52]. It is considered that integration between present experience and evocation of the past would fail in Schizophrenic-related pathologies, strongly linked to the mediating role of working memory. Other authors [58, 59] even consider the working memory impairment as the nucleus or common denominator of the cognitive deficits in schizophrenia.

In agreement with this postulate, differential diagnosis studies have compared the executive functioning between normal controls, patients with schizophrenia and patients with other non-spectrum psychiatric disorders, and concluded that the deficit in working memory could lead to a kind of "cascade effect," affecting other executive functions [60, 61]. Strikingly, significant links have also been found between this deficit and the social limitations [62]. In this perspective, failures to process situational and interactional information could be linked to interpersonal isolation.

### Cognitive Flexibility

The term cognitive flexibility refers to the ability of modifying a behavioral plan insight of contextual variations, intending to adapt the action plans in pursuit of the proposed objectives [63]. Flores Lázaro and Ostrosky-Solís [64] consider important in this area the ability to "monitor" the results of behavior. Classically, it is evaluated with the Wisconsin Card Sort Test (WCST) and is understood to be functionally related to the dorsolateral prefrontal cortex [45]. It is assumed that the poor planning ability, the excessive behavioral perseveration, and the social judgment difficulties characteristic of schizophrenic patients would be linked to weaknesses in cognitive flexibility [9].

As a consequence, they have been shown to have an increased tendency to make specific decisions, as well as a shorter delay to execute them in order to a greater severity of negative symptoms [18]. Recently, evidence has been provided about the relationship between the dysfunction and a poor ability to integrate contextual information in people with schizophrenic spectrum disorders [65, 66]. In appearance, these difficulties would not be sensitive to the person's educational level, and they could be surprisingly related to hand laterality, since higher levels of perseverance were found in non-dexterous participants [67].

## Links Between Cognitive Impairment and Comorbid Clinical Manifestations

From the perspective that we propose, the diagnostic and prognostic value of the neuropsychological evaluation in the SSD would be in

its possibility to broaden the understanding on the phenomenological and clinical manifestations of the disease. But these are far from being homogenous and include states and experiences originally attributed to other psychiatric disorders.

Buckley et al. [68] conducted an exhaustive review of spectrum comorbidities and opened the debate: Under which conditions could such edges be considered as original products of schizophrenia? Or should they be treated as mixed manifestations? The authors mentioned the perspective of Bermazohn et al. [69], who have proposed that those "intermediate terrain" emerging are so frequent that they should be considered as belonging to the spectrum. Despite of the grade of agreement with this statement, it is clear that the cognitive and socio-affective peculiarities of schizophrenia often cause problems that warrant specific evaluations, such as substance abuse and mood swings between anxiety and depression. The first point seems to be related to the lack of social skills, the limited executive control, the absence of supportive links, and problems related to low self-esteem [70, 71].

It is worth noticing that depression seems to be related to increased chronicity, bigger risk of relapses, and decreased adherence to pharmacological treatment. Since the intensity of depressive manifestations usually accompanies the positive symptomatology, it is considered that the intensification of the former may be a predictor of relapses: sadness, feelings of guilt, hypervigilance, lack of concentration, insomnia, and social isolation are conditions that are associated with prodromal instances [72] and can be easily confused with adverse effects of neuroleptic medication [73]. At the opposite pole, anxiety or panic symptoms seem to be more frequent in the paranoid pictures than in the other subtypes of the disease, and their appearance at early stages would be linked to increased positive production and increased suicide risk [68]. The shortcomings in the control of impulsivity, the reduced attentional performance, and the tendency to perseveration could be key cognitive aspects in relation to these conditions.

## Neuropsychological Assessment Instruments Applied to SSD

The field of cognitive evaluation in schizophrenia has been a subject of debate [28]. There is a wide range of applicable tests and batteries to neuropsychological evaluation in SSD but also a marked heterogeneity and lack of consensus in standards and protocols [74].

The most prominent and specific instrument is MATRICS. This battery, driven by the National Institute of Mental Health of the United States, was based on the search for an interdisciplinary consensus for neurocognitive evaluation in schizophrenia [75, 76]. The efforts resulted in a set of ten subtests for the exploration of seven domains: processing speed, monitoring, verbal and nonverbal working memory, verbal learning, nonverbal learning, and social cognition. Another strategic proposal is BACS – Brief Assessment of Cognition in Schizophrenia – covering six domains: verbal memory, working memory, motion speed, verbal fluency, attention-processing speed, and executive functions. The salient feature of this protocol is that its application is brief and can be completed in about 35 min [74].

General cognitive screening tests have also been used. For example, De Achaval et al. [29] used the Addenbrooke's Cognitive Examination (ACE-MMSe) [77] and the Frontal Assessment Battery (FAB) [78].

On the other hand, the papers present coincidences in the selection of the techniques used to evaluate cognitive functions in people with SSD, which could be thought as implicit consensus among experts. To evaluate attention, tests derived from the continuous performance task (CPT) and Stroop Test (ST) are the most used [52, 79]. Digit-letter retention tests and N-Back tests for working memory, words learning tasks for verbal memory, and verbal fluency tests to measure processing speed are preferred. The Wisconsin Card Sort Test (WCST) and the Tower of London (TL) are the most used to evaluate executive functions. Finally, facial expression recognition and emotional intelligence tasks are preferred to measure social cognition [9, 80, 81].

A future line of work of our team will involve the verification of these inferences through bibliometric studies.

## Considerations Regarding Cognitive Rehabilitation in SSD

While it is recognized that cognitive rehabilitation programs in schizophrenia produce moderate positive effects on social cognition and specific symptomatology, few studies have transcended the mere evaluation of the basic stimulated functions, whereas little or nothing can be inferred about the duration of its effects over time [82]. A meta-analysis of the results corresponding to 26 programs [83] concluded that the results are positive regarding cognitive performance, social performance, and symptomatology. However, the significance was medium-sized in relation to the first variable, lower in the case of the second and notoriously low in relation to the symptomatology. Finally, the authors emphasized the low efficiency of programs that did not include psychiatric treatment.

It should be noted that linear conceptions of information processing still have a remarkable impact on cognitive approaches, although it is accepted that complex functions cannot be understood outside a connectionist paradigm. According to Vargas [84], this idea seems to have conditioned the design of "module-centered" stimulation programs, suitable for basic functions (highly related to specific brain areas) but insufficient or detrimental to higher ones (based on diffuse cortical neural networks). This author based his proposal in Fuster's (2006) conceptualizations, discussing a rehabilitation model oriented to "Cognits." A Cognit can be defined as an "item of knowledge about the world, the self or the relationship between both" [85, p., 129]. The model assumes that reality representations are composed by the activation of networks which nodes are the sensorial attributes of the object. So, dysfunctional cognitions (Cognit) may lead to symptomatic misrepresentations of the self and the world.

The consideration of the properties of a Cognit leads to the planning of stimulation strategies that transcend behavioral reinforcement. In the first place, each Cognit is autonomous and has the mechanisms to function by it, regardless of the sensorial or mental stimuli that have been used to activate it (encapsulation). Secondly, each new Cognit incorporates properties of the inferior (inheritance). Thus, the stimulation of elementary functions has a certain impact on those with a higher level of abstraction. Thirdly, the polymorphism represents the possibility of an element to be part of different higher-level ones, so the stimulation of each one potentially affects all those that have it by component. Considering that schizophrenia comprises neurodevelopmental failures, possibly attributable to an excessive neural pruning, it may develop in a reduced synaptic capacity [86, 87], Vargas hypothesized that the formation of certain dysfunctional or maladaptive Cognits could expansively affect cognitive performance throughout the development of the individual. He also indicated that the goal of cognitive rehabilitation in schizophrenia would be to modulate the Cognits to achieve a better intrapersonal and contextual adjustment.

Whether or not aimed to cognitive differentiation [88, 89], to attentional capabilities [90, 91], to affect recognition [92], to reasoning skills [93], or to other spheres affected, it is necessary to consider that cognitive stimulation programs in schizophrenia and related pathologies cannot be understood as rehabilitation per se, because the challenge is not recovering prior to damage performance levels but rather to improve performance in the context of a dysfunctional early phenotypic development [84].

## Discussion and Conclusions

Nosography has had actual importance for diagnosis and treatment choices in schizophrenic spectrum disorders. Although a dimensional component is claimed for the evaluation of grades and scores in the experimental tests used, it cannot replace a categorical diagnosis. The evidences of the last

50 years have provided findings in this regard. Schizophrenia is a disease in the strict sense, and not just a mere state of mind or a personality trait. In this sense, there is a medical, categorical diagnosis, although then dimensional criteria may be applied to quantify findings, mainly concerning cognition in this pathological group.

Nor does the creation of consensus for neuropsychological evaluation seem simple. Although the cognitive alterations of the schizophrenic spectrum have been abundantly addressed in the last decades, each research team has opted for those evaluation instruments that it considered more suitable for its purposes. Thus, although an explicit consensus can be inferred regarding the use of classic tests (CPT, ST, WCDT), few studies have applied standardized batteries for the schizophrenic spectrum, such as MATRICS or BACS. This could hinder the transition from basic to applied knowledge, since the professionals dedicated to therapeutic care may not have the same time as the researchers to acquire and learn from a wide variety of tests. Also, evaluation tools would not be useful without regional normative values appropriate to its context. Advancing in a greater implementation and baremation on already accorded protocols could improve the cognitive clinic treatments.

Finally, and despite the fact that neurocognitive rehabilitation treatments in this spectrum pathologies appear to produce moderate results, we wish to emphasize the importance of promoting programs whose bases transcend behavioral reinforcement, which is inadequate or insufficient for the stimulation of higher functions. In clinical decisions, specific aspects of the patient's emotional and social life should be considered, since many of his daily difficulties are comprehensibly linked to basic conditions.

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# 28

# Dementia Resources in Argentina: Policy, Services, and Statistics Overview—Up to Date

Pablo M. Bagnati, Fabian Roman, Marcela Bonafina, Andrew Blake, and Ricardo F. Allegri

## Demography

Advances in science and in particular in medicine, over the recent decades, have led to an increase in the elderly population (over 60 years) causing an exponential growth in age-dependent pathologies such as dementia [1]. In the following years, it is a challenge not only for developed countries. A much greater growth is expected in developing countries, such as Argentina, where there is an inferior ability to cope [2].

Argentina, the second largest country in South America (3.8 million square kilometers), is populated by a mixture of different ethnic cultures; however, unlike other Latin-American countries, most Argentinean peoples (68%) are central and west European descent (Italian and Spanish). The second largest ethnic group is the mestizos (20%), a fusion of European immigrants and native aborigines, followed by a few natives' aborigines (less than 1%) who live in special reserves. The north and west are populated by a greater proportion of mestizos and natives living in rural areas, the center and the southeast by European descendant. The urban population was 88% of the total, and Buenos Aires City and the surroundings areas lodge 1/3 of population [3].

Nowadays, it is estimated that the total population of Argentina is 43,590,368 with 21,364,470 men and 22,225,898 women [4]. Within the period 2015–2020, life expectancy at birth (in years) is 73 for males and 81 for females. In 2014, the adult literacy rate was estimated to be 98% [5]. In 2016, the population over 65 years old reached more than 11% of the total population. Projections from the United Nations Population Fund (UNFPA) indicate that, by 2050, 25% of the Argentine population will be 60 years old or more [6]. Argentina's elderly population increased from 35% in 2001 to 40% in 2010. Despite the fact that in the last decade the overall number of inhabitants in Argentina grew by more than four million people, there are 25,378 children less than in the year 2001 [3]. In contrast, the number of inhabitants older than 100 years

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has reached approximately 7000, while in 2001 there were 1855.

Health care in Argentina is shared between the public and private sectors. The public sector provides care to low- and middle-income populations, mainly in general hospitals, whereas the private sector tends to provide care to middle- and high-income population, including home assistance. Unfortunately this distribution is not equitable. More than 17 million people (45% of the population) have access which is limited to the Public Health System: this segment of health care receives only 23% of the resources [7]. Argentina has traditionally been involved in caring for the elderly; in 1971, the National Government created the Institute for the Elderly (ISSPJP from the Spanish "Instituto de Servicios Sociales para Jubilados y Pensionados") to take care of the social and medical needs of retired people with the program PAMI (from the Spanish "Programa de Atencion Medica Integral," Program of Global Medical Assistance). The Institute provides care for approximately 70% of individuals over 60 years old and 90% of those over 75 years old. Nowadays ISSPJP has approximately 4,000,000 of affiliated (10% of global population) [8].

## Prevalence of Dementia

Dementia is a clinical syndrome that begins with a progressive memory loss and advances to a complete cognitive impairment with behavioral and functional impairment [9]. Dementia is significantly disabling for those who have it, and it may have devastating effects for the family and caregivers [2]. Around the world, life expectancy has increased; so does the risk to develop a dementia, and it is becoming to be a very serious public health problem [9]. Population aging is a process that is especially accelerated in some parts of the world. Latin America has to confront population "graying" in the context of an emerging economy [10]. This has had a major impact on public health and the economy leading to reviews of health, social, and economic policies in developed and developing countries [11]. Nearly 47 million people live with dementia worldwide, and this figure is projected to increase to more than 131 million by 2050. In addition, a much greater growth is expected in developing countries, such as Argentina, where there is an inferior ability to cope. Each year, there are 7.7 million new cases, one every 4 s. The majority of people with dementia remain undiagnosed, but even when this condition is diagnosed, the necessary care and treatments for the patient and his family are usually incomplete or insufficient with respect to their needs [12]. In most of the Latin American countries contacted general practitioners consider memory problems within the normal aging process, and they do not perform a very meticulous study. These patients arrive late to a specialized center [9]. After 60 years, some of the most common conditions are cognitive impairment in their different clinical stages (mild cognitive impairment and dementia). According to the WHO, these disorders are the leading cause of disability in this age group [13]. The study of dementia is lower than for chronic noncommunicable diseases such as cardiovascular disease or cancer [11]. Demographic transition has been faster in low- and middle-income counties (LMIC) than in high-income countries (HIC). The prevalence is higher in LMIC, attaining 7.1% in South America [11, 14, 15]. It is also higher in the lower-income population of Latin America below 70 years (more than four times), probably the result of low education, in access to primary care services, and lack of control of vascular risk factors [14, 15].

The epidemiological data in Argentina is partial, incomplete, and scarce [11]. Melcon et al. reported the first data in 1996 collecting the information from death certificates in the city of Junín, within the province of Buenos Aires, where the rates for dementia were 110.3/100,000, with significantly increases beyond the age of 75. The limiting factors of the study were that the results were based on reports by doctors made at the time of death of patients, and it was unusual to describe dementia as a cause of death during that period [16]. Pages Larraya et al. [17] found cognitive impairment in 23% of subjects over 60 years, but the study was conducted with

institutionalized subjects in nursing homes. Arizaga et al. [18] carried out a survey involving demographic data, risk factors, and a geriatric depression scale and Mini-Mental State Exam (MMSE) scores in a population over 60 in Cañuelas, 50 km from Buenos Aires, finding a cognitive impairment prevalence of 22.3% (individuals with 22 points or less on the MMSE).

In 2010 the National Department of Mental Health developed a Registry of Cognitive Pathologies in Argentina (ReDeCAr from the Spanish "Registro de Deterioro Cognitivo en Argentina") as a prospective case register in hospital and health centers throughout the country [19, 20]. In 2011 they published the pilot study of the registry (292 patients analyzed), 73% were women and 75% were living with their family, 20% alone, and 5% institutionalized. According to the diagnosis, 30% were AD, 27% mixed dementia, 16% vascular dementia, 6,2% Lewy bodies dementia, 2,7% frontotemporal dementia, and 17,4% mild cognitive impairment [21]. In 2011, with the change of the direction of the Department of Mental Health, the process was stopped, and finally the registry wasn't launched.

Bartoloni et al. [11] conducted an epidemiological study in a populated economically and socially vulnerable suburban area in the south of Buenos Aires city called "Matanza-Riachuelo Basin." This is a slum of 8,212,953 inhabitants with a lack of reliable sanitation services, supply of clean water, reliable electricity, law enforcement teams, and a low socioeconomic level, poverty, and social vulnerability. The authors assessed 2437 elderly in a door-to-door survey. The prevalence of cognitive impairment was 26.4% (18% for mild cognitive impairment (MCI) and 8.3% for dementia) with higher prevalence of dementia in younger peoples (2.9% in those aged 60–64 years and 5.5% in those 65–69 years) than rates reported in developed countries. One possible explanation is the limited access to primary care services, the low educational level (mean 5.6 years), and the low control of vascular risk factors [11]. Similar results reported by Nitrini et al. [15] in Latin-American studies were higher than figures observed in developed countries [15]. A pooled data of prevalence of dementia surveys from six Latin-American countries showed that the dementia rate among illiterates was 15.6%, whereas in literate individuals, it was 7.1% [15].

The presence of modifiable risk factors (through primary prevention) can change the presentation and progression of different cognitive pictures. It is noteworthy that, despite the particular social situation of the population studied, a starting point for the promotion of plans could be to prevent the advance and disability in older adults of cognitive impairment and dementias.

## Economic Burden

Dementia has a huge economic impact worldwide with a total estimated cost of USD 818 billion, and it is expected to reach a trillion dollar by 2018. In Argentina, the cost per patient has been calculated to be between USD 3400 and USD 14,000 per year. As the disease progresses, the patient becomes more dependent, therefore generating a great burden for the caregivers [22, 23]. Direct costs (such as medical treatment or social services) increase when the disorder progresses, the patient is institutionalized, or a formal caregiver is required. Drug therapies represent an increase in direct cost but can reduce some other direct or indirect costs involved. The paper of Rojas et al. [23] showed that the annual direct costs were USD 4625 for AD, USD 4924 for frontotemporal dementia (FTD), and USD 5112 for vascular dementia (VaD). In the post hoc analysis, VaD showed higher hospitalization costs than AD. VaD exhibited lower medication costs than FTD. AD exhibited higher antidementia drug costs; FTD had higher psychotropic costs. In the multivariate analysis, depression, activities of daily living, and caregiver burden were correlated with direct costs. Worldwide, more than two-thirds of people with dementia live at home, and most are cared by their relatives.

Argentina has similar profile [24]: most senior citizens live at home with their families, while approximately 15% are institutionalized in nursing homes [25]. Fortunately, the majority of older

adults have access to health insurance coverage provided by the Institute of Social Security (PAMI). This governmental agency is currently implementing a nationwide program to detect, diagnose, and treat cognitive impairment and dementia among over 4 million affiliates [26]. Discrete improvement has been observed in the detection of cognitive impairment and dementias by primary care physicians. A decade ago, the early detection of neurodegenerative disease and its differential diagnoses was not included in the formal training in neuropsychiatry or other clinical specialty programs [27].

Rojas et al. [28] analyzed the pattern of drug prescription related to the treatment of patients with dementia. Patients' mean income was 502.81 "Pesos Argentinos" which is equivalent to USD 152 per month (2007). 41.5% of the patients had dementia, 15.6% psychiatric diseases, and 15% mild cognitive impairment, and 27.7% were normal. Patients received an average of 2.84 drugs/day, 20% of the patients took at least one drug for cognitive impairment (9% memantine, 6% donepezil, and 4% nootropics, cerebral vasodilators, or antioxidants), and 39% received psychotropic medication (28% benzodiazepines and 9% atypical antipsychotics). Twelve percent of the patients with mild cognitive impairment were treated with anti-dementia drugs and 5% of normal subjects received anti-dementia drugs. Four percent of patients were exclusively treated with free samples. In this paper, authors showed irrational degree of using anti-dementia drugs and psychotropic agents in clinical practice in Argentina [28].

## Clinical Management

Regarding assessment, diagnosis, and treatment of dementia, Argentina has an unequal distribution of resources and specialists (neurologists, psychiatrist, and geriatricians). Most are located in large cities, while there is a shortage in small towns and rural areas. The facilities for accurate diagnosis are scarce, except in Buenos Aires City. There are a few specialists trained in cognitive neurology or neuropsychiatry, and neuropsychology doesn't exist as specialty [27]. In the last 10 years, the role of memory clinics has become more important. Most of these are based on private initiatives only two in the public system at the hospitals of Buenos Aires city (Alzheimer's center from Carlos A. Mangone at the Santojanni Hospital and Centre of Cognitive Neurosciences and Memory Disorders created by Ricardo F. Allegri at the Zubizarreta Hospital). Among its main findings, this survey showed that 70% of these memory clinics only cater to private patients. Eighty percent of patients are assisted by neurologists, probably may be by the psychoanalytic history of the argentine psychiatry. However every clinic had at least one psychiatrist on their staff. Only 35% of the centers perform clinical trials, 20% of the groups presented works in meetings, and 5% published original papers in peer review journals. Sixty percent of the centers have day care services; 35% of the clinics provide training and 80% counseling for spouses and caregivers [29].

In 2011, the Argentine Neurological Society Research Group on Behavioral Neurology and Cognitive Neurosciences published the last version of the Clinical Practice Guideline on Alzheimer's Disease. The guide was an excellent review of the state of the art concerning the 2010 knowledge on the management of this disease. It provided physicians with the usual standards provided by evidence-based medicine in order to reach the most adequate diagnostic and therapeutic measures [30]. But this guide was launched before the news AD biomarkers.

In 2012 Allegri et al. [31] published a review of recommendations and new diagnosis criteria for the mild cognitive impairment (MCI) due to Alzheimer's disease according with the revision of the National Institute of Aging and Alzheimer's Association from the USA [32]. The new diagnostic criteria for MCI due to AD based on the use of new AD biomarkers have a radical importance since they are potentially applicable in the clinical or research protocols and in all clinical settings where such markers are available.

Early diagnosis is another challenge with the incorporation of the biomarkers of the diseases, structural neuroimaging (medial temporal lobe or hippocampal volume by MRI), functional

neuroimaging (positron emission tomography (PET) with fluorine-18-labeled deoxyglucose), molecular neuroimaging (PET with Aβ-ligands (PiB)), and cerebrospinal fluid (Aβ42, tau, and f-tau). However the distribution of these biomarkers is limited to only one neurological center in Buenos Aires. Social Security and ISSPJP don't recognize the use of biomarkers, and they are only possible in the private clinical system or in research programs.

With this advancement, a new demand has been placed on professionals in the field to address the need of providing accurate diagnoses and observing the consequences, advantages, and disadvantages of the use of biomarkers. In 2012, our group studied a version of an international survey with the objective of evaluating the public's perception and degree of knowledge about Alzheimer's disease (AD) and the very early diagnosis with biomarkers [33]. Among the most significant findings of this study, it was concluded that more than 90% of the respondents prefer the early diagnosis, in the hypothetical case of having the disease. On the other hand, almost 90% of subjects in the sample would be willing to undergo a confirmatory study of the diagnosis of AD, while 80% would undergo a diagnostic study, if there was one available, to determine the presence or absence of the disease before having the symptoms [34].

This new paradigm of early diagnosis opens many questions about the current and optimal medical behaviors. Therefore, research should focus on:

- The current and future behavior of subjects before receiving an early or pre-symptomatic diagnosis
- The institutional response (e.g., Alzheimer Disease International, ADI; Argentina Alzheimer Association, ALMA; etc.)
- The professional response of those involved in the assistance and care of the patient

In 2015, we repeated this survey in a sample of more than 500 people with the purpose of determining the presence of any change in the abovementioned parameters. Our findings indicate that 90% of the respondents were willing to know the diagnosis and would be also eager to undergo a confirmatory study if the situations require it [35].

Regarding the possibility of providing an early diagnosis, one important question is whether people in Argentina who are 65 years or older consult a specialist in the nervous system, either a neurologist or a psychiatrist, when they are already experiencing some objective or subjective symptoms. A recent survey conducted in the city of Mar del Plata, province of Buenos Aires, among more than 2000 healthy individuals over 65 years of age, concluded that almost 20% of the people surveyed visited a neurologist or a psychiatrist in the year prior, being neurology the fourth most consulted specialty in medicine among older adults of the sample, behind ophthalmology, traumatology, and cardiology [36].

Other very useful guide has been issued by the Argentine Neurological Society about driving, a challenging topic where clinicians play a very difficult role: based on their assessment, these professionals could deprive individuals of their right to drive vehicles if safety problems are at stake both for patients and the public [37, 38].

In research of dementia, Argentina has a big presence in the world since the first works from Carlos Mangone in 1990 [39, 40]. Currently since late 2011, the Neurological Institute for Research (FLENI) based in Buenos Aires City joined ADNI (Alzheimer's Disease Neuroimaging Initiative, http://adni.loni.usc.edu/) a multinational public sector-industry partnership founded in 2004 to develop biomarkers of AD to predict the progression from normal aging or cognitive impairment to dementia phase of Alzheimer's disease [41]. The Argentina ADNI was the first ADNI center in Latin America. This research involves volumetric neuroimaging (3.0 T), positron emission tomography (PET) with fluorine-18-labeled deoxyglucose and Aβ ligands (PiB), and cognitive and neurological evaluation and analyses of cerebrospinal fluid biomarkers (Aβ42, tau, and f-tau) in the fields of dementia and biomarkers [41, 42]. Russo et al. [41, 42] showed that scores for the baseline measurements of the neuropsychological evaluation differed significantly among the three groups,

showing a continuum in their neuropsychological performance. No significant correlations were found between the principal measures (long-delay recall, C-Pittsburgh compound-β scan, left hippocampal volume, and APOEε4) and either age, sex, or education. Baseline amyloid deposition and left hippocampal volume separated the three diagnostic groups and correlated with the memory performance [42].

Chrem Mendez et al. [43] studied the frequency of PiB amyloid findings in different diagnostic syndromes grouped into high- and low-probability pretest categories, taking into account pretest clinical assumption of the presence of AD-related pathology. One hundred and forty-four patients were included for analysis (40 from Arg-ADNI and 104 from FLENI dementia database). The result was that only normal controls and DAT patients (typical and atypical presentation) were the most consistent across clinical and molecular diagnostics. MCI, non-logopenic PPA, and FTD were the syndrome diagnoses that most discrepancies were found. The study demonstrated that detecting in vivo amyloid plaques by molecular imaging is considerably frequent in most of the dementia syndromes and shows that there are frequent discordance between molecular diagnosis and clinical assumption only in atypical cases [43].

In 2016, the Argentinean branch of the DIAN (Dominantly Inherited Alzheimer Network, http://www.dian-info.org/) was established in FLENI, also the first in Latin America. Arg-DIAN is another multinational Alzheimer project similar to ADNI that works on dominantly inherited Alzheimer's disease with several collaborative papers in the field [44, 45]. In addition FLENI houses the only brain bank in Argentina and the most important in Latin America [46].

Clinical trials worldwide are growing as a result of considering dementia as an epidemic disease in the coming years; South America has larger urban populations than other emerging regions and could provide treatment-naïve patient populations for clinical trials. These population characteristics enable accelerated enrolment, high persistent recruitment levels, high patient retention rates, and simplified patient follow-up. These factors can make a dramatic difference in trial efficiency, in an environment of tighter timelines and funds [47]. Most principal investigators and sub-investigators in Argentina have completed their medical training in the USA or Europe, often including exposure to clinical trial participation. As a result, to qualify to conduct clinical trials, these investigators generally only need training in good clinical practices (GCPs) and consultation to ensure that facilities are appropriate [48]. Nowadays, of the 534 active clinical trials worldwide in Alzheimer's disease, only 7 take place in Argentina: studies of crenezumab in patients with prodromal AD and elenbecestat (E2609) in early AD are yet recruiting. Gantenerumab in prodromal AD is active but not recruiting. Trials with bapineuzumab and solanezumab in AD are terminated [49]. Argentina has suitable conditions for conducting and developing clinical trials, incorporating particularities of our cultures and necessities. There is a great market for drugs to control dementia, mainly AD; developing countries will be the main source of aging people in the future. Trials are becoming more complex, and clinical trial designs are changing: there are greater demands to meet requirements of the FDA and EMA (European Medicines Agency). At the same time, the new paradigm of prodromal AD has increased the inclusion of biomarkers (CSF Aβ42 and tau, FDG-PET, MRI hippocampal volume) in the majority of the trials, which can limit the number of places that use that technology. Argentina has large urban populations and high per site recruitment levels. There are well-equipped centers, memory clinics, and a great number of specialists in dementia, which are proved by an increasing number of publications. Together with an emerging financial evolution, we will remain important points of future research [48].

## Behavioral and Psychological Symptoms in Dementia (BPSD)

Cognitive symptoms of dementia have been those most widely studied. Recent years have seen the growth of recognition on behavioral and

psychological symptoms of dementia (BPSD), which have historically been referred to as "behavioral disturbances" [50]. In Argentina, the Neuropsychiatric Inventory-Q [51] is the most common tool used to assess BPSD. Pollero et al. [52] have looked at the frequency of BPSD in Argentina (87%) in 72 patients with dementia of Alzheimer type. The most frequent symptoms were apathy (55%), irritability (55%), depression (45%), and anxiety (50%). Other symptoms were agitation (33%), delusions (30%), hallucinations (30%), sleep disorders 29%), loss of inhibition (23%), appetite disorders (20%), and motor behavior (20%). The sample was divided in stages by the Clinical Dementia Rating [53] from 0.5 to 3, and mood symptoms were predominant in very mild and mild dementia, while psychotic symptoms were in moderate dementia. Apathy was the symptom most prevalent in all stages [52].

Demey et al. [54] studied the BPSD in mild cognitive impairment in Argentina. The most common symptoms in the MCI group were irritability (55%), dysphoria (44%), apathy (37%), and anxiety (37%). Statistically significant differences were observed between the MCI and control groups regarding the abovementioned symptoms. However, the differences between the MCI and mild AD groups were not found to be statistically significant. MCI in this paper was associated with a high rate of neuropsychiatric symptoms (irritability, depression, anxiety, and apathy) [54].

Taragano et al. [55] introduced for the first time in the world the term Mild Behavioral Impairment (MBI) as a risk concept of dementia. Behavioral symptoms in MCI are associated with a higher risk of dementia, but their association with dementia risk in patients without MCI is unknown. This study sought to compare MCI and MBI patients and to estimate the risk of dementia development in these two groups. Thirty-four percent of MCI patients and over 70% of patients with MBI developed dementia. MBI patients without cognitive symptoms were more likely to develop dementia. MBI patients were more likely to develop frontotemporal dementia (FTD) than dementia of the Alzheimer's type (DAT). MBI (specifically in those without cognitive symptoms) may confer a higher risk for dementia than MCI, and it is very likely an FTD prodromal in many cases [55].

## Caregiver Burden

The relationship between the caregivers' feelings of burden and the cognitive, behavioral, and functional impairment of patients with dementia has been investigated in an Argentinean study of 85 patients with DAT [56]. The study showed that caregivers' reports of patients exhibiting BPSD were the best predictors of burden on the part of the caregiver. Aggressiveness, pacing, moaning, and shouting were the predictors of caregiver burden. Younger and more educated caregivers experienced more inability to cope. Allegri et al. [57] report the neuropsychiatric symptoms as a predictor of caregiver burden using the NPI. In this study the burden was not related to cognitive impairment (MMSE) or stage disease (CDR). It is found correlation with delusion, hallucination, restlessness, anxiety, euphoria, disinhibition, unusual motor behavior, sleep disturbance, and appetite alterations as predictor of burden. No correlation was observed between apathy and depression [57].

The gradual progressive impairment and behavioral symptoms that may emerge in the course of Alzheimer's disease produce a high requirement for care and supervision of daily activities. This usually falls upon relatives acting as informal caregivers, causing them great burden and stress. The term caregiver burden refers to the consequences derived from caring for demented patients [57]. Behavioral disturbances are a common feature in dementia and cause significant caregiver burden [56, 58]. The symptoms that more frequently caused caregiver burden are aggression, wandering, and delusions [59]. Allegri et al. [57] studied in Argentina the predictive value of behavior-related burden on Alzheimer's disease caregivers. They report that 81% of the informal caregivers were women, while 54% were spouses and 36% were children of patients [55]. Caregiver burden was positively

related to behavioral disturbances in patients, as reported in other studies [54], and negatively to caregiver's educational level. The neuropsychiatric symptoms like delusions, hallucinations, restlessness, anxiety, euphoria, disinhibition, unusual motor behavior, sleep disturbances, and appetite alterations were the best caregiver burden predictors (NPI). All of these symptoms are the so-called positive symptoms. Most of the published papers showed similar findings for this group of symptoms, and some have even reported that such symptoms can trigger temporary or permanent institutionalization [58]. No correlation with cognition, disease stage, or negative neuropsychiatric symptoms (depression and apathy) was found. Increased caregiver burden was related to increased levels of patient behavioral disturbance. The only demographic caregiver variable correlating with burden was education. Age, gender, marital status, and family relationship were not significant. Thus, a lower educational level shows a higher burden index. Of these symptoms, hallucinations, unusual (motor) behavior, and abnormal behavior at nighttime were the most significant. No correlation with neuropsychiatric symptoms such as apathy and depression was found. This may have relevance to appropriate interventions for caregivers [57].

## Psychoeducation

The consideration of psychoeducation as the first step in the achievement of the goal set to give more and better information to family and caregivers has fueled the publication of the first book in the country about the care of people with dementia, initially published by our group in 2003 and reedited in 2016 [60]. In this most recent edition, it was included several chapters that address the main issues that the patient with dementia and his/her caregivers and loved ones face in their daily struggle with the disease, including, probable causes, early signs, behavioral symptoms, possible complications with driving, loss of independence, placement in nursing homes, as well as understanding and dealing with the eventual death of the patient and, finally, assimilating the concept of a brain bank. The relevance of the involvement of caregivers and family in support groups and psychoeducation programs is also emphasized [58].

Behavioral and psychological symptoms of dementia have a main impact on families and frequently derive in an eroding struggle and suffering among their members, thus being the most common cause of institutionalization and increased costs [61, 62].The relationship between the caregivers' feelings of burden and the cognitive, behavioral, and functional impairment related to the different stage of patients with dementia has been investigated in Argentina [56]. Behavior and Psychological Symptoms of Dementia (BPSD) and caregiver burden were assessed using the Functional Dementia Scale (FDS) from the Blessed Dementia Scale in conjunction with an adapted version of the Zarit Burden Interview. The findings of this study showed that caregiver self-reports of patients exhibiting BPSD were the best predictors of burden for them. Analysis of the FDS items identified aggressiveness, pacing, moaning, and shouting as independent predictors of caregiver burden. Interestingly, this same author showed that some treatments depend directly on psychosocial and demographic factors, therefore revealing marked differences between important cities, such as Buenos Aires and Cordoba, and impoverished towns and rural areas. Caregivers in central urban cities are more likely to be burdened by the symptom of "pacing or wandering" due to limited housing space than those living in outside the capital in provinces where patients reside in spacious houses surrounded by open spaces, with a low risk of getting lost. Illiterate caregivers and some natives living in small cities and rural areas are more tolerant of BPSD than those living in populated cities. Indeed, they seek treatment only when behavioral problems become severe and difficult to handle. Based on their traditions, spiritual values, or religion, these groups of caregivers are prone to care for their relatives without hesitation and with a tendency to hide the dementia-related symptoms. Prayers and faith are also a frequent part of the treatment among these groups [9].

A very common problem occurs when general practitioners perform clinical assessments since and under diagnose behavioral or cognitive symptoms as changes associated with normal aging. A geographical analysis of specialists in this field (e.g., neurologists, psychiatrists) reveals a disproportional distribution between urban and rural areas, whereby professionals conglomerate in populated cities [61]. Except from Buenos Aires and a few other large provincial cities, the possibility of receiving a very early diagnosis of dementia and implementing efficacious measures to address the most severe behavioral symptoms of this disease is still very low. However, in the past decade, the role of "memory clinics" to diagnose dementia has increased. These are mainly located in the private sector and are mostly run by neurologists [7]. In this sense, we have already commented on the different promising strategies currently implemented by the government to achieve the goal of educating primary care physicians in early detection of dementia.

## Argentine Association Against the Alzheimer (ALMA)

Dementia is the typical medical disease that allows the demonstration of the important value of support groups along with the significant role of institutions fighting against the disease. The uses of support networks are vital. ALMA (from the Spanish Asociación de Lucha contra el Mal de Alzheimer—Association Against Alzheimer's Disease) is a member of Alzheimer Disease International and Alzheimer Ibero América, working locally to promote and offer care and support for people with dementia and their caregivers. It has more than 20 local associations around the country [63] performing activities and benefits which include psychoeducation talks, support groups for caregivers, psychological help for relatives, stimulation workshops and music therapy for patients, memory stimulation groups for older adults, as well as diagnostic evaluation and treatment. There are two original activities mainly focused on the caregivers of patients which have been developed by ALMA as part of the comprehensive treatment of dementias. One is called "coffee with ALMA," a space for psychoeducation to promote the knowledge of the disease and battle for a better quality of life of people affected with cognitive impairment and dementia as well as for their families and loved ones. This approach has been recently declared "of interest for the Medical Sciences" by the Legislature of the City of Buenos Aires, Argentina [64]. The other activity is the "Twinning Program" of ADI (Alzheimer Disease International), a program launched in 2005 by this institution, which aims to take advantage of global knowledge and disseminate it around the world with the ultimate vision of ensuring that all people with dementia and their caregivers receive the best quality care and support regardless of where they live [65]. A recent experience similar to the guidelines of the Twinning Program has been carried out between ALMA and AUDAS (Uruguay Alzheimer Association and Similar) with the aim of the program and execution of support workshops for caregivers, relatives, and loved ones of people with dementia. This initiative is based on the positive results obtained with this model by AUDAS in Montevideo, Uruguay.

## G8, World Dementia Council and Action Plan from the World Health Organization

In 2012, the World Health Organization and Alzheimer Disease International wrote a report which makes a major contribution to our understanding of dementia and its impact on individuals, family, and society around the world. The report calls on governments, policymakers, and stakeholders to consider dementia as a public health priority [2].

Improving the health care of people with dementia is rallying countries to take individual or joint health actions to urgently confront this epidemic by focusing on prevention, early diagnosis, and best therapeutic resources. In December 2013, the G8 summit—currently G7—led by David Cameron (UK) in London created the World Dementia Council (WDC).

The WDC aims to focus and enhance all efforts to address the global dementia crisis, including awareness raising, research on causes, prevention, diagnosis, social stigma, treatment and care. Consequently, the WDC is conformed by 24 leaders from all sectors dedicated to this disease: researchers, NGOs (such as Associations and/or Alzheimer's Foundations), philanthropic institutions, the pharmaceutical industry, universities, the World Health Organization (WHO), and regulatory bodies and governments from different parts of the world [66].

More recently, a group led by Winbland denominated the Lancet Neurology Commission has called to fight against dementia with specific recommendations for its prevention, research, care, and treatment under the name "Defeating Alzheimer Disease and Other Dementias" [67]. This Commission understands that the European Union (EU) is prepared to take initiatives to prevent and lead the best practices against dementia [68].

With the First Ministerial Conference on the Global Action Against Dementia (Geneva, 16 and 17 March, 2015), governments commit to advancements in dementia research and care. At this WHO Conference, supported by the Department of Health of the UK of Great Britain and Northern Ireland and the Organization for Economic Cooperation and Development (OECD), 80 countries joined experts from the research, clinical, and advocacy communities to discuss how collectively they could move forward action on dementia at the global level [69]. Currently the WHO is launching a new global action plan on the public health response to dementia (2017–2025) [70].

The goal of the global action plan on the public health response to dementia is to improve the lives of people with dementia, their careers, and families while decreasing the impact of dementia on them as well as on communities and countries.

The action plan is grounded in the following seven crosscutting principles:

(a) Human rights of people with dementia
(b) Empowerment and engagement of people with dementia and their careers
(c) Evidence-based practice for dementia risk reduction and care
(d) Multisectorial collaboration on the public health response to dementia
(e) Universal health and social care coverage for dementia
(f) Equity
(g) Appropriate attention to dementia prevention, cure, and care

The plan comprises seven action areas:

(a) Dementia as a public health priority
(b) Dementia awareness and friendliness
(c) Dementia risk reduction
(d) Dementia diagnosis, treatment, care, and support
(e) Support for dementia careers
(f) Information systems for dementia
(g) Dementia research and innovation

Furthermore we know that the increase in dementia is and will be faster in the next 20 years in low- to medium-income countries than in richer nations. In this sense, Latin American countries (LAC) such as Argentina have shown a steady growth in the fight against dementia. However, the existence of different barriers of economic and social nature hinders the access to an early diagnosis and a better quality of care. Such difficulties coexist with the challenge of sustaining long-term public health policies that are likely to include state-of-the-art actions destined to address the multiple needs that surface as a consequence of dementia in this geographic area.

## Proposal for the Department of Mental Health in Argentina

For the reasons mentioned above, the country is currently in a process of steady growth in the treatment of dementia. In this regard, the current state policy is characterized by a comprehensive approach that encompasses specific interventions on areas such as prevention, planning, care, pharmacological and non-pharmacological

resources, as well as psychosocial aspects of this condition.

Our proposal for the National Department of Mental Health is a "Program of Cognitive Impairment and Dementias," of which the main objectives are:

1. To improve the quality of life of patients and their families
2. To reduce the impact of these diseases in our environment

Essentially, the program proposes:

(a) A centralized registry of cognitive diseases [20, 21, 71] with the objective to determine the burden of this condition and its different diagnoses based on region, level of deterioration, etc.
(b) Survey of available health resources in this area with the objective of surveying the quality and quantity of professionals and services (e.g., centers for detection, diagnosis, and treatment, including nursing homes) divided by health regions.
(c) A teaching- and research-oriented program aimed at training professionals in all levels of care of cognitive deterioration and early dementia including detection, diagnosis, and treatment. The organization of this program is hierarchical. Thus, training teams at the national level are set to instruct teams at the provincial level which, at the same time, are responsible for teaching activities within regional districts. The nature of this training is comprehensive as it encompasses physician, nurses, assistants, and caregivers.
(d) Prevention programs designed with the objective of promoting and increasing awareness of this medical condition among the general population and particular groups at risk.
(e) Cognitive study centers. These units are established in health-care facilities nationwide with the objective of the treatment and research of subjects with cognitive impairment organized by specific levels of complexity and using a unified system of diagnoses and treatment protocols.

The initiatives mentioned above could be complemented with the development of guidelines for the prevention, diagnosis, and treatment of this medical condition in the national health system. A committee of experts is responsible for the planning and implementation with actions. The next step of the *Program of Cognitive Impairment and Dementias* must be the proposal of a *Dementia National Plan* that encompasses initiatives and actions involving several government areas including the Ministry of Health (detection, diagnosis, and treatment of the disease), the Ministry of Social Development (social and environmental factors), and the Ministry of Science and Technology (research) [72, 73].

A novel and efficient way of medical education has been implemented recently by the Direction of Mental Health of the Ministry of Health of the Nation, and it consists in the use of remote teleconferences among hospitals, health centers, and universities, with the goal of providing an early detection program for screening of cognitive impairment. Such platform has been named eHealth Cyber-Salud [74]. In addition, a group of experts of the Neurological Society of Argentina has published a document known as "Clinical Guidelines for Alzheimer's disease" [75].

## Conclusions

In this paper, we analyze the reality of Argentina and the challenges that these face with regard to the issues associated with dementia. Undoubtedly, the extended aging of the overall population reflects the triumph of modern society through the improvement of global health, but it also highlights the special challenges that both developing and developed countries must confront in the twenty-first century. One of them is the increase of people with cognitive impairment and dementia whose deteriorated health condition constitutes one of the most important health topics for Argentina both in the present as well as for in the next decades. Argentina is currently in a stage of transformation aimed at strengthening, homogenizing, and channeling resources in its fight against dementia. Multiple plans in

progress and a growth in promotion and diffusion of available information derived from our own data are our most powerful weapons to confront historical, economic, political, and social difficulties associated with this epidemic in the area of public health. Although we have a long road ahead, the first steps taken by the organization and implementation of a plan at the national level constitute a hopeful challenge.

This review has updated the reality of the resources of dementia in Argentina. From this point on and throughout the next decade, the materialization of these promises into clear and achievable state policies to ensure the continuance of effective health actions against dementia appears to be the biggest challenge.

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# 29

# Genetic Factors Influencing the Development and Treatment of Cognitive Impairment and Psychosis in Parkinson's Disease

Santiago Perez-Lloret, Viviana Bernath, and Francisco J. Barrantes

## Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about 1 person out of every 1000 in their fifth decade and 19 out of every 1000 in their eighth decade or older [1]. The most characteristic motor symptoms are bradykinesia, rigidity, and tremor. Postural abnormalities and gait disorders are also frequent. Patients also suffer from non-motor symptoms, including cognitive impairment, mood disorders, sleep alterations, dysautonomia, and hallucinations, among others [2].

Progressive loss of the nigrostriatal dopaminergic pathway is the most characteristic, though not the only, histopathologic change in PD [3]. L-DOPA, which was introduced in the 1960s, is still the most effective treatment for motor symptoms [4].

Neuronal death may be preceded by a series of dysfunctional states, including loss of redox control, alteration of lysosomal activity, abnormal protein control mechanisms in the endoplasmic reticulum (ER) and in the ER-Golgi trafficking mechanisms, as well as synaptopathies. It is believed that these pathologies ultimately lead to abnormal accumulation of misfolded protein aggregates [5], which constitute the Lewy bodies, characteristic intracellular protein aggregates found in nerve cells in PD.

In this chapter we will discuss the basis of PD genetics and the relationships between gene mutations and cognitive impairment and psychosis in the disease, beginning in the following paragraphs with a brief review of the main characteristics of these symptoms. For in-depth reviews, the reader is referred to [6, 7].

Cognitive impairment and psychosis are common in Parkinson's disease, even at the earliest stages, and have important consequences for quality of life and daily functioning [7]. Patients with PD have a greater risk of developing dementia compared with age-matched individuals without PD [6]. In a 12-year population study of patients with PD, the cumulative incidence of dementia increased steadily with age and disease duration reaching 80–90% by age 90 years

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(conditional on survival) [8]. The diagnosis of PD dementia (PDD) is now made on the basis of a predefined set of criteria proposed by the International Parkinson's Disease and Movement Disorder Society [6]. The primary defining feature of PDD is dementia that develops in the setting of established PD. In this context, a "dementia" syndrome is defined as (i) impairment in at least two cognitive domains and (ii) cognitive deficiency severe enough to impair daily life (social, occupational, or personal care) that must be independent of impairment owing to PD motor symptoms.

Visual hallucinations (VH), illusions, passage, and presence phenomena are common psychotic symptoms in PD [7, 9]. Thought disorders, such as delusions, can also be observed. These symptoms may or may not be accompanied by awareness of the pathological nature of the symptoms and their severity sometimes requires psychiatric hospitalization. In PD, psychotic symptoms may be observed in up to 50% of patients [7]. They tend to evolve in a persistent and progressive manner [10]. Psychotic symptoms develop from a complex interplay of extrinsic and intrinsic factors. It was previously considered that VH in PD were caused by dopaminergic medications. However, other factors may contribute to their emergence, including cognitive impairment, older age, and more advanced disease stage.

## Overview of PD Genetics

Parkinson's disease is a complex disease involving environmental, genetic, and epigenetic factors [11]. The past 20 years of genetics research have shown that DNA sequence variants play a substantial role in the development of the disease. Notwithstanding, only 5–10% of all patients suffer from monogenic forms of PD caused by highly penetrant mutations, which are rare and tend to segregate with the disease in families. Conversely, the vast majority of PD cases are not related to these mutations, but acquire the disease through the combined action of DNA sequence variants displaying weak effects. In these patients, the development of PD is also related to environmental, lifestyle, and epigenetic factors.

The first mutations in PD were discovered in the 1990s [12]. The analysis of a large multigenerational Italian family (the Contursi kindred), in which parkinsonism segregated in an autosomal dominant pattern, led to the discovery of the first PD-related mutation, which affected the *SNCA* gene encoding for α-synuclein (PARK1) [13]. In the following 20 years several gene mutations have been discovered by linkage analysis (PARK1-15 locus) or by genome-wide association studies (PARK16-18) [14]. The classification has been recently revised in the light of newer evidence [15].

The findings that mutations of the *SNCA* gene could cause PD suggested that the protein that it encoded, α-synuclein, could be of importance for the development of PD [11]. Indeed, α-synuclein was described as the major constituent of Lewy bodies in PD shortly after [16]. It has become clear that α-synuclein misfolding and precipitation is one of the most important pathogenic factors in PD [17]. According to the "selective vulnerability hypothesis," α-synuclein aggregates first in a subset of neurons that are particularly susceptible to some adverse influence and subsequently aggregates also in less susceptible neuronal cells [18, 19]. In contrast, the more recent "pathogenic spread hypothesis" postulates that abnormal α-synuclein proteins or aggregates generated in one neuron are trans-synaptically transferred to a neighboring neuron [18, 19].

As opposed to *SNCA* mutations, which are a rare cause of PD, mutations in *LRRK2* (leucine-rich repeat kinase 2), which are also transmitted in an autosomal-dominant manner, are more frequent [20, 21]. A minimum of seven highly penetrant, pathogenic mutations have been described in *LRRK2* (Asn1437His, Arg1441Cys/Gly/His, Tyr1699Cys, Gly2019Ser, Ile2020Thr) [22, 23], among which the most common mutation, Gly2019Ser (rs34637584), has an estimated carrier frequency of 4% in "familial" and 1% in "sporadic" PD patients (i.e., in patients who do not have a family history of PD) [22]. *LRRK2* mutations may exert their effect through a toxic

gain of function, possibly due to an increase in autophosphorylation/kinase activity [24].

Causative *SNCA* and *LRRK2* mutations have been mapped and identified based on the "traditional" approach of linkage and subsequent positional cloning; however, new techniques have emerged in recent years enabling more extensive searches of new candidate genes [11]. For example, gene mapping in human diseases allows for the localization of genes underlying the clinical phenotypes of the disease on the basis of correlation with DNA variants (polymorphic markers), without prerequisite hypotheses on biological function [12]. Genome-wide association studies (GWAS) are one such technique. In GWAS, the identification of genetic risk factors for the development of PD is achieved by analyzing as many as 500,000 different single-nucleotide polymorphisms (SNPs) in groups of a few thousands of sporadic PD patients and healthy individuals per study and comparing *SNPs* frequencies in the two groups. If certain variants are more frequent in PD patients, they are considered to be "associated" with the disease.

Gene mapping techniques can uncover genetic variants with lower penetrance compared to gene mutations transmitting diseases from generation to generation in a monogenic manner [11]. Therefore, as discussed earlier, disease might manifest when environmental and lifestyle factors are combined with these genetic variants.

GWAS results from the USA, Germany, Greece, the UK, and France have been summarized in a recent meta-analysis, which included genome-wide SNP data from 13,708 cases with Parkinson's disease and 95,282 controls [25]. In an attempt to further identify which of the putatively associated loci were truly disease-related, each locus was replicated in an independent sample series using a semi-custom genotyping array called NeuroX. This array typed the >240,000 exonic variants available on the Illumina Infinium Human Exome Bead Chip and an additional ~24,000 variants proven or hypothesized to be relevant in neurodegenerative disease. The array included the 26 genome-wide significant candidate loci implicated in PD from the primary meta-analysis.

Association analysis showed replication of 22 of the 26 loci tested, based on a nominal one-sided P-value threshold of <0.05 and consistent direction of association that incorporated the premise of prior knowledge for most loci based on previous meta-analysis of GWAS data. Six additional loci, previously reported to be associated with risk for Parkinson's disease that did not show association at $p < 5 \times 10^{-8}$ in the discovery phase, were also explored. Two additional loci were found to be associated with PD. Presence of multiple independent risk alleles at any of the 26 genome-wide significant loci identified in the discovery phase was also investigated, four of these variants showing significant association. In total, Nalls et al. identified 28 independent risk variants for PD: 22 found in the discovery phase and confirmed by replication, 2 previously reported variants confirmed in the replication phase, and 4 variants identified by a second risk allele acting independently of the primary risk allele. One major finding of this study was that GBA gene (which encodes for the glucocerebrosidase enzyme) mutations conferred the greatest PD risk among the 28 SNPs identified. The association between *GBA* mutations and parkinsonism was first recognized in the clinic, where it was observed that patients with Gaucher's disease developed parkinsonian symptoms more frequently than expected [26], suggesting a link between mutations in *GBA* and PD. The frequency of *GBA* mutations was then studied in 5691 patients with PD (780 Ashkenazi Jews) and 4898 controls (387 Ashkenazi Jews) [27]. Among Ashkenazi Jewish subjects, L444P and N370S mutations were found in 15% of patients and 3% of controls ($p < 0.001$) and, among non-Ashkenazi Jewish subjects, in 3% of patients and less than 1% of controls ($p < 0.05$). Notwithstanding, when *GBA* was fully sequenced for 1883 non-Ashkenazi Jewish patients, mutations were identified in 7% of the cases, suggesting that sequencing the whole gene can help avoid false-negative results.

Genetic risk profiles (GRS) represent the contribution of the genetic load to subjects' risk of developing a given disease. GRS for PD were

generated using the 28 SNPs previously discussed, by adding the multiplication of SNPs' risk induction (as represented by beta coefficients) by the number of mutated alleles [25]. These authors reported that the predictive power for GRS scores was marginal, with areas under the receiver operator curves of 0.616 without age and sex included as covariates and 0.633 with age and sex included. Individuals with a genetic risk profile score greater than 1 SD from the population mean (indicative of roughly 34% increase in genetic risk score above the mean for controls) had a significantly higher risk of Parkinson's disease (from meta-analysis; OR = 1.51; 95% CI = 1.38–1.66; $p = 2 \times 10^{-16}$). Patients in the fifth quintile of genetic risk scores had a much higher genetic risk compared to those in the first quintile (OR = 3.31; 95% CI = 2.55–4.30; $p = 2 \times 10^{-16)}$).

In a further study, data on 6249 unrelated European ancestry PD cases with onset at the age of at least 18 years old, stemming from the USA, Holland, France, Germany, and Greece, were retrieved [28]. Samples including the 28 PD risk variants and a number of proxies from recent GWAS were genotyped on the NeuroX array at the Laboratory of Neurogenetics at the US National Institute on Aging, and genetic risk scores (GRS) were generated. Briefly, for each variant of interest, the allele dosage was multiplied by the previously published beta coefficient then summed per sample to create the GRS. Increasing GRS were significantly associated with an overall trend for earlier age at disease onset in pooled analyses (beta = −0.10, $p$-value = $2.92 \times 10^{-28}$, adjusted $r^2 = 0.27$).

GRS were related to PD characteristics in a single-center study of 336 patients [29] and significantly associated with time from diagnosis to Hoehn and Yahr stage 3, which is a marker of disability in PD, in a Cox regression model ($p < 0.010$).

## Genetic Abnormalities in PD Patients with Neuropsychiatric Disturbances

In this section, the relationship between neuropsychiatric symptoms and genetic mutations in PD will be discussed. A double-entry table is provided to summarize the evidence (Table 29.1).

### *APOE* and Other β-Amyloid-Related Genes

According to the amyloid hypothesis, formation of β-amyloid plaques depends on an imbalance between β-amyloid production and clearance [30]. In sporadic forms of Alzheimer's

**Table 29.1** Association between genetic mutations and cognitive disturbances or psychosis in PD

| Genes | CSF $A\beta_{1-42}$ levels | Cognitive deterioration | Risk of dementia | Psychotic symptoms |
|---|---|---|---|---|
| *APOE ε4* | ↓ | ↑ | ↑ | 0 |
| *MME* | 0 | – | – | – |
| *CST3* | ↓ | – | – | – |
| *MAPT* | – | 0 | – | 0 |
| *SNCA* | – | 0 | – | ↓* |
| *LRRK2* | – | ↓ or 0 | – | ↓ |
| *GBA* | – | ↑ or 0 | ↑ | ↑ |
| *PARP4* | – | ↑ | – | – |
| *MTCL1* | – | ↑ | – | – |
| *BDNF* | – | ↑ | – | – |
| *COMT* | – | ↑ | – | – |
| *CCK* | – | – | – | ↑ |

Dashes indicate absence of data about the association between a given feature and a particular gene
*APOE ε4* apolipoprotein E, *MME* membrane metalloendopeptidase, *CST3* cystatin C, *MAPT* microtubule-associated protein tau, *SNCA* α-synuclein, *LRRK2* leucine-rich repeat kinase 2, *GBA* γ-glucocerebrosidase, *PARP4* poly [ADP-ribose] polymerase 4, *MTCL1* microtubule cross-linking factor 1, *BDNF* brain-derived neurotrophic factor, *COMT* catechol-O-methyl transferase, *CCK* cholecystokinin, *CSF* cerebrospinal fluid, $A\beta_{1-42}$ β-amyloid 1–42 fragment
*The effect was nonsignificant ($p < 0.08$)

disease, impaired clearance appears to be the most important factor for plaque formation [31]. β-Amyloid plaques can also be found in PD and are associated with increased risk of dementia [32].

The influence of genetic variations in the enzymes that metabolize β-amyloid in PD –mainly *APOE*, membrane metalloendopeptidase (*MME*), and cystatin C (*CST3*) [33] – has been assessed in a recent trial [34]. This study included 353 PD patients without dementia and 103 PDD. The following SNPs were studied: *APOE* rs429358 (to determine the *APOE ε4* carrier status), *MME* rs6776185, and *CST3* rs1064039. Genotyping was performed using either matrix-assisted laser desorption/ionization time of flight mass spectrometry method (MassARRAY system; Sequenom, San Diego, CA) or SNaPshot single-base extension (Applied Biosystems, Foster City, CA; software, GeneMapper) with capillary electrophoresis. Mutations in the *LRRK2* (G2019S) and in the *GBA* (L444P, N370S, E326K) were ruled out. Results showed that risk variants in the genes *APOE* and *CST3* were associated with lower cerebrospinal fluid β-amyloid$_{1–42}$ levels, which are a marker of β-amyloid plaques. Interestingly, patients with two risk alleles in *CST* tended to show a shorter interval from age at onset of PD to age at onset of dementia.

Several pieces of evidence suggest a prominent role of *APOE* mutations in Alzheimer and Parkinson's dementia. The primary function of the apolipoprotein E (APOE) is to maintain the structure of lipoprotein particles and to direct lipoproteins to specific cell surface receptors. APOE influences the rate of β-amyloid fibrillization and clearance [35]. The transport of β-amyloid$_{1–42}$ was found to be isoform-dependent, being slowest with *APOE ε4* [36]. Consequently, the ε4 isoform confers a higher risk for AD by increasing the parenchymal β-amyloid load.

As shown in one study, the frequency of *APOE ε4* was significantly higher in Alzheimer's disease (38.1%), Alzheimer-Lewy body dementia mix (40.6%), pure Lewy body dementia (31.9%), and PDD (19.1%) groups compared with the control group (7.2%; overall chi-sq = 185.25; $P = 5.56 \times 10^{-39}$) [37].

In another study, cognitive status data from 390 PD patients from the Parkinson's Progression Markers Initiative (PPMI) cohort study at baseline and after a 2-year follow-up period were analyzed [38]. In this study, patients with two mutated ε4 alleles showed a 3.7 higher risk of cognitive deterioration after 2 years, as assessed by the Montreal Cognitive Assessment (MoCA) tool.

The profile of cognitive impairment has been studied in 1079 PD patients [39]. Patients underwent assessments of memory (Hopkins Verbal Learning Test-Revised [HVLT-R]), attention and executive function (Letter-Number Sequencing Test and Trail Making Test), language processing (semantic and phonemic verbal fluency tests), visuospatial skills (Benton Judgment of Line Orientation test), and global cognitive function (Montreal Cognitive Assessment). The *APOE ε4* allele was associated with lower performance on the HVLT-R total recall ($P = 6.7 \times 10^{-6}$), delayed recall ($P = 0.001$), and recognition discrimination index ($P = 0.004$); a semantic verbal fluency test ($P = 0.002$); the Letter-Number Sequencing Test ($P = 1 \times 10^{-5}$); and Trail Making Test B minus Trail Making Test A ($P = 0.002$). In non-demented carriers, lower scores on the HVLT-R total recall and on the semantic verbal fluency were found. In this study, patients also underwent genotyping for the *MAPT* H1/H2 haplotypes and *SNCA* rs356219. These variants were not associated with scores on any tests.

The association between mutations in *APOE*, *MAPT*, and *SNCA* with psychosis was studied in 500 PD patients [40]. Presence of psychotic symptoms was assessed by means of the *Unified PD Rating Scale* Item #2. *APOE* and *MAPT* mutations did not show any relationship with psychotic symptoms. One mutation in the *SNCA* gene was associated with increased risk (OR = 2.35, 95% CI = 0.91–6.05) but was non-significant ($p < 0.08$).

In another case-control study involving 44 PD patients with visual hallucinations and 44 parkinsonian controls that had never hallucinated, *APOE* mutations showed no relationship to hallucinations [41].

### *LRRK2*

The G2019S mutation (a glycine to serine substitution at amino acid 2019) in the *LRRK2* is one of the most common genetic contributors to PD [42, 43]. The hypothesis that *LRKK2* mutation carriers could be phenotypically different from non-carriers was tested in a study with 50 carriers and 50 age-, disease duration-, and disease severity-matched PD non-carriers [44]. Carriers showed the worst gait function and more frequent falls. Conversely, there were no major differences in cognitive function tests, including MoCA, Trail Making Test, verbal fluency, digit span, and Stroop test.

Further studies were carried out on a cohort of 1447 PD patients enrolled in the PD Cognitive Genetics Consortium [45]. *LRRK2* mutation carriers ($n = 29$) demonstrated better performance on the mini-mental state examination ($p < 0.03$) and the Letter-Number Sequencing Test ($p < 0.005$). A smaller proportion of *LRRK2* mutation carriers were demented ($p < 0.03$). There were no relevant differences in age, sex, education, and disease duration between carriers and non-carriers. The authors suggested that these findings may be related to the fact that *LRRK2* mutation carriers had less Lewy body pathology [46]. Nonetheless, this was a cross-sectional study that included a small sample of carriers. A study with a Spanish sample of 27 PD patients with *LRRK2* mutations (12 G2019S and 15 R1441G) and 27 non-carrier PD patients confirmed these results [47]. Interestingly, carriers also showed less hallucinations, as shown by the neuropsychiatric inventory (NPI).

### *GBA*

The phenotypical characteristics of *GBA* mutation carriers have been widely studied. In one of the first studies, mutations were studied in 790 PD patients and 257 controls [48]. Cycle sequencing was performed for each exon and the flanking intronic sequences using the dye terminator sequencing kit (Applied Biosystems) and run on an ABI 3700xl genetic analyzer (Applied Biosystems). Results showed a significantly higher frequency of mutations in PD compared to controls (4.18% vs 1.17%, $p < 0.01$; odds ratio = 3.7; 95% confidence interval = 1.12–12.14). Interestingly, diffuse neocortical Lewy body-type pathology tended to occur more frequently in the group with *GBA* mutations compared to matched Parkinson's disease controls. Fifteen out of the 31 (48.39%) PD patients with *GBA* mutations developed symptoms of cognitive decline during the course of the disease. Furthermore, visual hallucinations were present in 45.16% (14/31) of patients. Cognitive impairment was also found in about 50% of a small sample of US *GBA* mutation carriers [49]. In both studies, patients showed good responsivity to L-DOPA during the course of the disease.

In a later study, the *GBA* coding region was fully sequenced in 225 Parkinson's disease patients, 17 pathologically confirmed Lewy body dementia patients (LBD), and 186 controls from Spain [50]. Mutations were more frequent in PD and LBD as compared to controls (9.8% and 11.8% vs 0.5%, $p < 0.01$ and $p < 0.02$). Dementia was found in 50% of carriers vs 23.6 of non-carriers ($p < 0.01$). Carriers also showed less frequent rigid-akinetic phenotype and more frequent tremor phenotype. Carriers also showed a good response to L-DOPA.

In another study, DNA from 1000 patients initially diagnosed with idiopathic PD was subjected to mutational screening for two of the most common mutations of the GBA gene (N370S, L444P) by genotyping with restriction enzymes [51]. A total of 33 patients with PD heterozygous for one of the two *GBA* mutations from all over Germany were identified, of whom 20 consented to be further evaluated. Patients with *GBA* mutations had lower MoCA values; higher neuropsychiatric inventory scores for depression, anxiety, and apathy; and higher Beck Depression Index II scores. The authors hypothesized that these disturbances could be related to the diffuse neocortical Lewy body-type pathology observed in *GBA* mutation carriers [48].

In a more recent study, time to fully developed dementia and psychosis was compared between Japanese *GBA* mutation carriers ($n = 19$) and

non-carriers ($n = 167$), by means of a retrospective cohort study [52]. Carriers showed a significantly earlier development of dementia (6 years vs >10 years, $p < 0.001$) and psychosis (8 years vs 12 years, $p < 0.017$), compared with subjects without mutation. After adjusting for sex and age at PD onset, hazard ratios were 8.3 for dementia (95% CI, 3.3–20.9; $p < 0.001$) and 3.1 for psychosis (95% CI, 1.5–6.4; $p < 0.002$).

The cognitive profile of *GBA* mutations carriers was further studied in 60 carriers vs 1055 non-carriers [53]. Participants underwent assessments of learning and memory (Hopkins Verbal Learning Test-Revised), working memory/executive function (Letter-Number Sequencing Test and Trail Making Test A and B), language processing (semantic and phonemic verbal fluency), visuospatial abilities (Benton Judgment of Line Orientation), and global cognitive function (MoCA). Carriers had a higher prevalence of dementia (OR = 55.1; $p < 0.0001$). Carriers also showed lower performance on Letter-Number Sequencing, Trail Making B-A, and Benton Judgment of Line Orientation. These results suggest that *GBA* mutations are associated with a distinct cognitive profile characterized by greater impairment in working memory/executive function and visuospatial abilities in PD patients that differs from the profiles associated with other mutations. For example, lower performance on semantic verbal fluency and word-list learning has been found in non-demented *APOE ε4* carriers, as discussed earlier [39].

Follow-up data were available for a subset of these patients [54]. The mean (SD) duration of follow-up was 3.0 (1.7) years. During the study, a higher proportion of *GBA* E326K carriers (10 of 21 [47.6%]; $p < 0.01$), but not other mutation carriers (5 of 18 [27.8%]; $p < 0.69$), progressed to mild cognitive impairment and dementia compared with non-carriers. The association with conversion to MCI and dementia was also significant for the combined GBA variant group (15 of 39 [38.5%]; $p < 0.04$).

Effects of *GBA* mutations were further studied in a cohort of 532 well-characterized PD patients and 542 controls from southern Spain [55]. The potential pathogenicity of the identified variants was assessed using in silico analysis and subsequently classified as benign or deleterious. This analysis allows for the assessment of the pathogenic effect of the amino acid substitutions on the three-dimensional protein structure and its impact on protein function. Deleterious mutations included N370S, L444P, W312R, V457D, T369M, E326K, c.116-8C>T, and others. Interestingly, the progression of the disease to cognitive impairment was influenced by the presence of deleterious GBA variants (HR = 2.6; 95% CI 1.25–3.88; $p < 0.001$). Visual hallucinations were also influenced by the presence of deleterious GBA variants (HR = 3.15; 95% CI 1.71 ± 5.79; $p < 0.001$).

Patients with benign mutations also showed visual hallucinations, though the authors apparently did not compare groups of mutations.

In a recent study, 2764 unrelated consecutive PD patients, of whom 123 were *GBA* mutation carriers (67 mild-p.N370S and 56 severe mainly p.L444P), were followed for 2 years [56]. Carriers had greater risk for dementia compared to mild mutations (HR = 3.16, 95% CI = 2.3–4.4, $p < 0.001$). Interestingly, carriers showed reduced posterior parietal and occipital cortical synaptic activity and nigrostriatal function than PD non-carriers. The authors highlighted the fact that these results are in line with neuropsychological profiles of *GBA* carriers, which, as discussed earlier, are constituted by disturbances of visuospatial and nonverbal (mainly visual) memory tasks with relatively preserved executive functions and attention [53]. The former are associated with posterior cortical areas, whereas the latter depend on the frontal lobe.

Finally, in a very recent study, 1105 PD patients were genotyped for 249,336 variants using the NeuroX array [57]. Patients also underwent the full set of cognitive assessment tools: learning and memory (Hopkins Verbal Learning Test-Revised [HVLT-R]), working memory/executive function (Letter-Number Sequencing and Trail Making Test [TMT] A and B), language processing (semantic and phonemic verbal fluency), visuospatial abilities (Benton Judgment of Line Orientation [JoLO]), and global cognitive function (MoCA). Eighteen common variants in

13 genomic regions exceeded the significance threshold for one of the cognitive tests. These included *GBA* rs2230288 (E326K; $P_{FDR} = 2.7 \times 10^{-4}$) for JoLO, *PARP4* rs9318600 ($P_{FDR} = 0.006$) and rs9581094 ($P_{FDR} = 0.006$) for HVLT-R total recall, and *MTCL1* rs34877994 (PFDR = 0.01) for TMT B-A. These results have not been replicated.

### *BDNF* and *COMT*

Data from the PPMI study allowed the assessment of the relationship between some SNPs and cognitive impairment. In a sub-analysis of these data, 423 newly diagnosed patients with idiopathic PD were followed for 3 years [58]. Genotyping was performed with NeuroX. For this sub-study, SNPs previously associated with cognitive impairment or decline in PD were examined (i.e., *APOE ε4*, *GBA* [N3705], *LRKK2* [G20195], *SNCA* [rs3910105 and rs356181], microtubule-associated protein tau [*MAPT*; rs17649553, which is in linkage disequilibrium with the H1 haplotype], brain-derived neurotrophic factor val66met [*BDNF* val66met], and catechol-O-methyltransferase val158met [*COMT* val158met]). *BDNF* and *COMT* mutations predicted incident cognitive impairment. *BDNF* val66met C/C was associated with higher risk compared to C/T (HR = 2.327, 95% CI 1.008–5.373, $p < 0.05$). COMT val158met A/G also increased risk compared to G/G. These results have not been replicated.

### *CCK*

Cholecystokinin, a neuropeptide found in the gut and central nervous system, has been implicated in dopaminergic regulation. The *CCK* gene is active in dopaminergic neurons in the central nervous system. The relationship between polymorphisms in this gene and hallucinations has been explored in a number of trials. One of the first studies involved 116 PD patients [59]. Four polymorphic sites of the CCK gene (−196G:A, −45C:T, 1270C:G, 6662C:T) were found in PD patients. The CT allele was significantly more frequent in patients who displayed hallucinations (65.2% vs 5.2% CC or 8.7% TT, $p < 0.02$). In another study conducted in 45 PD patients with and 45 PD without hallucinations, the CCK CT/TT genotype was associated with a 4.429-fold increased risk for visual hallucinations in PD [60]. Finally, a case-control study involving 28 PD patients with hallucinations and 35 without showed the T allele to be more frequent in the former (19% vs 9%) but with the difference being of only borderline significance ($p < 0.06$) [61].

## Conclusions and Future Perspectives

The genetics of PD are only beginning to be unraveled. The cost of genetic testing has dropped to a few thousand dollars, and it is expected that it will continue to fall. Yet, medical understanding of the consequences of having one or more deleterious mutations is still limited, thus imposing barriers on the utilization of genetic results in clinical decision-making.

Genetic information may prove very useful for the management of cognitive disturbances and psychosis in PD. Available evidence suggests that several genetic mutations modify the risk of developing these neuropsychiatric symptoms. For example, patients carrying the *APOE ε4* allele or *GBA* mutations have a well-documented increased risk of cognitive deterioration and dementia [39, 53]. Interestingly, *APOE ε4* allele has been shown to correlate with reduced cerebrospinal fluid $A\beta_{1-42}$ levels, which are a marker of parenchymal amyloid plaque deposition [62]. Mutations in the *CST3* gene have also been correlated with cerebrospinal fluid $A\beta_{1-42}$ levels and with PDD [34]. Conversely, the positive association between cognitive impairment and mutations in the *BDNF*, *COMT*, *PARP4*, and *MTCL1* genes [57, 58] has not been replicated, and there is no data on subsequent progression to PDD. Finally, *LRKK2* mutation has been shown to reduce the risk of cognitive impairment [45], but there is no data on dementia. It should be mentioned that definitions of dementia vary from

study to study and that the currently most widely accepted definition of PDD, proposed by the *International Parkinson's Disease and Movement Disorder Society* [63], has been used in a minority of reports.

The effects of *GBA* and *LRRK2* mutations on visual hallucinations followed the same trend as those on cognitive performance, i.e., the former increased risk [52], whereas latter reduced it [47]. It is therefore not clear whether these are real effects on hallucinations or by-products of mutation effects on patients' cognitive status [40]. The case of *CCK* may be different, as cholecystokinin is known to regulate dopamine, which is the main substrate of hallucinations [64].

Genetic information may serve for establishing a prognosis in clinical practice. As mentioned earlier, several pieces of evidence link genetic mutations to the development of cognitive impairment and possibly also psychosis. In the event that a genetic risk score is validated to predict the development of dementia, then high-risk patients can be selected for closer follow-up and early behavioral stimulation or administration of neuroprotective therapies, when they become available. This "personalized" approach can thus help medicine focus on high-risk individuals [65] and achieve higher efficacy with administered treatments. Furthermore, this focalization will help avoiding unnecessary therapeutic interventions in patients who will ultimately not develop cognitive impairments, thus reducing costs and safeguarding patients from exposure to adverse events.

Knowledge of genetic factors may also help direct the course of research. The protective effects of *LRRK2* mutations as well as the deleterious effects of *GBA* mutations have been hypothesized to be related to decreased and increased neocortical Lewy body pathology, respectively [46, 48]. However, the finding that *SNCA* mutations do not affect cognitive status could indicate that these mutations may not be related to the formation of Lewy bodies. One hypothesis is that such mutations affect the distribution of Lewy bodies rather than their formation. Further research is needed to further clarify this important issue.

As discussed earlier, the domains of cognitive impairment impacted by *APOE*, *GBA*, *PARP4*, and *MTCL1* differed [39, 57]. This suggests, in the first place, that PDD may not be a single entity. It seems logical to suggest that a first division be made between mutations affecting β-amyloid metabolization and thus eventual plaque formation, from those that may affect Lewy bodies' disposition, such as *LRRK2* or *GBA*. Indeed, degeneration appears to follow two different patterns, i.e., frontal lobe dysfunction if the predominant pathology is related to β-amyloid or a posterior parietal alteration in the case of α-synuclein pathology [56, 66]. This is further supported by the finding that parkinsonian *GBA* mutation carriers with impaired cognition show levels of CSF β-amyloid similar to those of healthy controls, whereas non-carriers with cognitive impairment show reduced CSF β-amyloid levels [67]. Genetic information may therefore be essential for differentiating one type of dementia from another. This may have important implications for the therapeutic strategies to follow. For example, β-amyloid immunization [68] may work in one case but not in the other. Patients with *GBA* mutations, on the other hand, could be treated by drugs targeting the production of glycosphingolipids, such as the molecule named GZ/SAR402671, which is undergoing phase II clinical trials.

The manner in which the different mutations cause dementia remains to be explored. For example, cholinergic dysfunction in the basal forebrain (i.e., the nucleus basalis magnocellularis) is the hallmark of cognitive impairment in Alzheimer's disease [69]. Cholinergic disturbances also underlie PDD [70], and it is tempting to hypothesize that this will further correlate with β-amyloid pathology and *APOE* mutations. But cholinergic disturbances may not underlie dementias related to other mutations in PD. For example, *LRRK2* mutations are protective from the cognitive standpoint but are also related to gait disturbances. This suggests that *LRRK2* mutations may not affect cholinergic pathways, which are known to regulate gait [70]. There is no data available for the other mutations. A better understanding of the neuropathological

processes underlying cognitive disturbances in PD calls for further study of the precise manner in which these mutations induce the malfunction or degeneration of particular nuclei. Such studies will also broaden the scope of potential targets for the development of new therapeutic agents.

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# Neuroimaging Studies in Psychotic Disorders

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## Introduction

Schizophrenia is perhaps one of the most worrisome psychiatric illnesses [1], affecting approximately 1% of the general population [2]. The term psychotic episode refers to a set of disorders characterized by the presence of positive symptoms (delusions and hallucinations), as well as negative, cognitive, and affective symptoms, among which we find schizophreniform disorder, schizoaffective disorder, schizophrenia, bipolar disorder, and occasionally major depressive disorder. The prevalence of psychotic disorders in the general population is around 3% [3].

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The first psychotic episode usually occurs between 15 and 30 years of age, although it may present earlier in life [4]. The course of the disease is often chronic and quiet variable, leading to a significant loss of quality of life for both the patient and his/her family and to high cost to society as it accounts for 10% of the global burden of mental disorders in Europe [5].

In contrast to previous lines of work that studied specific diagnostic groups such as schizophrenia or affective disorders, research from the last decades shows the heterogeneous etiology of schizophrenia and affective disorders, in which genetic and environmental factors play a key role. Heritability of disorders such as schizophrenia or bipolar disorder is estimated at around 80% [6].

In addition, it has been shown since the first studies that the greater the genetic load shared with the affected family member, the higher the disease prevalence [7]. As a result, investigation of psychotic episodes has received special emphasis. Among psychotic episodes, the ones presenting early on, before pharmacological treatments alter the basic mechanisms of the disease, are of particular interest.

Evidence suggests that exposure to certain environmental factors in association with genetic factors may induce alterations in dopaminergic transmission, neuroendocrine function, cognitive function, patterns of interpersonal interaction, and mood processing among others, all of which may lead to an increased risk of psychopathology [8–10].



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According to the literature, environmental risk factors include prenatal stress, malnutrition, infections, hypoxia, paternal age, history of prior traumatic events, use of cannabis, and belonging to an ethnic minority group, among others. The increased risk is associated with a previous exposure to adulthood, suggesting an interaction with the other developmental processes. Several meta-analyses show that prior history of obstetric complications multiplies the subsequent risk of schizophrenia by two [11], and these are associated with an earlier onset age [12]. Specifically, the most common obstetric complications are diabetes, Rh incompatibility, preeclampsia, birth weight less than 2000 g, and urgent cesarean section, among others [13].

There is a clear relationship between cannabis use and psychosis. Research studies have shown high percentages of substance abuse in people with schizophrenia or psychotic disorder, ranging between 20% and 60% [14, 15].

Cognitive issues have been well-documented in patients with first episodes of psychosis, showing attention, executive function, language, and memory deficits. In this context, cognitive issues are known to be present from the first psychotic episodes, having a high endophenotypic value for the investigation of underlying neurobiological and morphological correlates, detectable through neuroimaging. They also have a high predictive value regarding patient's evolution and psychosocial and clinical function [16].

## Structural Neuroimaging

There are several studies that have demonstrated the value of the information obtained through neuroimaging in the study, diagnosis, monitoring, and evolution of schizophrenia, bipolar disorder, and other psychotic disorders both at the transverse [17, 18] and longitudinal levels [19, 20].

Studies in schizophrenics have shown an increased neuronal density of 10% in the occipital area 17 of Brodman [21]. A decrease in gray matter and larger third ventricle volume has also been observed in schizophrenic patients with cognitive deficits [22].

Structural imaging studies have confirmed the presence of cortical abnormalities in chronic schizophrenia, especially in the prefrontal and temporal cortex [23–25]. In recent years, these cortical abnormalities have also been identified in patients with first episodes of psychosis. Reductions in gray matter volume in the lower frontal cortex, bilateral cingulate cortex and medial-lateral temporal cortex have been observed [26].

In early episodes of psychosis in adolescents, a loss of gray matter has also been observed in the frontal, temporal, and parietal lobes [27]. In non-affected relatives of schizophrenic patients, these abnormalities have been found as well [28]. Abnormalities in the cortex not detected with voxel-based morphometry techniques have been observed with magnetization transfer techniques [29, 30] and FreeSurfer [31].

In addition, it has been possible to observe different involvement of the gray matter and the white matter in chronic schizophrenic patients, with changes in white matter being more sensitive [22, 32]. Some brain imaging methods may show microstructural and volumetric differences in white matter, as well as differences in functional connectivity (abnormalities in the corpus callosum in first episodes of psychosis) [33, 34].

Recent studies suggest that the age of the first episode determines the type of brain structural abnormality found in patients with early psychotic episodes [35]. To date, cross-sectional and longitudinal studies have consistently shown abnormalities of the gray matter volume and thickness in the parietal regions of patients with first episode schizophrenic spectrum disorders – beginning in infancy or early adolescence [36–38]. However, according to scientific publications, patients in whom the disease appears in late adolescence or early adulthood show volume and thickness abnormalities in the prefrontal and temporal cortical gray matter [39–42] as well as in the medial cortical regions, cingulate cortex, superior temporal gyri, insula [43, 44], and subcortical regions such as the hippocampus [45, 46], basal ganglia [44], and thalamus [47, 42]. In addition, patients with affective psychoses (including type I bipolar disorder and unipolar

depression with psychotic features) and schizophrenic spectrum disorders show similar brain volume and age of disease onset, being quantitatively larger and more widespread in the latter group [42, 48–51]. All these findings suggest that the structural brain abnormalities detected at the onset of psychosis are modulated by the individual's stage of brain development.

Our group [52] recently performed a cross-sectional study with a large cohort of patients with wide range of age (12–35 years) who presented with first psychotic episode and a group of healthy controls matched by age, gender, and laterality. The objective was to explore the nonlinear relationship between the age of the patient and measurements of parenchymal volume and cortical thickness in a given number of brain regions.

The results of this study showed that in the context of affective psychosis, patients with schizophrenic spectrum disorder showed reductions in volume and/or cortical thickness at early ages in the frontal lobe (before 15 years) and in the temporal lobe (before 20 years), differences that were not present in cases of later onset. Similarly, they showed significantly larger volumes of the caudate nucleus, putamen, and third ventricle, only if the onset of the disease occurred before 20–25 years of age. As for patients with affective psychosis and in comparison to healthy controls, several morphometric abnormalities were found in different regions of the brain, such as the cingulate cortex or caudate nucleus (resulting in a significantly smaller volume only in patients with earlier onset of the disease at 20 years of age), and in the temporal and occipital lobes, which were found to be thicker only in patients with disease onset before 15–18 years of age.

In addition, the group of patients with affective psychosis seemed to show constant age-related (age range 12–35 years) volume enlargement in the frontal and parietal lobes. Thus, the stage of brain maturation at the time of the first psychotic episode conditions the location of morphological abnormality. Hence, the diagnosis of the disease and the imaging studies that evaluate different brain parameters in a patient with first psychotic episode (which include subjects with broad age range) should take into account the nonlinear effect of age on the structure of the brain.

## Magnetic Resonance Spectroscopy

Since 1990, there have been over 100 studies using magnetic resonance spectroscopy in patients with schizophrenia [53].

With magnetic resonance spectroscopy, metabolic abnormalities have generally been found in the frontal and temporal lobes. In a review on spectroscopy [54], the most frequent abnormality observed in chronic patients was a decrease of the N-acetylaspartate/creatine ratio in the hippocampus and in the prefrontal region. Another group of authors found a decrease in the N-acetylaspartate/creatine ratio at the level of the left dorsolateral prefrontal cortex during the first psychotic episodes, and this finding had correlation with poor prognosis of disease [55]; however other studies have not found similar results [56]. The glutamate and glutamine abnormalities are more subtle and require high magnetic fields with short echo times, although such abnormalities have already been observed in the first episodes of psychosis [57].

A systematic review of chronic schizophrenia [58] revealed specific associations between cortical/subcortical measures and cognitive issues in chronic schizophrenic patients. The levels of N-acetylaspartate have also been correlated with cognitive deficits [59].

"First-generation" studies, focusing on phosphorus magnetic resonance spectroscopy, have suggested abnormalities in membrane phospholipid metabolism in the early phases of schizophrenia, but not in chronic cases [60].

Issues regarding sensitivity, specificity, measurement reliability, and functional significance of findings in magnetic resonance spectroscopy need to be further clarified. The noninvasive nature of magnetic resonance spectroscopy facilitates longitudinal studies of patients in the different phases of schizophrenia and among individuals at genetic risk for this illness. Future

studies need to address confounding factors such as history of prior treatment and illness chronicity, should take advantage of current pathophysiologic models of schizophrenia, and should be hypothesis driven.

## Functional Neuroimaging Techniques

Connectivity abnormalities between the frontal and temporal regions have been documented [61]. Susceptibility of genes in schizophrenia involves synaptic processes which leads to malfunction of cortical microcircuits and structural changes in the cortex [62]. Abnormalities in the frontal and temporal cortex may explain the cognitive damage observed in schizophrenic patients [63], and this cortical abnormality may be more indicative of a connective defect between both regions rather than an anatomical lesion per se [64].

## Diffusion Tensor Imaging

Microstructural changes in the white matter can be demonstrated with specialized MR imaging techniques such as diffusion tensor imaging (DTI). Recent in vivo diffusion brain imaging studies of schizophrenic patients have revealed microstructural abnormalities, with low diffusion anisotropy present throughout much of the cortex and the white matter. Brain tissue anisotropy occurs when proton motion leads to physically restricted water movement, for example, by myelin sheaths. Conditions that increase self-diffusion, such as edema, may also alter the longitudinal and transverse relaxation time of protons, and it is possible that such changes could explain the decreased anisotropy seen in schizophrenia. Schizophrenic patients had significantly longer mean white matter T2 and gray matter T2, which suggests that the abnormal anisotropy may be related to increased interstitial water in patients with schizophrenia [65].

Other studies have shown a decrease of fractional anisotropy in the splenium of the corpus callosum [66], in the frontal white matter, and in the gray matter of the anterior prefrontal cortex [67]. The reduction of fractional anisotropy in the inferior frontal white matter was predictive of high motor impulsivity and of increased relationship with severe negative symptoms [68]. A study in patients with schizophrenia showed that high fractional anisotropy in the inferior frontal white matter was predictive of increased aggressiveness [69]. However, it was shown in another study that decreased fractional anisotropy in the uncinate fasciculus of the left cerebral hemisphere may contribute to the cognitive and memory disturbance characteristic of schizophrenia [70].

Some authors have reported decreased fractional anisotropy in the parietal region, in adolescents with schizophrenia [71]. However, other studies in early-onset schizophrenia have found reduction in fractional anisotropy in the frontal regions [72, 73], in the hippocampal-prefrontal connections [74], in the left inferior temporal and occipital white matter, as well as in the left inferior longitudinal fasciculus [75]. Diffusion tensor imaging studies in people with adult-onset schizophrenia have generally reported reductions in fractional anisotropy in areas corresponding to the major fasciculi connecting the frontal, temporal, and parietal cortices, although there is a significant degree of variation between studies regarding the distribution of these changes [76]. Compared with their respective controls, individuals with adolescent-onset schizophrenia showed decreased fractional anisotropy in the parietal regions; individuals with adult-onset schizophrenia showed additional reduction of fractional anisotropy in the frontal, temporal, and cerebellar regions. A differential effect of age at onset (adolescent vs. adult) was noted bilaterally in the medial prefrontal white matter [77].

### Conclusion

Some scientists have criticized the diversity, complexity, and lack of consistency of imaging data; however this is directly related to the complexity of the brain. It is more gratifying to use images of the brain to look for specific neuropathology than to use it to search for

pathognomonic findings. Furthermore, future research will eventually confirm some of the findings, lead to reinterpretation of some other findings, and provide a radical change of contextual meaning, which should invite us to pause in our analysis of each study.

Different brain imaging techniques increasingly converge in the demonstration of certain abnormalities. These abnormalities delineate specific neural networks (such as those involving elements of the prefrontal cortex), which appear to be part of the underlying pathophysiology of mental illness. We must therefore believe that most of the data that is generated is gradually improving our base knowledge regarding how the brain works and how it is affected by pathological processes.

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# Neuroimaging of Post-stroke Depression

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## Introduction

Depression in patients with stroke represents a paradigmatic example of the empirical foundations of psychosomatic psychiatry: there is mental (specifically depressive) high morbidity in somatically injured patients, and there is inadequate detection and treatment; herein there are subsequent serious negative implications [1].

The frequency of depression in stroke patients has been well-documented by the pioneering group of Robinson et al. in Iowa [2]. Later, a meta-analysis offered a rather "conservative" figure of prevalence of approximately 33% in patients with stroke and concluded that there is an urgent need for further research to improve clinical practice [3]. The negative implications for quality of life and rehabilitation of patients with stroke and depression have been well-documented [4, 5], including increased mortality [6]. In support of the above, other authors [7, 8], the group of Iowa and our team [9], have reported the beneficial effect of early treatment of depression, including not only improvement in quality of life but also in physical rehabilitation. A reduction in mortality with antidepressant treatment has also been reported [10]. Early antidepressant treatment appears to enhance both physical and cognitive recovery from stroke and might increase survival up to 10 years following stroke [11].

Stroke represents a significant medical and social problem with a considerable prevalence (4.8%, 95% CI 4.47–5.21, from 65 to 84 years) and incidence (8.72 cases per 1000 person-years according to the EURODEM project of the European Union) [12]. Stroke is one of the leading causes, worldwide and in our country, of permanent disability and death [13]. The relevance of depression in stroke patients has also been reported during the ZARADEMP project. In a representative population sample ($N = 4.803$, > = 55 year-old) – and after logistic regression adjustment for other somatic diseases – a preferential association between stroke and psychic (often depressive) diseases was found [14].

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It has been suggested that there is an "organic" post-stroke depression, but the category has not been adequately validated. The International Classification of Diseases (ICD-10) and more specifically the DSM-IV-TR contemplate depression categories related to stroke, but there is very little documentation for validation. For instance, there is controversy about the possible overlap of post-stroke depression and the so-called vascular depression to which current studies with magnetic resonance imaging (MRI) appear to support [15, 16].

Most authors agree regarding the possible multifactorial origin of the depression in the post-stroke setting [17]. Some authors believe in the "organic" depression, especially for "major" depression [18]. They noted the frequent location of brain damage in the left frontal lobe and in the left basal ganglia [19]. More recent studies have supported this hypothesis, including a meta-analysis [20], and other contributions with MRI [21]. Others have strongly contested these findings, especially the left hemispheric location; they posit that post-stroke depression is mainly due to their relationship with psychosocial factors such as the disability that generates the cerebrovascular accident [22]. The dispute has not been resolved. We believe that new studies should focus on assessing depression during the first weeks after the stroke. It is in this period of time when an association between clinical and neuroanatomical findings has been more clearly found [23].

## Biological Techniques

Decreased heart rate variability is correlated with the risk and prognosis of depression after myocardial infarction [24]. It has been postulated as an indicator of changes in the sympathetic-parasympathetic system in major depression [25] and also as predictor of poor prognosis after a stroke [26].

Endothelial dysfunction has been linked to both depression [27] and the risk of stroke [28]. A number of studies have documented rather consistently elevated circulating cytokines in depressed patients [29] which can play an important role in the pathogenesis of symptoms [30]. Treatment with antidepressants is associated with normalization of immunological parameters in a number of relevant studies [31]. In a recent study, a total of 355 patients – who had experienced ischemic stroke – participated in inflammatory cytokine detection by ELISA; in addition they were tested for depression, quality of life (QOL), and body performance. Interleukin (IL-6) was positively associated with the risk of post-stroke depression and may predict its development in patients following ischemic stroke. Post-stroke depression correlates with patient outcome. Overall, an effective management of post-stroke depression may improve the prognosis of patients [32].

## Cerebral Neuroimaging Techniques

Computed tomography (CT) has been clearly inconsistent to clarify an association between depression and location of the lesion after stroke [33]. The first studies in depression post-stroke were conducted with MRI [19]. This technique may have a significant potential in this field: it has higher morphological definition than CT and can localize the lesions more accurately, providing better classification and size of the stroke, especially in deep gray matter structures.

Modern magnetic resonance neuroimaging such as functional MRI (fMRI), magnetic resonance volumetry, diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and also PET and SPECT imaging provide important insights into the etiology, pathogenesis, and therapy options of depressive disorders.

### Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT)

Depression was associated with increased hippocampal activity and decreased activity in the posterior cingulate and prefrontal cortex in 13 patients [34]. After 6 weeks of treatment, patients

who had responded to treatment showed a reversal of this pattern, whereas nonresponders continued to show abnormalities. Remission was also associated with decreased ventral frontal lobe metabolism, ventral anterior cingulate cortex and anterior insula activity, and increased dorsolateral prefrontal cortex metabolism [35]. It has been postulated that anterior cingulate cortex or amygdala activity was predictive of clinical response to antidepressant medication [36].

## Perfusion MRI

The bilateral subgenual anterior cingulate cortex, left prefrontal dorsomedian cortex, left anterior cingulate cortex, and left subcortical areas (putamen, pallidum, and amygdala) demonstrated statistically significant increased perfusion in the depressed patient group compared with the healthy control group [37]. This study, using arterial spin labeling (ASL) at 3 T (a safe perfusion technique that seems appropriate for the investigation of functional abnormalities in psychiatric disorders), confirmed the involvement of the subgenual anterior cingulate cortex in depression, particularly in patients with chronic and treatment-resistant depression.

## Functional MRI

Using functional magnetic resonance imaging (fMRI) paradigms, hypoactivity to fearful faces in the rostral anterior cingulate cortex (rACC) and hyperactivity in the limbic regions have been found in depressed patients [38]. Normalization of these abnormalities was correlated with remission of depressive symptoms [39].

Oxygen is delivered in a synchronous way to centers responsible for a specific brain process. That property can be studied by means of the resting state functional magnetic resonance. While the patient is at rest, a sequence detecting changes in oxygen delivery acquired during 7 min will be processed and reconstructed and finally show the synchrony in this patient and for a given function. After that, the patient's study is compared to a pool of normal controls obtaining a brain map with areas where there is abnormally decreased connectivity or increased connectivity with a chosen brain center.

Connectivity functional magnetic resonance imaging (fMRI) studies have also suggested a decrement in the "communication" between the amygdala and anterior cingulate cortex regions that could lead to a failure of the anterior cingulate cortex to serve its inhibitory role in emotional regulation [40].

It has been found modest evidence of amygdalar interhemispheric functional connectivity in non-depressed brain, whereas there was strong evidence of functional connectivity in depressed brain. This has been interpreted in the context of dysfunctional frontocortical – amygdalar interactions which accompany clinical depression [41].

Functional connectivity of the resting state yielded several results. The cognitive control network, the default mode network, and the affective network demonstrated increased connectivity to the same bilateral dorsal medial prefrontal cortex region (also known as the dorsal nexus) in depressed individuals as compared with controls [39]. Refractory depression has been associated with focused disruption of functional connectivity in the thalamocortical circuits, whereas nonrefractory depression has been associated with a widespread decreased connectivity in the limbic-striatal-pallidal-thalamic circuit [42].

## Morphometric MRI

Overall, functional studies point to changes in the basal ganglia, frontal cortex, and limbic system (hippocampus and amygdala) in depressive disorders. This is consistent with morphological alterations in regions of the brain related to emotions. There are quantitative magnetic resonance imaging (MRI) studies that provide a possible association between structural and biochemical substrates and severe drug-resistant major depression. A study showed that the volume of the left hippocampus was significantly smaller in depressed patients compared with controls, and

both groups exhibited significant hippocampal asymmetry (left smaller than right) [43].

The patients, but not the controls, had significant asymmetry of the amygdalar volumes (right smaller than left) and mesial temporal lobe. Some MRI studies have also reported anatomical abnormalities in the corpus callosum and its subdivisions in patients with major depressive disorder compared with healthy subjects. The patients with familial major depressive disorder had a significantly larger middle genu area compared to healthy controls and significantly larger middle genu, anterior splenium, and middle splenium areas compared to patients with non-familial major depressive disorder [44].

After a pioneering work reported an inverse correlation between the severity of post-stroke depression and the distance of the anterior border of the lesion to the frontal pole [45], several MRI studies have attempted to explore the neuroanatomical background of post-stroke depression. Unfortunately, there is conflicting data in this clinical setting. A systematic review offered no support for the hypothesis that the risk of depression after stroke was affected by the hemispheric location of the brain lesion or by the position of the lesion along the anteroposterior axis [46].

Infarcts in the hippocampus, basal ganglia, and frontal areas, as documented by MRI, have been classically associated with post-stroke depression [47–49].

Another study shows that depressive symptoms were found to be related to total brain white matter hyperintensities but not to basal ganglia hyperintensities in mid-adult life and that the physical disability appears to play an important role in this association [15].

Other authors found that the severity of affective depression was associated with left frontal lobe damage whereas apathetic depression was mostly related to basal ganglia damage [50]. In another study – including 95 consecutive autopsy cases of elderly patients with stroke and negative lifetime history of depression – [51] no relationship was found between the development of focal and multifocal vascular pathology in specific brain areas and post-stroke depression. Among demographic variables, only younger age at death was significantly related to post-stroke depression. This fact confirms that depression after stroke is also a predisposing factor for earlier death. An article proposed that depression after stroke may be related to cumulative vascular brain pathology rather than side and severity of a single stroke [52]. In this perspective, patients with chronic vascular burden could develop a post-stroke depression with a lower rate of spontaneous recovery and higher risk of chronic depression, whereas patients with a macrovascular stroke lesion could develop an early post-stroke depression episode with spontaneous remission.

## Diffusion Tensor Imaging

Microstructural changes in white matter can be revealed by specialized magnetic resonance imaging techniques such as diffusion tensor imaging (DTI). Diffusion tensor imaging is a sequence that senses the motion of water particles along the nerve fiber tracts. This characteristic is the base for the 3D reconstruction of the fiber tracts and makes possible the exploration of broken connections. Measures of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) are used to study the movements of extracellular water on the brain. Measurements are most likely related to the integrity of the cell membrane and its modulation by myelin [53].

Disruption of this connectivity can result in brain dysfunction manifested by impaired cognitive functions and the development of clinical symptoms.

Magnetic resonance T2 hyperintensities in the white matter are more common in elderly depressed patients than in control subjects, and they appear to predict poorer responses to antidepressant therapy [54]. On diffusion tensor imaging, there is higher apparent diffusion coefficient (ADC) and lower fractional anisotropy (FA) on these T2 hyperintense regions compared to normal regions of the brain. However, these diffusion characteristics do not appear to differ between depressed subjects and control subjects [55].

Using diffusion tensor imaging as well, it was found that fractional anisotropy was significantly lower and apparent diffusion coefficient was significantly higher in white matter tracts that connect to the emotional regulation (prefrontal lobe, frontal lobe, and limbic structures), in late-life depressed patients as compared with controls [56].

In geriatric depression, a decrease in white matter fractional anisotropy in multiple frontal limbic brain areas (including the rostral and dorsal anterior cingulate, dorsolateral prefrontal cortex, genu of the corpus callosum, white matter adjacent to the hippocampus, multiple posterior cingulate cortex regions, and insular white matter) relative to those who achieved remission has been observed [57].

## Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is the sequence that gave birth to MRI. The protons in the body have characteristic resonance frequencies, and those frequencies can be displayed in a graph showing the multiple metabolites in the brain. Differences in electronic shielding of the protons produce the different resonance frequencies recognized in the graph. This is a procedure that allows us to characterize in a safe and reproducible way [58] the level of in vivo local metabolites in brain tissue. Various markers are used, to include N-acetylaspartate (NAA) (neuronal and axonal viability and density), glutamate (Glu) (the highest stimulatory neurotransmitter) and glutamine (Gln), creatine (Cr) (a marker of brain metabolism), or choline (Co) which reflects cell proliferation and alteration of membrane [59].

Mood disorders are associated with structural, metabolic, and spectroscopic changes in prefrontal region. Specific patterns of MRS have been documented in affective disorders, such as decreased glutamate in the frontal lobe and hippocampus and increased choline/creatine in the basal ganglia [60]. MRS has also been used in the evaluation of depression in elderly patients with cardiovascular risk factors [61, 62].

In the case of depression associated with stroke, there is little information about the biochemical profile on MRS of the above-described brain regions. To our knowledge, only one study has evaluated the utility of MRS in patients with post-stroke depression [63]. In this study, depressed post-stroke patients were examined during the first 10 days. They found a significant increase in the glutamate/creatine ratio in the contralesional frontal hemisphere, compared to non-depressed patients. The same group found a significant reduction of N-acetylaspartate after 7–12 days of stroke in the right frontal lobe in patients with post-stroke apathy [64].

An astrocytic deficit may account for the alterations in glutamate/GABA neurotransmission in depression. Reductions in the density and ultrastructure of oligodendrocytes are also detected in the prefrontal cortex and amygdala in depression. Factors such as stress and glucocorticoids, variations in neurotropic factors or glial transporters, and changes in the extracellular levels of neurotransmitters released by neurons may modify glial cell number and affect the neurophysiology of depression [65].

We believe that due to its high sensitivity, MRS can be used for studying depression on post-stroke patients and also in elderly patients with psychosomatic alterations and/or cerebrovascular risk factors.

### Conclusion

Depression after stroke is considered a complex problem with potentially serious economic consequences for affected individuals as well as public healthcare systems. Magnetic resonance imaging appears promissory not only in the evaluation of structural abnormalities in this type of patients but also in the functional evaluation of the brain. Different cognitive networks, particularly the default network and limbic association areas, appear affected in depression to variable degrees. In addition, vascular changes (as evaluated by perfusion imaging) as well as white matter and metabolic alterations (as evaluated by DTI and MRS, respectively) can give insights into this important pathologic state and should

be the topic of further research. Thus, improving our understanding of post-stroke depression would benefit the prognostic and quality of life of our patients.

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# 32

# Locomotor Movement-Pattern Analysis as an Individualized Objective and Quantitative Approach in Psychiatry and Psychopharmacology: Clinical and Theoretical Implications

Svetlozar Haralanov, Evelina Haralanova, Emil Milushev, and Diana Shkodrova

## Introduction

Brain dysfunctions are considered to underlie mental disorders since the dawn of psychiatry as a science. However, for more than 120 years, all attempts to prove objectively detectable brain pathology at a single-subject level remain unsuccessful. Yet, it is revealed only statistically, by group comparisons between patients and healthy controls. In the everyday clinical practice, the diagnostic decisions and the monitoring of treatment effects are still based mainly on the patients' subjective reports about their subjective experiences. Although these over-subjective data are compared with the patients' objective (psychomotor and behavioral) expressions, the evaluation of the latter is also subjective, as it is influenced by the psychiatrist's qualification and clinical experience. Assessment of the treatment effects is even more subjective. In fact, it is based on subjective comparison between two consecutive subjective reports about the subjective states of the patient, which are subjectively compared with the subjectively evaluated changes in the patient's psychomotor and behavioral expressions. Even the commonly used rating scales for "objective" quantification of the wanted and unwanted effects of the pharmacological treatment do not solve the problem of over-subjectivity. These scales improve just the comprehensiveness and comparability of the evaluation but could not even get closer to the objectivity of the laboratory tests and instrumental measurements in the other fields of medicine and clinical pharmacology. Similarly to the clinical evaluation (on which they are actually based), the rating scales could be acceptably reliable and practically useful, but are not valid enough, since they are influenced by various psychological and social factors (such as simulation, dissimulation, placebo effect, conscious or subconscious psychotherapeutic influences), which could lead to erroneous conclusions and clinical decisions. The problem becomes even more important in case of the clinical trials of new psychotropic drugs, which are aimed at distinguishing the specific therapeutic effect of the medication from the

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nonspecific placebo effect. For that reason, new approaches for objective measurement of the brain and mental pathology, as well as its dynamics during treatment, are needed for use in the everyday clinical practice at an individual level. This need is expressed in the slogan of the 26th European Congress of Psychiatry (EPA 2018): "Integrate, Innovate, Individualize."

## Integrative Objective Quantification of Latent Brain Dysfunctions at an Individual Level

Above and beyond the traditional imaging and functional methods for direct detection and quantification of the existing brain pathology, indirect integrative behavioral methods for objective and quantitative recording of latent brain dysfunctions are developed in other fields of clinical neurosciences, like clinical equilibriometry. Instrumental equilibriometric methods serve for individual objective recording and measuring of the human equilibrium function during upright stance and bipedal locomotion in various neurological and vestibular disorders [1–4]. They are routinely applied for objective quantification of the individual brain and sensory-motor dysfunctions, which are presumed to lie behind the subjective vestibular symptoms (vertigo and dizziness), as well as for objective quantification of the antivertiginous treatment effects. Subjective vestibular symptoms are on the borderline between neurootology and psychiatry [5] and could be viewed as organic vestibular hallucinations [6–8] with underlying brain and vestibular dysfunctions, which are objectively manifested by equilibrium and locomotor dysfunctions. The latter are objectively measurable by instrumental equilibriometric methods that could also record and measure their changes during pharmacological, physical, or psychological treatment.

Cranio-corpo-graphy (CCG) is among the basic tools of clinical equilibriometry. It is a functional imaging method for objective recording, representing, and measuring the human equilibrium and locomotor functions by analyzing the head and body movements during the execution of static and dynamic equilibriometric tests, most frequently the static standing test of Romberg and the locomotor stepping test of Unterberger [1–3]. The original photo-optical CCG has been invented in 1968 by the German Professor of neurootology Claus-Frenz Claussen, who is the founder and long-standing President (nowadays Honorary President) of the International Neurootological and Equilibriometric Society, being among the creators of clinical equilibriometry as well. The method was based on Polaroid camera recording of the movements of four light markers (two on the head and two on the shoulders of the investigated person). Later on, in parallel with the development of new computer technologies, the CCG undergoes multiple improvements which make it very appropriate for screening examinations of the motor behavior in healthy individuals as well as in psychiatric and neurological patients with latent or manifest neuromotor and psychomotor disturbances [1, 4, 9–21]. The latest version of the method is the computerized ultrasound CCG, which is very simple to perform, reliable, reproducible, noninvasive, and not time-consuming (1 test = 1 min). Its principle is illustrated for the locomotor test of Unterberger, i.e., stepping in place with eyes closed, starting from Romberg's standing position (Fig. 32.1).

This method allows a very precise equilibriometric quantification of the human motor behavior during stepping locomotion. Among others, its great advantage consists in a computer database that simultaneously may detect and reconstruct the single traces of both the shoulder and the head markers. The technical precision of the computerized ultrasound CCG permits measurement of the acoustic impulse run time on a scale of a very small fraction of a second (50 msec), and a relative determination of the location of the source can be achieved at a sensitivity of 0.1 mm. Equilibriometric analysis is achieved by the well-established polar reference net. The head and shoulder movements then appear as the radar-like images of four moving objects, progressing in an interrelated direction. The computer program automatically measures the standard equilibriometric parameters and displays them on the screen. For the stepping locomotion they are: longitudinal displacement (cm), lateral sway (cm), angular deviation (degrees), and


**Fig. 32.1** Computerized ultrasound cranio-corpo-graphy of the locomotor stepping test

self-spin (degrees). Additionally, the computer program automatically measures and displays the number of steps and the movements of the head as compared with the shoulder movements, assessed by the head-torsion and head-nod angles (degrees). The graphical and numerical results are displayed on the computer screen, and their values are automatically compared with the normative data. Thus, immediately after the end of each test, it can be seen whether the parameters are pathological or within the normal limits. The results could be printed out in order to provide a hard document, called a cranio-corpo-gram. Together with the numerical data, the graphical images are also important for discriminating between normal and abnormal stepping locomotion. As an illustration, we demonstrate a prototypical normal stepping-test cranio-corpo-gram (Fig. 32.2):

To understand the information about the latent brain dysfunctions from the cranio-corpo-grams, it is important to know that due to the loss of visual feedback during stepping in place with eyes closed, the investigated subjects rely only on their vestibular and kinesthetic systems [1, 22, 23], which provide data to the cerebellum for coordinating equilibrium and locomotion [24, 25]. The frontal cortex, thalamus, basal ganglia, and other motor brain structures also play an important role [26] as well as psychological factors [27]. Due to biomechanical causes, the normal tendency for anterograde displacement of the body center of gravity leads to unconscious forward movement (propulsion). Normally there

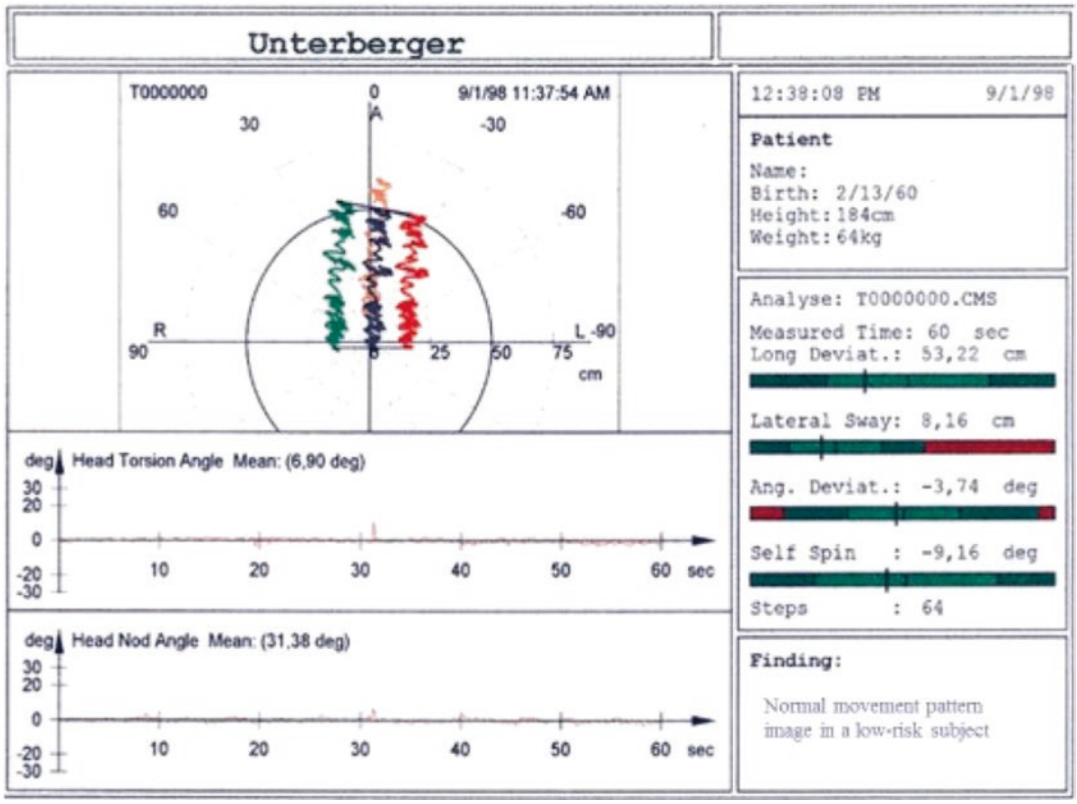


**Fig. 32.2** Prototypical normal stepping test cranio-corpo-gram in a healthy subject

could be mild left or right deviations, reflecting asymmetry in the bilateral motor coordination as a result of eventual underlying asymmetry in the integrative cortical or sensory (vestibular and kinesthetic) functions. Locomotor abnormalities are evident in comparison with the normal graphic images and numerical values. Their subsequent dynamic follow-up allows for objective and quantitative evaluation of any spontaneous fluctuations or experimental and therapeutic effects of various pharmacological challenges or treatments.

## Pioneering Application of Individual Objective Quantification in Psychiatry

For many years the routine medical application of CCG has been limited to the ambulatory neurootological practice, where it was used for objective quantification of vestibular and balance dysfunctions in vertigo patients and for objective monitoring of their antivertiginous treatment [1–3]. The method was also used regularly in the occupational medicine as a screening tool for subclinical detection of latent vestibular and balance dysfunctions in candidates to work at height. The CCG has not been applied in the clinical psychiatric practice until 1994, when our team (together with Claus-Frenz Claussen) for a first time began to use it for equilibriometric investigations in psychiatric patients, initially in association with our research on the mechanisms of their vertigo and dizziness complaints [3, 5–8, 28–32]. The idea at that time was to objectively quantify the supposed equilibrium and locomotor abnormalities and to compare them with the patients' subjective vertigo and dizziness complaints, in order to get information whether the latter are "functional," possibly due to psychological factors, or "organic," possibly due to brain and vestibular dysfunctions [5, 8]. Accordingly, our cranio-corpo-graphic investigations rapidly revealed that in anxious and depressive patients,

there is dissociation between the intensive and even dramatic subjective vertigo/dizziness complaints and the subtle or absent objective equilibriometric vestibular abnormalities [3]. On the contrary, we found different degrees of objective equilibriometric vestibular abnormalities in the majority of the investigated schizophrenic patients, even in those of them without subjective vestibular complaints [22, 23]. Besides, in a significant proportion of schizophrenic patients, we found a concomitant equilibriometric (subclinical) locomotor ataxia [11, 12, 22, 33–35]. Most of these equilibriometric locomotor abnormalities were not described until that time in the cranio-corpo-graphic literature and revealed the presence of subclinical motor and balance coordination deficits [33, 35, 37–39]. Having in mind the established data for subtle vestibular-kinesthetic-spatial diathesis in schizophrenia [8, 40–45], the revealed locomotor abnormalities could be explained in the light of the genetic concept of schizotaxia [33, 38, 46–48]. According to this concept, schizotaxia is the neurological phenotype of the schizophrenia genotype (schizogene) and is clinically manifested by subtle objectively detectable neurological (sensory and motor) schizotaxic signs. They are regarded as pleiotropic manifestations of the schizogene, which are closer to the presumed neural integrative defect (reduced neuronal selectivity or hypokrisia) than are the subjective symptoms of the personality phenotype (schizotypy) or the psychotic phenotype (schizophrenia). From such a point of view, the locomotor abnormalities, discovered by us, could be viewed as objective schizotaxic signs of hypokrisia, which are more direct objective (neurological) manifestations of the putative brain dysfunctions underlying schizophrenia than are the patients' subjective (psychiatric) symptoms. A prototypical schizophrenic cranio-corpo-gram is shown below in order to illustrate the remarkable difference (noticeable at first glance) of its gestalt image with reference to the norm (Fig. 32.3):

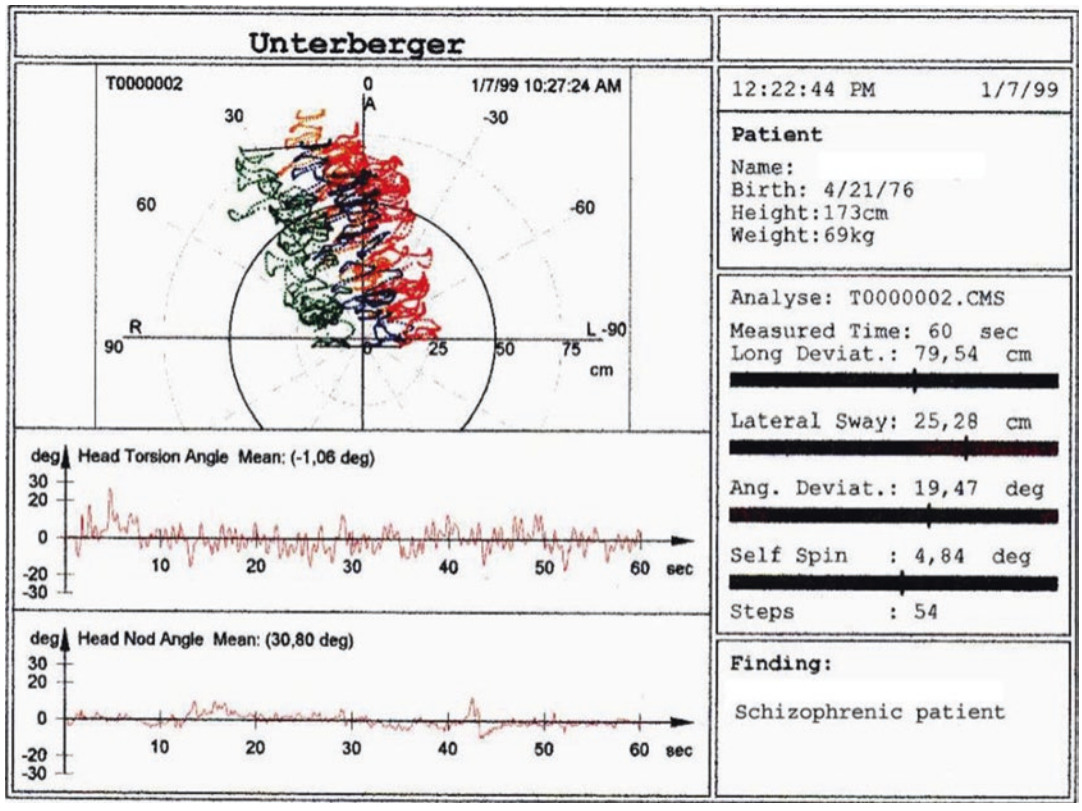


**Fig. 32.3** Prototypical stepping-test cranio-corpo-gram in a schizophrenic patient

Our further research discovered that the prototypical schizophrenic equilibriometric locomotor abnormalities are found not only in medicated but also in never-medicated and neuroleptic-free patients. This is illustrated by prototypical equilibriometric locomotor ataxia in a never-medicated schizophrenic patient (Fig. 32.4). As could be noticed, it is also easily distinguishable from the norm (Fig. 32.2):

The equilibriometric locomotor ataxia in treated and untreated schizophrenic patients proved to be rather similar, which suggests the existence of common mechanisms, eventually reflecting the underlying schizophrenic process in the brain, which are not resulting from the antipsychotic treatment. The relative specificity of the revealed subclinical (equilibriometric) locomotor ataxia in schizophrenia could be contrasted with a prototypical stepping-test cranio-corpo-gram in a depressive patient (Fig. 32.5):

It is obvious that the depressive cranio-corpo-gram is clearly discernible not only from the normal one (Fig. 32.2) but also from the schizophrenic cranio-corpo-grams (Figs. 32.3 and 32.4). On the other hand, it is in apparent contrast with the prototypical manic cranio-corpo-gram (Fig. 32.6):

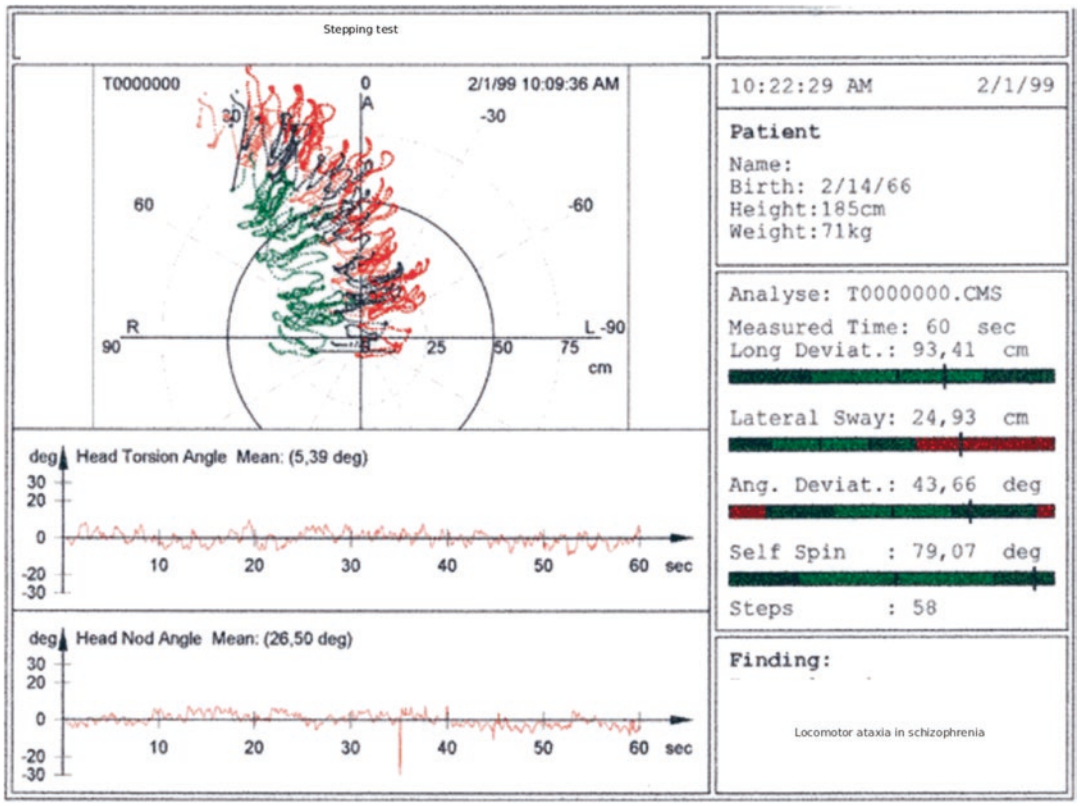


**Fig. 32.4** Prototypical locomotor ataxia in a never-medicated schizophrenic patient

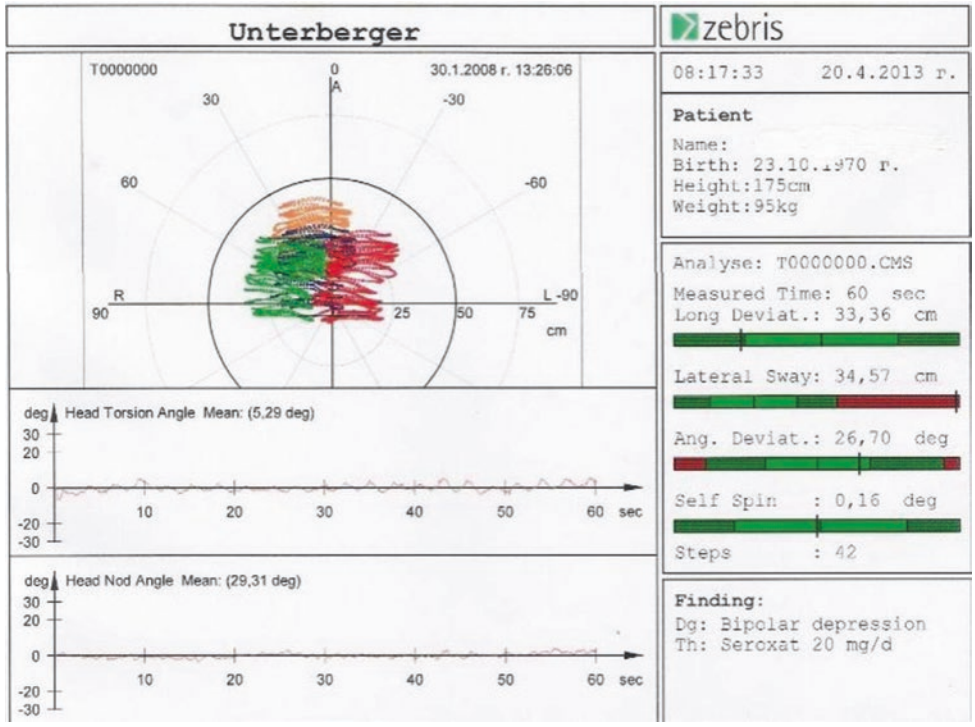


**Fig. 32.5** Prototypical stepping-test cranio-corpo-gram in a depressive patient

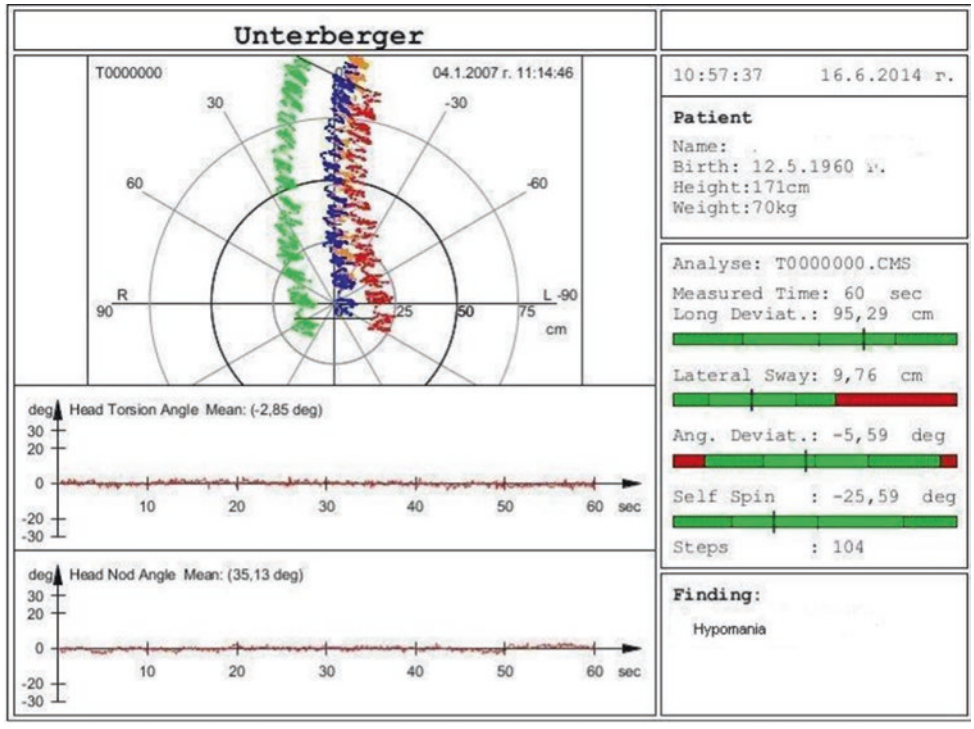


**Fig. 32.6** Prototypical stepping-test cranio-corpo-gram in a manic patient

## Objectively Measurable Locomotor Abnormalities in Psychiatric Patients

Comparing the prototypical schizophrenic, depressive, and manic equilibriometric locomotor abnormalities, we might analyze not only their relatively specific gestalt images but also the numerical values of the standard equilibriometric parameters. Our investigations have revealed that the parameter "longitudinal deviation" is typically associated with the degree of unconscious and automatic anteropulsion during stepping in place with eyes closed, which is *inhibited* in case of neuroleptic-induced or idiopathic Parkinsonism, reflecting the allegedly underlying mesocortical and/or nigrostriatal hypodopaminergia, as well as exogenous amygdala hypoactivation, both of them leading to decreased exogenous physiological and emotional arousal [3, 11, 14, 16, 49]. On the contrary, it is *disinhibited* in case of mesocortical, nigrostriatal and/or mesolimbic hyperdopaminergia, endogenous amygdala hyperactivation, and increased endogenous physiological and emotional arousal [3, 11, 14, 16, 49]. At the same time, the parameter "number of steps per minute" reflects the rate of conscious and volitional locomotor *activity*, which is accelerated or decelerated depending on the level of mesocortical, nigrostriatal, and/or mesolimbic dopaminergic neurotransmission, the level of endogenous or exogenous amygdala activation, and the level of endogenous or exogenous physiological and emotional arousal [3, 11, 14, 16, 49]. The parameter "lateral sway" usually reflects the velocity of unconscious and automatic locomotor *reactivity* aimed at maintaining the upright balance, which is increased or decreased depending on the high or low level of mesocortical, nigrostriatal, and/or mesolimbic dopaminergic neurotransmission. Large lateral sway (hypermetria) means more retarded unconscious and automatic locomotor reactivity, and vice versa, narrow lateral sway (hypometria) means hasty reactivity. We must note that particularly large lateral sway was revealed in patients with neuroleptic-induced or idiopathic Parkinsonism, suggesting its association with nigrostriatal and mesocortical hypodopaminergia [3, 11, 14, 16, 49]. More generally speaking, the combination among inhibited longitudinal deviation, decreased number of steps per minute, and enlarged lateral sway implicates bradykinesia and hypolocomotion, while the opposite combination among disinhibited longitudinal deviation, increased number of steps per minute, and narrowed lateral sway implicates tachykinesia and hyperlocomotion. Finally, the asymmetrical cranio-corpo-graphic parameters "angular deviation" and "self-spin" reflect the lateralization of the cortical control on the locomotion or unilateral vestibular dysfunctions. Their leftward deviations reflect left-sided vestibular or right-hemisphere brain hypofunction, whereas their rightward deviations reflect the opposite direction of lateralization [1, 3, 21].

Our data provide evidence that in schizophrenic, depressive, and manic disorders could be found different combinations of the locomotor abnormalities listed above. Comparing them with the prototypical normal stepping locomotion (Fig. 32.2), the following can be noticed:

1. Prototypical stepping locomotion in schizophrenia (Figs. 32.3 and 32.4) is more or less dysmetric and dysrhythmic (spatially and temporally dysregulated).
2. Prototypical stepping locomotion in depression (Fig. 32.5) is much more regular but with markedly decreased longitudinal deviation, decreased number of steps per minute, and enlarged lateral sway.
3. Prototypical stepping locomotion in mania (Fig. 32.6) is also relatively regular, but contrary to that in prototypical depression, it is with slightly increased longitudinal deviation, increased number of steps per minute, and narrowed lateral sway.

It could be said that, in general, the prototypical depressive and manic cranio-corpo-grams are *quantitatively* different from each other and from the norm. Prototypical depressive cranio-corpo-grams reveal decelerated rate of conscious and volitional locomotor activity, inhibited unconscious and automatic anteropulsion, and retarded unconscious and automatic locomotor reactivity,

i.e., subclinical *hypolocomotion*, involving a combination of hypoactivity and brady-reactivity. In contrast, prototypical manic cranio-corpo-grams reveal the opposite deviations from the norm: accelerated rate of conscious and volitional locomotor activity, disinhibited unconscious and automatic anteropulsion, and hasty unconscious and automatic locomotor reactivity, i.e., subclinical *hyperlocomotion*, involving a combination of subtle hyperactivity and tachy-reactivity. The prototypical schizophrenic cranio-corpo-grams, on the other hand, differ from both the depressive and manic ones, as well as from the norm, not only quantitatively but also *qualitatively*. In fact, they could be both with high or low activity and with fast or slow reactivity but at the same time typically remain more or less dysregulated with various degrees of spatial dysmetria and temporal dysrhythmia. Just this combination of spatial-temporal irregularities is the core of the subclinical (equilibriometric) locomotor *ataxia* in most patients with schizophrenia.

## Innovative Method for Objective Quantification of Locomotor Dysmetria and Ataxia

Since the prototypical schizophrenic locomotor abnormalities are markedly dysregulated in space and time (Figs. 32.3 and 32.4), their irregular or ataxic locomotor movement patterns (LMPs) are not satisfactorily measurable by the classical equilibriometric parameters [1–3]. Accordingly, they could be assessed on the cranio-corpo-gram only qualitatively, based on the gestalt image (Figs. 32.3 and 32.4). For such spatially and temporally chaotic LMPs, we have developed (together with Claus-Frenz Claussen) an innovative method, which is especially designed for their more precise quantification in psychiatric and neurological patients. It was recognized as an invention and was internationally patented [e.g., 50]. The novel method comprises much more detailed graphical, geometrical, mathematical, and statistical computerized analyses of the objectively recorded irregular (dysmetric and ataxic) LMPs [15, 34, 35, 36, 39, 51–58]. For the first time in the history of the CCG, a three-dimensional (3D) analysis of the stepping locomotion was introduced, together with the fourth dimension (time) and its derivatives (velocity and acceleration) for four-dimensional (4D) analyses. Besides the rectangular coordinates for fitting together spatial-to-spatial measures (as on the standard cranio-corpo-gram), additional spatial-to-time measures were introduced. The novel method differs from the standard CCG by shifting the focus from the gestalt graphical and numerical analyses of the equilibriometric locomotor abnormalities to the parameters of the separate steps (single-step analysis) and the comparison between them along the test. Its quantitative approach was based on the comparison of each separate step with the previous and the following ones. Different types of statistical analyses, like amplitude and frequency analyses, variation analyses, fractal dimensional analyses, histograms, and Fourier analyses were applied. Thus, after just 1 min of stepping locomotion, we have the opportunity to collect a huge amount of quantitative data. Their analyses discovered that in the prototypical schizophrenic locomotor abnormalities (Figs. 32.3 and 32.4), there are unpredictable (chaotic) fluctuations between hypermetria and hypometria of the consecutive steps (equilibriometric locomotor dysmetria), mainly due to dysmetric reactive (defensive) movements during the monopedal (swing) phase of the locomotor cycle (Fig. 32.1), which are trying to correct the anterior-posterior and medial-lateral sways and thus to prevent the falls. It turned out that the newly discovered locomotor *dysmetria* could be objectively measured by the degree of unpredictability of the quantitative parameters of every single step along the stepping locomotion. In such a way, it became possible to detect and measure locomotor and equilibrium coordination deficits [15, 34, 36, 37, 51, 54, 55, 57], which were not detectable and measurable on the standard cranio-corpo-grams. Unlike equilibriometric locomotor ataxia, which is manifested by more obvious locomotor abnormalities, being visible with naked eye on the standard (spatial) cranio-corpo-grams (Figs. 32.3 and 32.4), the equilibriometric locomotor dysmetria is a more subtle abnormality

that could be detected and measured only by additional mathematical and graphical analyses. In order to simplify its measurement and to make it practically easier, an empirically determined index was calculated to integrate the multitude of data from the computer analyses and to bring the results down into one single measure for every single marker during the stepping test [54–56]. It is called "equilibriometric dysmetria index" (EDI) and is calculated automatically by the original computer software STEMPA (Spatial-Temporal Equilibriometric Movement-Pattern Analysis), developed by our team [34–39, 50–58]. This software allows separate measurement of the data from the four markers in the 3D space (x/y/z), as well as a function of the time dimension (x/t, y/t, z/t), followed by serial comparisons between them. The measurements are made for each single step along the stepping test. In such a way, it becomes possible to detect and measure dysmetric LMPs in the movements of each separate marker, not only when they are grossly ataxic (visible with naked eye) but also when they are more subtle and discrete (difficult to distinguish with naked eye). By the value of EDI, it became possible to make quick (within few seconds) comparisons between different groups and subgroups of patients and corresponding healthy controls, as well as between multiple investigations of one and the same individual. Such comparisons allow making objective assessment of the existing locomotor irregularities and their extent of deviation from the norm, as well as of their subsequent natural or therapeutical dynamics. The objectively measured values of EDI have led to the separation of three logarithmically increasing degrees of equilibriometric locomotor dysmetria, normometria (EDI between 1 and 10), dysmetria (EDI between 10 and 100), and extreme dysmetria or ataxia (EDI between 100 and 1000), as illustrated below (Fig. 32.7) with prototypical individual examples from the three variants of LMPs, shown in a simplified version (in order to be more understandable for non-specialists), only for the frontal head marker and just in the 2D space (x/y – projection viewed from above),

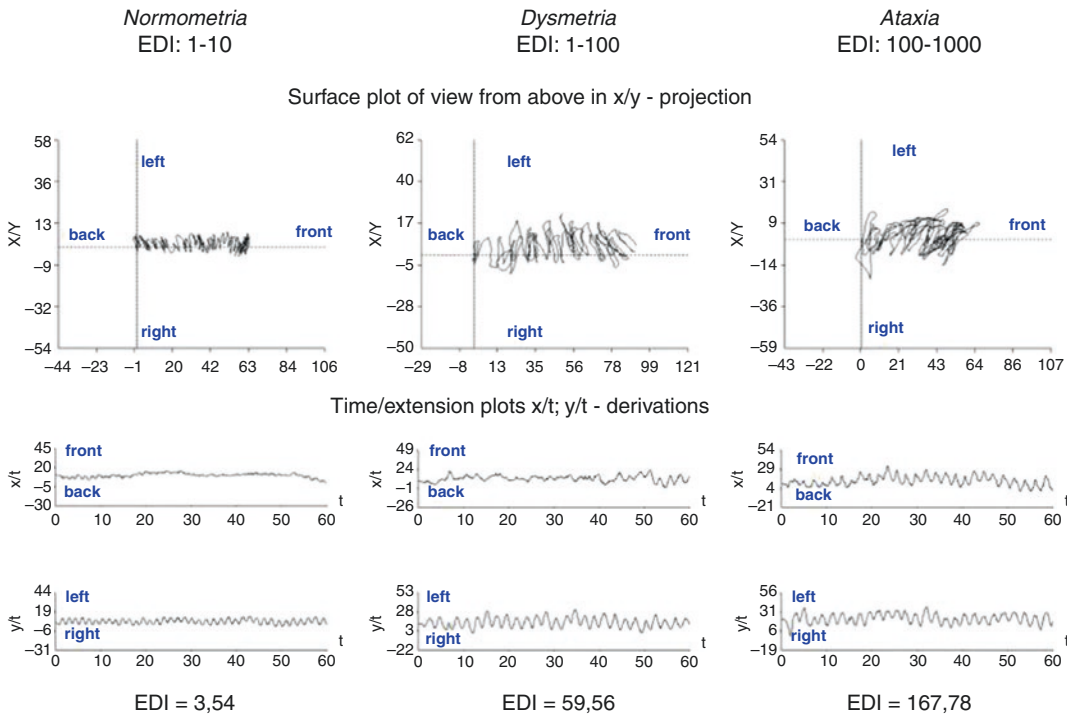


**Fig. 32.7** Individual examples of locomotor normometria, dysmetria, and ataxia

plus the two time-dimensional derivations (x/t and y/t). Graphical gestalts and numerical values of EDI could be contrasted at first glance.

## Prototypical and Atypical Locomotor Movement Patterns in Individual Patients

The automatic calculation of EDI by STEMPA provides a unique opportunity for quick (screening-like) differentiation between normal and abnormal LMPs, as well as between different degrees of severity of the individual locomotor abnormalities. The collected database permitted us to take a broad view on the investigated individual psychiatric and neurological patients, as well as low-risk and high-risk clinically healthy controls. This determined our conclusion that the normometric locomotion is prototypical for clinically healthy individuals, the dysmetric one for schizophrenic patients, and the ataxic for some more severe cases of schizophrenia, as well as for almost all neurological patients with clinically detectable locomotor ataxia, such as those with multiple sclerosis or cerebellar ataxias. We have to notice that, together with the irregular LMPs, some more regular LMPs could be found in the majority of the investigated psychiatric patients. As a rule they are objectively measurable by the classical equilibriometric parameters, discussed above. It turned out that analogous regular LMPs could be seen in some neurological patients as well, such as those with Parkinsonism. We demonstrated that the prototypical parkinsonian stepping-test LMPs [3, 13, 14] are graphically and numerically similar to the prototypical depressive ones (Fig. 32.5). On the one hand, this fact makes obvious that the equilibriometric evaluation alone is not sufficient to make inferences about the diagnostic category of the individual LMPs, but on the other hand, such trans-diagnostic similarities suggest a dimensional continuum among psychiatric and neurological diagnostic categories and their underlying neurobiological mechanisms. At the same time, the fact that abnormal LMPs are found sometimes in clinically healthy individuals (some of them being at high risk for developing psychiatric disorders, having first-degree relatives with such disorders) could be explained theoretically as a detection of latent locomotor (psychomotor or neuromotor) dysfunctions that might be predictive for future development of psychiatric or neurological disorders [15, 33, 35, 39, 52, 55, 59]. Such findings advocate for a possible continuum of LMPs between clinically healthy individuals and psychiatric, as well as neurological patients. On the other side of the coin are the intradiagnostic dissimilarities of the LMPs, which can help separate out subgroups within the same nosological category. For instance, we have found prototypical manic LMPs in a significant proportion of patients, clinically diagnosed as having a major depressive disorder, thus revealing a latent bipolarity in them [16, 17, 49, 60–62]. Analogous example is the finding of prototypical manic LMPs in some schizophrenic patients with systematized delusions of persecution and grandeur. Such a finding reveals a locomotor (neuromotor and/or psychomotor) continuum between manic and schizophrenic patients with dominating positive symptoms, which might explain their common treatment with antipsychotic drugs [11, 23, 33, 52, 55, 63]. Just the opposite is the finding of prototypical depressive LMPs in some schizophrenic patients with the syndrome of psychomotor poverty (with dominating negative symptoms). It reveals a locomotor (neuromotor and/or psychomotor) continuum between negative symptoms in schizophrenia, Parkinsonism, and depression [3, 11, 12–18, 22, 39, 49].

We may define the prototypical LMPs as typical for more than 50% of the members of a given diagnostic (psychiatric or neurological) category. However, they are not diagnostic biomarkers for that category, because (1) they are detected in most but not all individuals of the same clinical category and (2) they could be also detected in some (although not many) individuals from other clinical categories. For example, normometric LMPs are typical for clinically healthy individuals but could be also observed in some psychiatric

or neurological patients, e.g., in a state of medication-induced or spontaneous remission. On the other hand, such LMPs are not found in all clinically healthy individuals. In a small number of them could be detected abnormal (e.g., slightly hypometric, hypermetric, or dysmetric) LMPs. In such cases it could be suspected that there are locomotor (neuromotor or psychomotor) abnormalities, which are not clinically manifested, being subclinical or latent. Similarly, dysmetric LMPs are typical for the majority of schizophrenic patients, but not for all of them. A minority of schizophrenic patients in remission or in early prepsychotic states could be with prototypically normal LMPs, i.e., their locomotor dysmetria could be temporary compensated, thus becoming not only clinically but also subclinically latent. Another minority of schizophrenic patients could be with therapeutically compensated locomotor dysmetria, which is replaced by neuroleptic-induced Parkinsonism (with hypolocomotion and brady-reactivity). The situation is analogous for a minority of neurological patients with multiple sclerosis or cerebellar ataxias, whose locomotor ataxia could be therapeutically reduced to locomotor dysmetria and sometimes even normalized (exceptional cases of normometria in multiple sclerosis patients during therapeutical remission). Generally speaking, the most frequent type of LMPs for a given clinical category is considered prototypical, which is not equivalent to *diagnostic*, since many other cases (though minority) from the same category are with dissimilar types of LMPs. These cases are considered atypical for that category. At the same time, they could be prototypical for another clinical category. An example is the finding of prototypical manic or schizophrenic LMPs in some patients, who are clinically diagnosed to be with major depressive disorder. In such cases the actual presence of latent bipolar disorder or latent schizophrenia could be supposed. Their LMPs, which are atypical for depression, at the same time are prototypical for mania or schizophrenia, respectively. Likewise, the finding of prototypical depressive LMPs in some schizophrenic patients is atypical for schizophrenia, and then the actual presence of latent depression or latent Parkinsonism could be assumed. The principle is that within a given clinical (psychiatric or neurological) diagnostic category, various combinations of prototypical and atypical LMPs are possible, while some LMPs, which are prototypical for a given psychiatric or neurological diagnostic category, could be detected as atypical LMPs in other psychiatric or neurological diagnostic categories. Our data provide evidence that the treatment decisions in psychiatric patients are much more appropriate if they are guided by the objectively measured LMPs than by the subjective psychopathological symptoms [9, 11, 14, 19, 23, 36, 49, 53–58, 62, 64–72]. Such an objective and quantitative approach is in line with the modern tendency for personalized [73, 74] and precision [75, 76] medicine in the psychiatric research, aimed at replacing the pure categorical (nosological) approach with a more dimensional one [76–81] and to search for "theranostic" [82], rather than for diagnostic biomarkers [79, 81, 83]. It is interesting to note that just in the last few years, the motor dimension was proposed to be included in the neuroscience psychiatric research [77, 78].

## Objectively Measurable Dynamics of the Individual Locomotor Movement Patterns

The clinical importance of the discovered objectively measurable dysmetric and ataxic LMPs in schizophrenic patients is most understandable when we follow up their natural or therapeutical dynamics. Our longitudinal studies show that the objectively measurable locomotor abnormalities precede the clinical manifestation of subjective psychopathological symptoms of schizophrenia, but their severity markedly increases during psychotic decompensation and subsequently returns to its prepsychotic level after clinically effective antipsychotic treatment [23, 36, 52–58, 63–70]. Thanks to the objective quantification by EDI, this individual locomotor dynamics could be measured very precisely. Since the duration of stepping test is only 1 min and the calculation of EDI requires just a few seconds, each individual patient could be investigated unlimited number

of times to monitor the dynamics of its locomotor abnormalities. For illustrating the principle, prototypical examples for the main types of dynamics of schizophrenic locomotor dysmetria and ataxia are presented below (Figs. 32.9, 32.10, 32.11, and 32.12). The prototypical lack of substantial dynamics in a healthy individual is presented for direct comparisons (Fig. 32.8). The first investigation is always marked as D-0, the second one after 30 days as D-30, and the third after 60 days as D-60. For more understandable visualization, we present the data only for the frontal head marker and just in the 2D space (x/y – projection viewed from above) and the two time-dimensional derivations (x/t and y/t).

The different types of dynamics of the objectively measurable normometric, dysmetric, and/or ataxic LMPs, presented above (Figs. 32.8, 32.9,

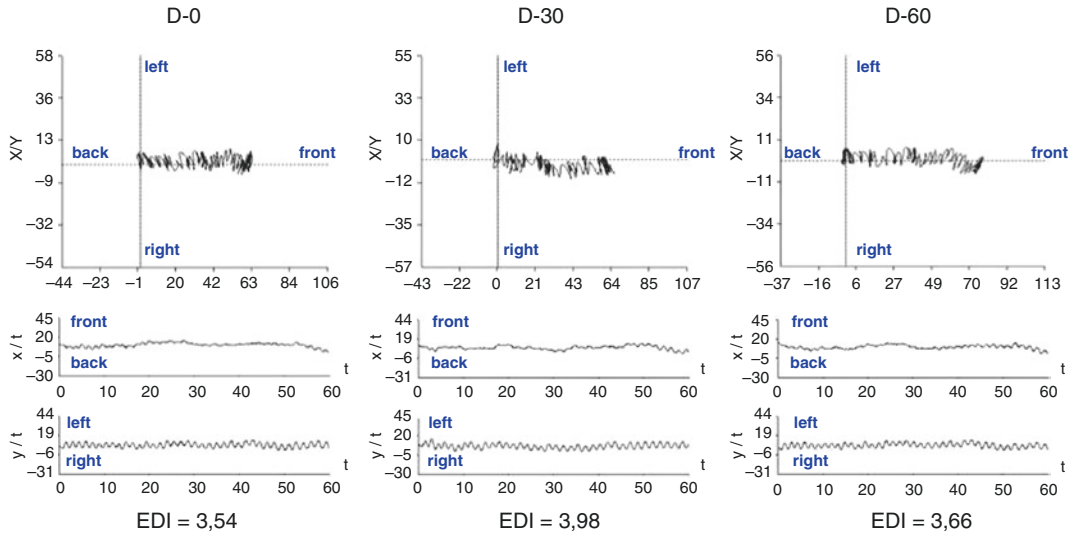


**Fig. 32.8** Lack of dynamics in the locomotor movement patterns in a healthy individual

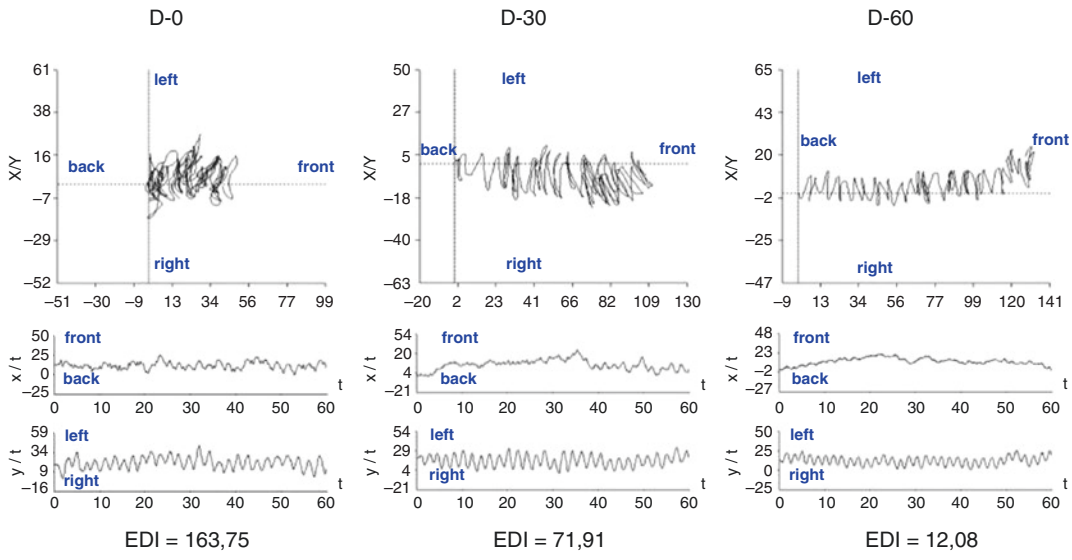


**Fig. 32.9** Dynamics toward therapeutic normalization in a schizophrenic patient

32.10, 32.11, and 32.12), could easily be integrated in one single illustrative diagram (Fig. 32.13).

In such a way, just with three consecutive investigations (each one for 1 min only) within 2 months of follow-up, we could grab at first glance the dominant tendency in the individual dynamics of the LMPs during antipsychotic treatment, compared with the normal lack of substantial dynamics in healthy individuals. In a similar way, we can integrate the subclinical dynamics of the objectively measured (by EDI) dysmetric and ataxic LMPs for a longer period in a state of post-psychotic clinical remission in a schizophrenic patient, followed up during maintenance antipsychotic treatment (Fig. 32.14).

Thanks to the automatic calculation of EDI, a quick identification of subclinical locomotor

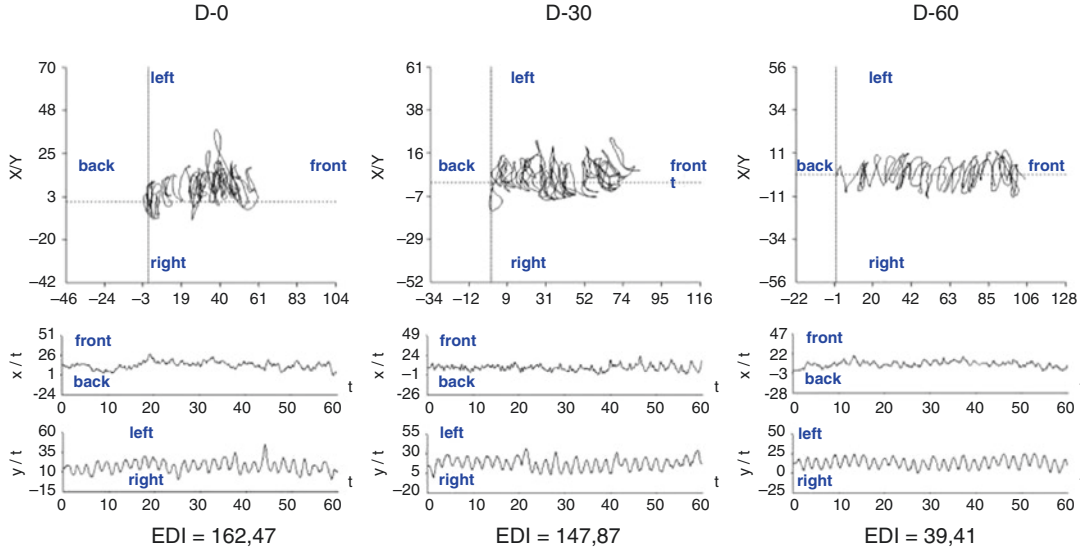


**Fig. 32.10** Dynamics toward therapeutic improvement in a schizophrenic patient

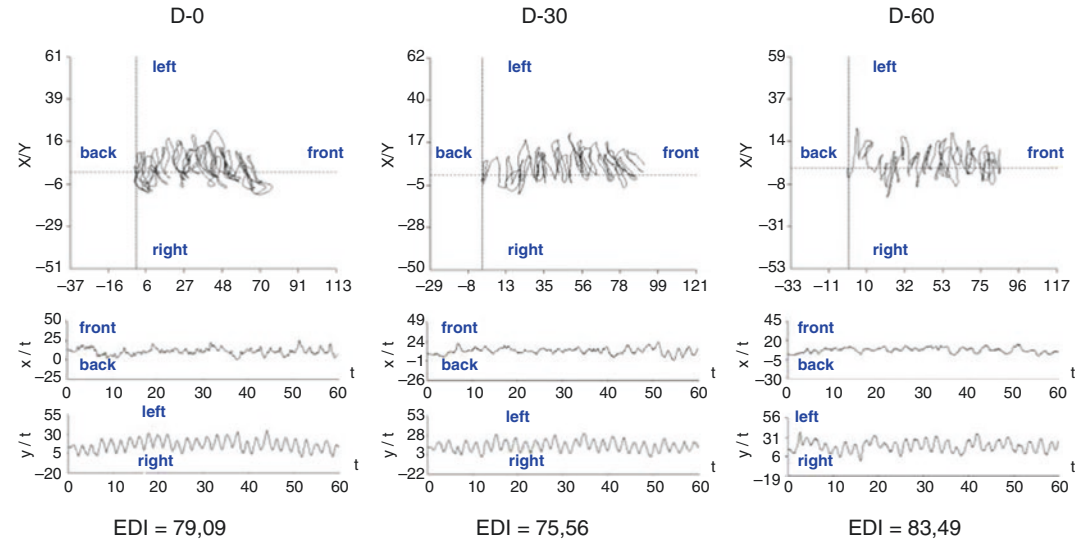


**Fig. 32.11** Lack of significant therapeutic dynamics in a schizophrenic patient

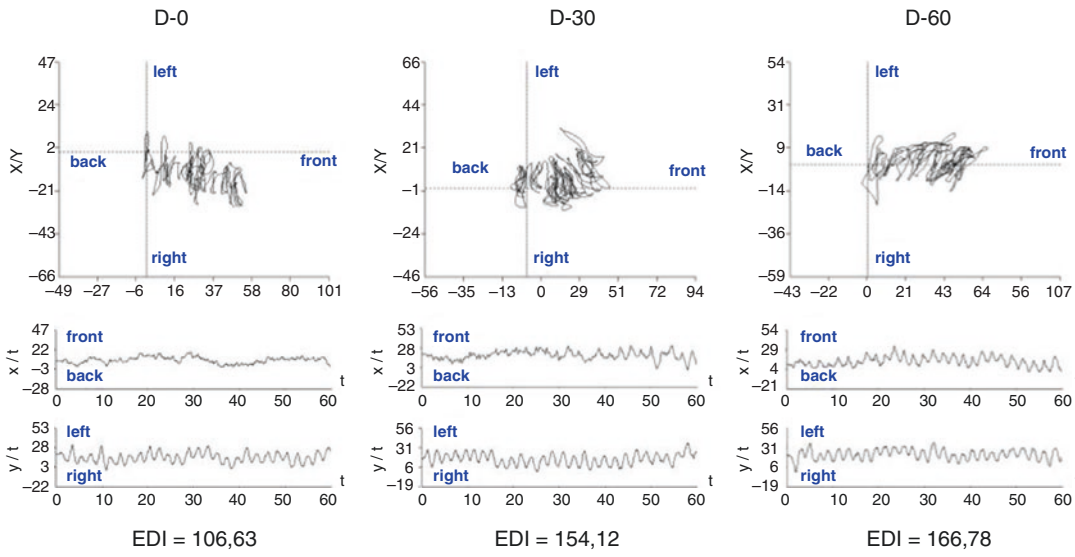


**Fig. 32.12** Dynamics toward worsening despite treatment in a schizophrenic patient

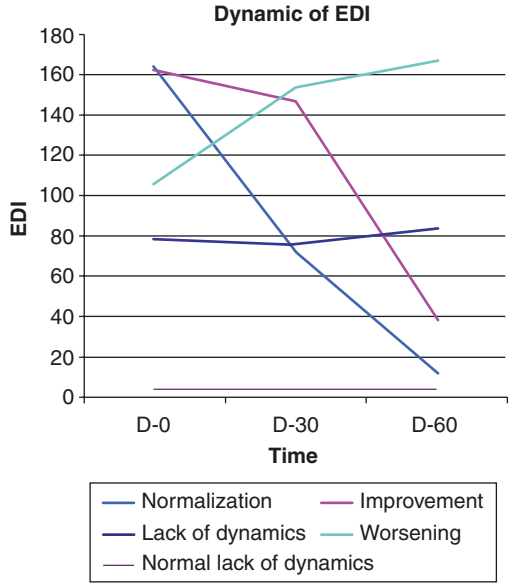


**Fig. 32.13** Integrative representation of the locomotor movement-pattern dynamics

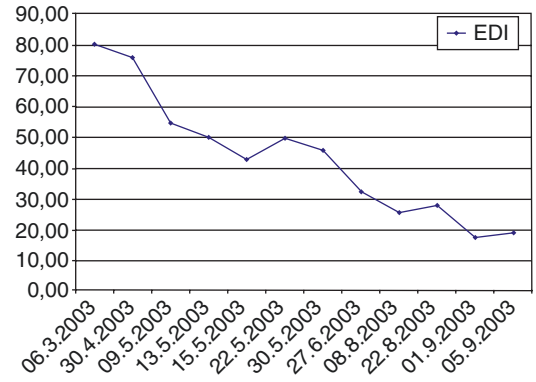


**Fig. 32.14** Improvement of the subclinical locomotor dysmetria in a schizophrenic patient during maintenance treatment

dysmetria and ataxia, as well as an integrative quantification of their severity, is possible. The short procedure allows to investigate unrestricted number of patients, their relatives, and healthy controls, as well as to follow-up their individual normal or abnormal LMPs. Results from the practical application of this innovative, integrative, and individualized approach in schizophrenic patients have confirmed our hypothesis that the objectively measured dynamics of EDI reflects the dynamics of the underlying schizophrenic process in the brain during its psychotic decompensation. It is manifested by the transitory intensification of the abnormal prepsychotic LMPs during florid psychotic episode and their return to the prepsychotic level in case of successful antipsychotic treatment. Thus, by the monitoring of EDI during acute or maintenance

antipsychotic treatment, we could objectively quantify the individual dynamics of subclinical locomotor abnormalities and compare it with the clinically assessed dynamics of the subjective psychotic symptoms in one and the same patient [53–58, 64, 67, 69, 70].

The accumulated results have made it evident that the dynamic follow-up of EDI reflects the objective neurobiological (neurochemical and neurophysiological) therapeutic effects of a given antipsychotic much more precisely and adequately than the subjective clinical evaluation of its impact on the patients' subjective psychotic symptoms. But we certainly do not intend to oppose the two approaches and prefer to combine and compare them. Theoretical analyses allow us to admit that both of them actually reflect different (complementary) aspects of the antipsychotic effects. For that reason we consider the parallel examination and subsequent comparisons between the clinical dynamics and the dynamics of EDI during the antipsychotic treatment to be the most effective and practically applicable pharmacodynamic approach in schizophrenia. Its advantages are due to the fact that the dynamics of EDI reflects the therapeutic effect not only on the objective psychomotor expressions [11, 12, 63] of the subjective psychotic symptoms, but also on the objective neuromotor neurological signs [11, 15, 35–39, 44, 46–48, 52–59, 64–70], which reflect the same objective neurobiological mechanisms that lie behind the clinical dynamics of the subjective psychotic symptoms. In other words, up to now, the monitoring of EDI could be considered as the most adequate objectively measurable surrogate pharmacodynamic biomarker of the antipsychotic treatment effect.

However, its application is not limited to schizophrenia. It is an integrative measure of the abnormal LMPs and their dynamics, which can be spontaneous, evoked (by external or internal challenges), and therapeutical. EDI is calculated in such a way that it can be used for objective treatment monitoring in other psychiatric disorders, like alcohol withdrawal syndrome [9, 19, 20] and major depressive episode [49, 62, 71, 72], as well as in some neurological disorders, such as neuroleptic-induced Parkinsonism [14], multiple sclerosis [4, 10, 51], and other movement disorders [13, 21].

## Further Individualization of the Locomotor Movement-Pattern Analysis

A single cross-sectional examination of the stepping-test LMPs in a particular clinical state (at a given moment of time) takes just 1 min, and it is informative enough for screening purposes such as to detect subclinical locomotor abnormalities in clinically diagnosed patients and their first-degree relatives with genetic high-risk, schizotypal individuals with clinical high-risk, and even healthy controls with latent predisposition to psychiatric or neurological movement disorders. However, in these conditions, the interpretation of the detected abnormal LMPs is not unequivocal. As we have already mentioned, some phenomenologically similar locomotor abnormalities could be found within diverse psychiatric and neurological diagnoses. Prototypical schizophrenic locomotor ataxia (Figs. 32.3 and 32.4) might be observed in some depressive or manic patients (though infrequently), in some clinically healthy first-degree relatives of schizophrenic patients (high-risk individuals), and in particular (exceptional) cases of healthy controls (supposedly with latent predisposition to psychiatric or neurological movement disorders). In principle, comparable (though more abnormal) ataxic LMPs were also found to be prototypical for almost all neurological patients with multiple sclerosis [3, 4, 10, 13, 39, 51] and cerebellar ataxias [21, 33–39, 59]. Likewise, prototypical depressive LMPs (Fig. 32.5) are also prototypical for psychiatric and neurological patients with neuroleptic-induced or idiopathic Parkinsonism [3, 11–18, 21, 49, 52, 60–62, 84, 85] and for non-psychotic schizophrenic patients with predominant negative symptoms [11, 23, 33, 39, 49, 52, 60, 63].

In order to distinguish among the phenomenologically similar LMPs with dissimilar neuromotor or psychomotor mechanisms, it was necessary

to create and apply novel tests for further individualization of the locomotor movement-pattern analysis by measuring their adjustment to specific challenging requirements and tasks. First, we introduced a modification of the standard stepping test, which requires stepping in place not only with eyes closed, but also with eyes open, with subsequent comparisons between both conditions. The results from those comparisons serve to explore the role of visual deprivation for the normal and abnormal stepping locomotion. Thanks to them it was found out that the opening of eyes usually results in marked locomotor improvement in almost all psychiatric patients with abnormal LMPs. On the contrary, in most neurological patients, there was no or minimal improvement in eyes-open condition. Later on, we developed tests combining stepping locomotion with motor (e.g., diadochokinesia) and cognitive (e.g., backward counting) tasks. In these dual-tasking (motor-locomotor and cognitive-locomotor) and multitasking (cognitive-motor-locomotor) stepping tests, the investigated subjects are required to divide their attention. Thus, a latent cognitive and/or motor vulnerability might provoke locomotor decompensation with emergence of dysmetric or ataxic LMPs, which permits to detect and record latent locomotor abnormalities even in patients and clinically healthy individuals who perform well on the standard stepping test. However, we were surprised to find out that increased requirements not always result in locomotor decompensation. In a minority of psychiatric patients, the locomotor abnormalities did not get worse but even improved or normalized during dual-tasking and multitasking stepping tests. Hence, it became possible to make a distinction between individuals who are prone to decompensate and individuals who show the opposite tendency – toward compensation of the existing locomotor abnormalities or in some cases toward their hypercompensation (with manic-like LMPs). In such a way, the newly introduced stepping tests provided an opportunity for more detailed individualization of the objective locomotor movement-pattern analysis. Its further individualization was achieved by multiple applications (at least twice) of the same locomotor tests in order to measure the dynamics of LMPs after a certain period of time (e.g., 1 month) or immediately after the first examination. In such a way, it became clear that the detected locomotor abnormalities in neurological patients are more stable and usually are persisting and long-lasting, especially in case of underlying organic disease, like multiple sclerosis or cerebellar ataxia. On the contrary, in most psychiatric patients, the locomotor abnormalities are more unstable, with a tendency toward spontaneous or therapeutic fluctuations within relatively short periods, sometimes within few hours.

During the last 20 years, we have gradually collected a huge database from cross-sectional and longitudinal investigations of more than 1000 psychiatric and neurological patients, their first-degree relatives, and appropriate healthy controls, part of them investigated multiple times in the course of days, weeks, months, and even years. Thanks to this database, now it is possible to compare the results from every single examination with those from the normative data and also with the previous results (whenever available) of the same individual. In such a way, it could be instantly determined whether the results are abnormal or are within the normal limits. In addition, comparison with previous results (when available) of the same individual could provide information whether there is improvement, worsening, or stability of the detected locomotor abnormalities. These comparisons are used by STEMPA to differentiate automatically between normal and abnormal LMPs, as well as among their distinct types of dynamics (spontaneous, therapeutical, or after experimental challenges).

## Psychomotor and Neuromotor Mechanisms of the Discovered Locomotor Abnormalities

Psychomotor activity encompasses all movements (facial expressions, gestures, gait, posture, overall behavior) reflecting, in one way or another, the mental state of both healthy and diseased persons at a given moment. It is an objective expression

of the subjective mental states. Clinically, a significant proportion of psychiatric patients express various psychomotor disturbances [11, 12, 16, 17, 49, 60, 61, 63, 71, 72, 84–95]. It could be stated that the psychomotor disturbances represent the objective side of the subjective mental pathology. They reflect almost all psychopathological states. Despite their objective character, in the everyday clinical practice, the psychomotor disturbances are still recorded and analyzed mainly subjectively, by means of clinical observation and description. Just in the recent few years, some motion analysis laboratories began to investigate them by objective instrumental methods as well [86–90, 92–93]. Therefore, we hypothesized that in many psychiatric patients, the abnormal LMPs, recorded and measured by CCG and/or STEMPA, essentially reflect psychomotor disturbances [11, 12, 16, 17, 49, 60, 61, 63, 71, 72, 84, 85].

Alternatively, a significant proportion of these abnormal LMPs (mainly in schizophrenic patients) might be explained by neuromotor dysfunctions [11, 15, 22, 23, 33–39, 52–59, 77, 78, 96–132]. They could be due to subtle brain dysfunctions, that particularly involve prefrontal cortex, cerebellum, and basal ganglia [15, 33–35, 37, 38, 47, 48, 52, 59, 77, 78, 96, 98–100, 106, 113, 121, 124, 125, 133–148], supposedly underlying the psychotic disorders. Most probably, these types of abnormal LMPs are subclinical equivalents of the cerebellar (neuromotor) neurological soft signs, which are commonly assumed to objectify the genetically determined schizotaxic brain dysfunctions at the level of motor behavior [33–39, 44, 46–48, 52, 59, 77, 78, 96, 116, 117, 119–124, 130, 131, 137–139, 142–146, 149, 150].

On the other hand, our analyses suggest that the subclinically detected abnormal LMPs with psychomotor origin are at least three distinct types. The first one is associated with the negative symptoms as psychopathological manifestations of the assumed disease process in the brain. This type of locomotor abnormalities is part of the clinical syndrome of psychomotor deficit (bradykinesia) in schizophrenic and depressive patients. Phenomenologically their prototypical abnormal LMPs (Fig. 32.5) are manifested as hypolocomotion and resemble those in patients with Parkinsonism [11, 14, 49, 52]. Correspondingly, they might be due to dopaminergic deficits (mesocortical and/or striatal hypodopaminergia). In contrast, the second type of abnormal psychomotor LMPs is strongly related to the clinical syndrome of psychomotor excitation (hyperactivity) and is manifested as hyperlocomotion. It is prototypical for the majority of manic patients and for some schizophrenic patients with predominantly positive symptoms (manifested clinically mostly as systematized paranoid delusions), without clinically manifested negative symptoms, whose kind of psychosis is usually defined as paranoia or paraphrenia. Phenomenologically their prototypical abnormal LMPs look like those in patients with mania (Fig. 32.6) and consequently could be due to dopaminergic excess (mesolimbic and/or striatal hyperdopaminergia). The third type of abnormal psychomotor LMPs could be viewed as a specific combination of the other two psychomotor types, but at the same time, it is phenomenologically equivalent to the dysmetric and ataxic LMPs, which are prototypical for the schizophrenic patients (see Figs. 32.3, 32.4, 32.7, 32.9, 32.10, 32.11, and 32.12), as well as for almost all neurological patients with multiple sclerosis [4, 10, 51] and cerebellar ataxias [21, 33–39, 59]. The fact that similar abnormal LMPs might be observed in psychiatric and neurological patients poses the question whether they are neuromotor or psychomotor disturbances. A more concrete answer could be provided with dynamic follow-up after appropriate treatment. Improvements of the abnormal LMPs in parallel with the clinical improvement (Figs. 32.9, 32.10, and 32.13) would be an indicator for their psychomotor origin. Conversely, eventual persistence or worsening despite the treatment (Figs. 32.11, 32.12, and 32.13) would suggest their neuromotor origin. The level of severity of the abnormal LMPs that is reflected in the value of EDI could also provide information whether they are psychomotor (EDI <100) or neuromotor (EDI >100). Future research, designed specifically to discriminate between psychomotor and neuromotor components of the abnormal LMPs, may provide more

detailed information. For the moment, we consider that the prepsychotic locomotor abnormalities in schizophrenia are of neuromotor origin, while their intensification during the active psychosis and their return to the prepsychotic level after successful antipsychotic treatment are due to superimposed psychomotor mechanisms. On the other hand, according to our clinical, experimental, and theoretical investigations, the majority of abnormal LMPs, revealed in depressive and manic patients, most probably are due to psychomotor disturbances. At the same time, the abnormal neuromotor LMPs in psychiatric and neurological patients could be subdivided into "functional" and "organic" ones, the former being more unstable and responding to drug treatment (such as neuroleptic-induced Parkinsonism), the latter being more stable and poorly responding to drug treatment (such as idiopathic Parkinsonism, multiple sclerosis, and cerebellar ataxias).

For improved differentiation between neuromotor and psychomotor mechanisms of the abnormal LMPs, it would be useful to apply not only the standard stepping test but also its new versions, discussed above. Besides, it might be beneficial to apply various additional experimental and therapeutic interventions, on the individual motor behavior. From a theoretical point of view, we might say that the abnormal neuromotor LMPs are more directly connected to the brain pathology that underlies the psychiatric illness, and therefore they are not mere consequences from the subjective psychotic symptoms. On the other hand, the abnormal psychomotor LMPs are objective (external) expression of the patients' subjective symptoms. From a chronological point of view, the abnormal neuromotor LMPs usually precede the subjective symptoms (except the neuroleptic-induced LMPs), while the abnormal psychomotor LMPs are behavioral consequences or external expressions of the subjective symptoms [11]. Finally, it is important to note that the psychomotor deficits in schizophrenia (leading to hypolocomotion and bradykinesia) are an objective expression of the primary negative symptoms and usually precede the first psychotic episode, whereas the psychomotor hyperactivity (leading to hyperlocomotion and tachykinesia) is associated with the psychotic symptoms. Our investigations also revealed that the prototypical schizophrenic dysmetric and ataxic LMPs usually precede the psychosis and are frequently detected in nonpsychotic first-degree relatives of patients. This fact brings them closer to the neuromotor disturbances. During psychosis they worsen (the value of EDI increases) but subsequently return to their prepsychotic level (the value of EDI decreases) in case of effective antipsychotic treatment. This transitory psychosis-associated dynamics brings them closer to the psychomotor disturbances. Therefore, we might conclude that the dysmetric or ataxic LMPs are composite (not only quantitatively but also qualitatively distinct from the norm) abnormalities of the motor behavior that combine simultaneously hypolocomotion and hyperlocomotion, as well as neuromotor and psychomotor disturbances.

## Clinical Implications of the Novel Approach in Psychiatry and Psychopharmacology

Undoubtedly, the most important advantage of the developed novel integrative and individualized approach to the psychiatric disorders and their treatment is its immediate applicability in the everyday clinical practice at the level of individual patient. The computerized ultrasound CCG (Fig. 32.1) is a user-friendly method, and every clinician might work with it, investigating his/her patients personally. Since a single test is only 1 min, even a battery of six different tests is not time-consuming. Our clinical experience shows that almost all psychiatric patients readily accept the execution of the tests and frequently compare them with physical exercises. The stepping test itself is nonverbal and very easy to perform. So, it does not require any serious efforts from the patients. With relatively few exceptions (limited to the most disorganized and severely psychotic or negativistic patients), the majority of psychiatric patients usually follow the instructions and cooperate adequately for the execution of the stepping test. Further individualization

might be achieved by its additional (eyes-open, dual-tasking or multi-tasking) versions or by following up the patient with consecutive examinations during the treatment (Figs. 32.9, 32.10, 32.11, 32.12, 32.13, and 32.14). The latter could detect subclinical tendencies toward improvement, normalization, or worsening (Fig. 32.13). Thus a large amount of individual data could be accumulated, which might help the clinician to take more adequate diagnostic and therapeutical decisions. As mentioned before, one of the basic clinical applications of the new method is to serve as an objectively measurable biomarker of the treatment effects, i.e., as a surrogate pharmacodynamic biomarker [9, 13, 14, 19, 49, 53–58, 62, 64–72]. It is already evidenced that the objectively measurable neuromotor and psychomotor disturbances more reliably reflect the neurobiological mechanisms of the psychiatric illness than the subjective symptoms [82, 89, 99, 123, 127]. The same is even more valid for the objectively measurable LMPs, which are more sensitive not only to the momentary state of the patient but also to its objectively measurable dynamics.

Other clinical implications of the developed novel approach are associated with the opportunity to make quantitative comparisons among distinct groups and subgroups of patients and healthy individuals, such as patients and healthy controls, patients with different psychiatric and neurological diagnoses, subgroups of patients within the same diagnostic category, one and the same patient in different clinical states, and even different subgroups or individual states of healthy controls. These comparisons could have various further practical applications in the clinical neuroscience, as well as in psychiatry and clinical psychopharmacology. The chance of detecting objectively measurable functional pathology at an individual level in psychiatric patients and healthy controls is an incomparable precedent for the psychiatric and psychopharmacological practice, having in mind that even highly sensitive and expensive neuroimaging methods for direct examination of the brain functions are not yet capable to detect specific dysfunctions at a single-subject level, at least in the real clinical practice. Detecting equilibriometric locomotor ataxia in individuals at high risk for developing schizophrenia provides an opportunity to reveal the underlying schizophrenic process in the brain long before its clinical manifestation by symptomatic psychosis. Thus the subtle locomotor abnormalities, recorded by CCG and measured by EDI, permit a novel objective approach to the early (prepsychotic) detection of subclinical neurological soft signs, which are widely considered to predict the conversion to full-fledged psychosis in predisposed high-risk or prodromal individuals [116, 117, 119, 120, 124, 131, 136–139, 142, 143, 149, 150]. On the other hand, the detection of abnormal LMPs in already diagnosed patients makes possible the objective and quantitative individual follow-up of their natural and therapeutic dynamics, even during non-symptomatic clinical remission (Fig. 32.14). As the assessment of dysmetric and ataxic LMPs is made easier by the automatically calculated EDI, its subclinical increase or decrease (or relative stability) might guide the treatment decisions in the absence of clinically manifested symptoms. It is also possible to follow up the subclinical dynamics of EDI in high-risk relatives of patients. Such an opportunity could be used for primary prevention of schizophrenic psychoses, as well as in genetic schizophrenia research by including latent (subclinically schizotaxic) forms of the illness within the same family. Longitudinal follow-up of already identified locomotor ataxia in nonpsychotic high-risk individuals provides an opportunity for early detection of the impending first schizophrenic episode or psychotic relapse. This is a prerequisite for taking timely preventive and therapeutic measures for avoiding (or at least delaying) the development of full-fledged psychotic episode and consequently a secondary prevention of its complications. When the psychosis is clinically manifested, the follow-up of its subclinical dynamics by the measuring of EDI during the treatment allows for objective and quantitative monitoring of the antipsychotic-treatment efficacy (Figs. 32.9, 32.10, 32.11, and 32.12).

Subgrouping of schizophrenic patients and their relatives, based on the type and severely of the detected locomotor ataxia and its dynamics,

gives a chance to compare the different subgroups with other methods for examining the brain and mental functions, including for revealing their genetic bases. This would also allow discovering more fundamental differences between the particular subgroups of patients, which lie behind their differently abnormal LMPs. As a result, the prevention and treatment of full-blown psychosis could be more differentiated and individualized.

The schizophrenic process in the brain becomes more accessible for objective examination and analysis through the abnormal LMPs regardless of its subjective psychotic symptoms or in parallel with them. However, unlike the subjective psychotic symptoms, the subclinical locomotor abnormalities are objectively measurable, nonverbal behavioral expressions of the disease process, which are not dependent either on the subjective report of the patient or on the subjective interpretation of the psychiatrist. Moreover, the subclinical LMPs are under the level of consciousness and thus are immune against simulation or dissimulation. From a neurobiological point of view, they are more reliable objective sources of information about the schizophrenic process in comparison with the subjective psychotic symptoms, although most informative are their parallel cross-sectional and longitudinal analysis.

Through the newly developed analyses and tests (discussed above), we hope that in the near future, it would be possible to better differentiate among patients with different endogenous (schizophrenic, manic, and depressive) psychoses as well as among psychiatric and neurological patients. For the moment, the subclinical detection of dysmetric and ataxic LMPs, despite the absence of clinically manifested signs and symptoms, indicates merely a high probability (risk) for early (latent) phase either of schizophrenia or of neurological disorder that determines ataxic locomotion (e.g., multiple sclerosis or cerebellar ataxia). Only the dynamic follow-up and the applications of other locomotor tests, beside the standard stepping test, would differentiate whether the detected dysmetric and ataxic LMPs are indicative of psychiatric (mainly psychomotor) or neurological (mainly neuromotor) movement disorders [52].

## Theoretical Implications of the Novel Approach in Psychiatry and Psychopharmacology

Empirical comparisons among the prototypical LMPs in schizophrenia, mania, and depression have discovered three distinct types of locomotor abnormalities. Two of them (in mania and depression) are quantitatively distinct from the norm and dichotomously bipolar, and the third one (in schizophrenia) is not only quantitatively but also qualitatively different from the norm. The prototypical manic LMPs reflect subclinical hyperlocomotion (comprising hyperactivity and tachy-reactivity), while the prototypical depressive LMPs reflect subclinical hypolocomotion (comprising hypoactivity and brady-reactivity). Theoretically, the former might be determined by mesolimbic and striatal hyperdopaminergia while the latter by mesocortical and striatal hypodopaminergia [49, 151]. Therefore, neuroleptics that are nonselective dopamine antagonists (like haloperidol) could effectively treat manic symptoms but are otherwise depressiogenic, whereas most antidepressants could effectively treat depressive states but are likely to induce manic and psychotic states. On the other hand, the prototypical schizophrenic LMPs simultaneously integrate elements from the other two (manic and depressive) types, frequently demonstrating a dissociation between locomotor hyperactivity and brady-reactivity, though other contradictory mixtures are also possible. Moreover, the schizophrenic LMPs are irregular and chaotic (combining hypermetria with hypometria of the separate single steps) and as a whole are manifested by disorganized amalgam of alternating hypolocomotion and hyperlocomotion, leading to subclinical locomotor dysmetria and ataxia. Although the dissociation between manic hyperactivity and depressive brady-reactivity might be explained by hypothetical dissociation between mesolimbic hyperdopaminergia and mesocortical

hypodopaminergia and chaotic alternation between striatal hyper- and hypodopaminergia, most of the dysmetric and ataxic LMPs might be further explained by underlying glutamatergic dysfunctions and altered brain connectivity, most probably due to impaired myelination [15, 33–39]. Apart from the qualitatively distinct dysmetric and ataxic LMPs (Figs. 32.3, 32.4, 32.9, 32.10, 32.11, and 32.12), the locomotor abnormalities in the prototypical schizophrenic patients reveal concomitant quantitatively distinct internal bipolarity between depression-like LMPs (Fig. 32.5), which are associated with negative symptoms and supposedly with underlying mesocortical and striatal hypodopaminergia, on the one hand, and mania-like LMPs (Fig. 32.6), associated with positive symptoms and supposedly with underlying mesolimbic and striatal hyperdopaminergia, on the other hand. Every single schizophrenic patient shows an individual mixture of prototypical schizophrenic, depression-like, and mania-like abnormal LMPs. Hence, it is not surprising that the reactions to antipsychotic and antidepressant drugs vary from patient to patient, but in principle it is more or less predictable by the LMPs of the individual patient. The combination between depression-like and mania-like abnormal LMPs within the prototypical schizophrenic LMPs suggests that their treatment might combine neuroleptics with antidepressants, which is actually achieved in most atypical antipsychotics [64–70]. It the light of our data, it is quite understandable that in the clinical practice, the atypical antipsychotics are effective not only in manic and schizophrenic but also in depressive (especially bipolar) patients.

Theoretically, the schizophrenic subclinical locomotor ataxia could be viewed as a kind of subtle or latent cerebellar ataxia, which is in line with at least three influential concepts for schizophrenia. According to the classical genetic concept of schizotaxia as a pleiotropic neurological phenotype of the schizophrenic genotype [33, 38, 44, 46–48], most of the schizotaxic (soft neurological) signs might be associated with cerebellar dysfunctions, especially motor coordination and balance deficits. The term "schizotaxia" is a neologism, which is composed of two parts: "schizo-" and "ataxia," where the middle "a" is omitted for euphony, thus meaning "ataxia associated with the schizogene." So, from the point of view of the schizotaxia concept, the revealed schizophrenic subclinical locomotor ataxia could be viewed as a neurological (schizotaxic) expression of the primary synaptic neurointegrative deficit (hypokrisia) in the schizotaxic brain, which is predisposed or vulnerable to develop schizophrenia. Consistent with the concept of cognitive dysmetria [15, 34–38, 133, 134, 138, 148], the schizophrenic locomotor dysmetria and cerebellar neuromotor soft signs could be regarded as objective neurological expressions of the same dysfunctions within the cortico-cerebello-thalamo-cortical circuit that underlies the subjective schizophrenic symptoms. Very similar is the neurological concept of the cerebellar cognitive-affective syndrome in patients with cerebellar lesions [15, 34–38, 145–146]. According to this concept, such patients combine cerebellar ataxia and dysmetria with cognitive-affective dysfunctions that are clinically manifested by negative and positive schizophrenia-like symptoms. Schizophrenia is considered as a psychiatric version of the cerebellar cognitive-affective syndrome, i.e., with underlying cerebellar dysfunctions. Our findings also suggest that the schizophrenic dysmetric and ataxic LMPs are subclinical equivalent of the cerebellar soft neurological signs and more specifically of the balance and motor coordination deficits, which are often found in schizophrenic patients and in their first-degree relatives [15, 34–37, 98, 124, 131, 136–138, 142, 143, 149, 150]. After all, the objectively detected equilibriometric locomotor ataxia indirectly confirms that schizophrenia is a brain disease (affecting functional brain circuits involving the cerebellum). Thus, the cerebellar neurological signs are present in parallel with the psychotic symptoms (and regardless of them) as an expression of the same brain pathology. From the viewpoint of the locomotor ataxia, the schizophrenic process in the brain becomes accessible for objective examination and analysis, independently from the subjective psychotic symptoms, but with subsequent comparisons with them.

As we consider the discovered abnormal subclinical LMPs as a locomotor biomarker for early detection of psychiatric disorders and their subsequent treatment monitoring, such an approach includes our research findings within the modern neuroscience tradition of personalized biomarker research [73–83, 92, 93, 110, 111, 123, 132, 152], which is strongly associated with the classical translational animal research [83, 93, 110, 111, 132, 152–153]. Since the locomotor behavior is frequently used as an objectively measurable biomarker in animal models of psychiatric disorders [132, 152, 154], which serve for testing novel experimental treatments [153, 155–157], the discovered subclinical locomotor abnormalities could be viewed as a reverse translational human equivalent of the animal locomotor models [132, 152]. From these animal models, it is well-known that the experimentally induced hyperdopaminergia (e.g., by dopamine agonists) typically leads to hyperlocomotion. The latter is routinely used as a biomarker for testing and measuring the effects of novel candidates for antipsychotic drugs. By dampening the experimental hyperdopaminergia, the novel drugs should decrease and normalize the concomitant hyperlocomotion. In contrast, the experimentally induced hypodopaminergia (e.g., by dopamine antagonists) typically leads to hypolocomotion. Likewise, the latter is routinely used as a biomarker for testing and measuring the effects of novel candidates for anti-parkinsonian drugs. So, our clinical findings markedly correspond to those in the animal model literature. This parallel might be a reason to regard the discovered locomotor abnormalities as a translational human equivalent of the animal locomotor models for studying the dopaminergic dysregulation in the brain.

## Future Directions and Perspectives

Among the most important advantages of this clinically applicable, individualized, objective, and quantitative approach is the fact that it is easy to perform and nonverbal. So, it might be applied in various countries, and the databases from diverse laboratories could be compared and analyzed with the perspective to create a global database. The dysmetric and ataxic LMPs are much more precisely measurable subclinical equivalent of the cerebellar soft neurological signs in schizotaxia and schizophrenia. Therefore, they could be used as a novel type of behavioral biomarker for large-scale screening procedures, aimed at early prepsychotic detection of individuals, who are predisposed to develop schizophrenia or some neurological movement disorders (such as cerebellar ataxias or multiple sclerosis). As the method is noninvasive and very concise, the screening procedures could be applied at regular basis for large groups of young individuals in order to detect in them very early signs of subclinical locomotor abnormalities in order to take appropriate prophylactic measures to prevent their eventual progression toward clinically manifested psychiatric or neurological movement disorder. The good news is that the fast development of computer technologies creates new opportunities for more precise and wireless recording and measuring of the locomotor abnormalities in psychiatric and neurological patients. Every year the commercially available inertial biomarkers for ambulatory motion analysis become more and more miniature, lighter, and cheaper, which makes their clinical application for non-restricted ambulatory motion analysis very promising [87, 158–164]. In the near future, the locomotor movement-pattern analysis could be accessible in every psychiatric clinic, ambulatory, or private office. New types of markers for detecting and measuring LMPs would allow additional improvement of its individualization for the aims of the modern personalized and precision psychiatry [73–76, 81, 82]. One such potential development would be to upgrade the sensitivity of the method by additional markers that are placed at the arms and legs of the investigated subject (Fig. 32.1) with the intention of recording and measuring their abnormal movements during the stepping locomotion. This added information would permit to amplify the level of individualization of the novel objective and quantitative approach, since to date these concomitant movements are investigated only qualitatively, by clinical observation and evaluation. However,

we have observed typical abnormal movements of the patients' arms and legs during the equilibriometric recording of their LMPs, and these observations would theoretically and practically justify their future objective recording and measuring by additional markers.

## Conclusion

Thanks to the development of an original method for objective recording and quantitative analysis of the equilibriometric LMPs, we discovered prototypical locomotor abnormalities, which suggest the existence of three axial locomotor continua among healthy individuals and psychiatric and neurological patients. The first one is subclinically manifested by hypolocomotion, supposedly determined by mesocortical and striatal hypodopaminergia. It is clinically manifested by depressive, negative schizophrenic, and parkinsonian symptoms. In contrast, the second one is subclinically manifested by hyperlocomotion, supposedly determined by mesolimbic and striatal hyperdopaminergia. It is clinically manifested by manic, positive schizophrenic, and hyperkinetic symptoms. The third type of locomotor continuum integrates the other two simultaneously and is manifested by disorganized mixture of alternating elements of hypolocomotion and hyperlocomotion, leading to locomotor dysmetria and ataxia. It is supposedly determined by a combination of mesocortical hypodopaminergia and mesolimbic hyperdopaminergia, as well as glutamatergic dysfunctions and altered brain connectivity, most probably due to impaired myelination, being clinically manifested by schizotaxia and cerebellar ataxia (both involving locomotor ataxia).

The discovered locomotor abnormalities proved to be valid behavioral biomarkers that could help the early detection of the respective psychiatric and neurological disorders, as well as to guide and objectively monitor their pharmacological treatment. Although some classical animal models have used hyperlocomotion as a behavioral biomarker of hyperdopaminergia and hypolocomotion as a behavioral biomarker of hypodopaminergia, this is the first attempt to employ the same interrelations in a human model that uses prototypical locomotor abnormalities as behavioral biomarkers. It is the first objective and quantitative method that allows early detection of brain dysfunctions and their subsequent treatment monitoring at a single-subject level in psychiatry and clinical psychopharmacology. Moreover, the method is successfully applied in the everyday clinical psychiatric practice as it is very cheap, concise, and user-friendly.

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# Schizophrenia: A Complex Mental Illness

33

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## Introduction

The history of schizophrenia can be traced back to the documents that were written by Egyptians in 2000 B.C. Many signs and symptoms of schizophrenia were also described in ancient Greek, Roman, and Chinese manuscripts.

However, schizophrenia was initially described by the German psychiatrist Emil Kraepelin (1856) who used the term "dementia praecox" to describe a new nosological entity based on the descriptions of Ewald Hecker and Karl Ludwig Kahlbaum, respectively. Kraepelin attributed dementia praecox to organic changes in the brain and distinguished at least three clinical varieties of the disease: catatonia, hebephrenia, and paranoia. In 1911 Eugen Bleuler introduced the term "schizophrenia" published in "Dementia praecox Oder Gruppe der Schizophrenien" to describe the disorder previously known as dementia praecox. He thought that it was more appropriate to term as "schizophrenia" whose meaning is "split mind." Since its initial description, many researchers were dedicated to the study of schizophrenia. Kurt Schneider (1887–1967) provided a characterization of schizophrenic symptoms, using clinical observations without considering progression and prognosis of the disease [1]. Subsequently, Gabriel Langfeldt (1895–1983) pioneered the diagnostic criteria for schizophrenia by describing procedures that led to the identification of "schizophreniform psychosis" as a different disorder than "true schizophrenia" [2]. Although both mental disorders could be accompanied by delusions, hallucinations, disorganized speech, catatonic behavior, and social withdrawal, it is worth noting that the impairment level and duration of the disorder are different [3]. Examining the response to drug therapy, Timothy J. Crow classified schizophrenic patients in two types. The type I develop psychotic symptoms and exhibit a good response to neuroleptic agents, whereas type II is affected by negative symptoms and have a bad response to atypical antipsychotic agents [4]. Another prominent neuroscientist and psychiatrist is Dr. Nancy C. Andreasen, who carried out the first quantitative magnetic resonance study of schizophrenia and developed the first scale to measure schizophrenia symptoms. She also conducted a study using neuroimaging and genomic techniques. Peter Liddle studied the patterns of the cerebral blood flow associated with three syndromes of schizophrenia: psychomotor poverty, disorganization, and reality distortion. Psychomotor poverty syndrome is associated with decreased prefrontal dorsolateral cortex perfusion, while disorganization syndrome and

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distortion of reality are associated with increased perfusion of the right anterior part of the cingulate and medial temporal lobe, respectively [5].

In recent years, the human brain has been described as a complex network of structural and functional regions that are interconnected. Thus, brain function is not only attributable to the properties of certain regions or connections, but it arises from the organization in the brain network as a whole, the "human connectome." Therefore, the brain dysfunction could be a result of abnormal connections of neuronal networks. The altered connectivity could lead to a system integrity reduction as well as changes in the brain dynamics, producing a lower integration of information in the different brain systems [6]. In conclusion, schizophrenia is now thought as a disconnection disorder of functional brain networks [7].

## Clinical Description

Schizophrenia is a mental illness characterized by psychosis, apathy, and social withdrawal in combination with the cognitive impairment that causes substantial changes in the patient's life. Among psychiatric disorders, schizophrenia is the most disabling disease that requires a large amount of health resources. New antipsychotic treatments were developed so that schizophrenics can lead a reasonably normal life. The estimated annual incidence is 0.2–0.4 per 1000, and the frequency of occurrence is similar in both sexes, although it is more benign and tends to appear later in women [8].

Schizophrenia is a complex disease characterized by three clinical symptoms: positive or psychotic symptoms, negative symptoms, and cognitive impairments. Firstly, a prodromal or clinical high-risk syndrome has been described in which a young person manifests attenuated forms of delusions and hallucinations, associated with a high risk for conversion to full psychosis within a few years. Among the individuals who convert, approximately 80% of the diagnostic outcomes are found in schizophrenia spectrum, and the remaining 20% are related to mood disorders and atypical forms of psychosis [9, 10]. It should be noted that positive symptoms occur as outbreaks throughout the patient's lifetime, while negative symptoms are described as a reduced basic behavior in the course of the pathology. Cognitive impairments are described as attentional disturbance and alterations in concentration, memory, and operational function alterations. Negative symptoms and cognitive disorders impact the patient's social life since the patients may be exposed to alcoholism, substance abuse, or post-traumatic stress disorder resulting in a high suicide rate (calculated at 5%) and accident risks [8].

An experimental approach has been applied to study the most relevant symptoms of schizophrenia. Delusional perception is studied as representative of positive symptoms, while affective flattening is used to examine negative symptoms. Cognitive impairments are studied by impairment of working memory and acquisition deficits. All these researches lead to the implication of glutamatergic neurotransmission in the nucleus accumbens septi (NAS), another brain structure involved in schizophrenia [11].

*Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)* is an American Psychiatric Association publication that describes the following schizophrenia subtypes: paranoid, disorganized, catatonic, undifferentiated, and residual type. However, *DSM-V* (2013) modified the method of classification since it decided to joint all these categories in a single heading: schizophrenia. Therefore, an individual has to manifest at least one of the following symptoms—delusions, hallucinations, and disorganized speech—to be diagnosed as a schizophrenic patient. Schizophrenia is considered a spectrum disorder represented by symptoms that occur in a continuum and certain characteristics shared across the spectrum in which these symptoms are manifested in markedly different forms and degrees [12].

## Etiology

Schizophrenia is a neurodevelopmental disorder which is the result of multiple factor interactions such as viral illnesses during pregnancy,

environmental agents, immunological dysfunction, or obstetric complications. The neurodevelopmental theory states that patients acquire schizophrenia from an immature brain injury that results in abnormal neuronal growth and damage. The subsequent psychotic outbreaks can originate a neurotoxic phenomenon, so the disease is now considered both neurodegenerative and neurodevelopmental disorders [13].

Then schizophrenia may be produced by prenatal factors which are pathological situations that occur in the second trimester of pregnancy, a crucial period of maturation and differentiation of the primitive CNS. In addition, perinatal factors that are obstetric complications during the birth also predispose to schizophrenia**.** Social factor can lead to schizophrenia in vulnerable patients, who have a genetic basis for disease development, for instance, patients with a family history of psychosis and urban residence as a social factor [14, 15].

The gene loci 22q11–13, 6 p, 13q, and 1q21–22 are linked to different neurological functions, i.e., genes that regulate the biological system at the molecular level [16]; a single gene does not encode for schizophrenia, but many genes would be involved in forming a chromosomal basis of risk for developing schizophrenia [17].

Several lines of evidence have confirmed that catechol-o-methyl transferase allelic variants (an enzyme which is involved in the metabolic degradation of cathecholamines, especially dopamine in the prefrontal cortex) influence significantly abnormal psychological performance of schizophrenic patients [18]. The breakthrough of specific synaptic dysfunctions in schizophrenia drives the attention to genes that encode synaptic proteins. DTNBP1 encodes dysbindin-1 protein, which is located within chromosome 6p22.3. Dysbindin-1 is a 40–50 kDa protein that binds to α- and β-dystrobrevin, both components of the dystrophin glycoprotein complex. Dysbindin-1 is located in postsynaptic densities in certain brain areas; thus any variation in DTNBP1 might confer risk of schizophrenia due to effects on postsynaptic structure and function [19].

Neurotransmission systems like GABAergic, glutamatergic, and dopaminergic are implicated in the schizophrenia, and their synaptic receptors are associated with G protein and regulated by RGS proteins, so that an alteration in RGS4 gene would be producing a significant decrease in cortical RGS protein level in schizophrenics [12]. The World Health Organization (WHO) has studied the incidence of schizophrenia in several countries. The stress produced by the impossibility of accessing to a mental health system is a problem that affects at about 50% of schizophrenics.

In general, schizophrenics do not receive an adequate treatment because they are less disposed to seek medical assistance or cannot afford their treatments (therapy drugs, psychotherapy, etc.) [17]. In terms of neurodevelopment, schizophrenia is considered as the result of a complex interaction between genes that contribute to the risk and genes that offer protection, added to environmental factors that are expressed in the course of the development. Therefore, the environmental factor can modify genetic basis; thus the interaction between genes and environment could be involved in the genesis of psychosis [20].

Schizophrenia and other major psychiatric disorders are also associated with abnormalities in multiple epigenetic mechanisms, resulting in altered gene expression during development and adulthood [21]. The epigenetic mechanisms are modifications that occur in the genetic material that do not change the nucleotide sequence but instead may cause modifications in DNA conformation. Thus, epigenetic deregulation of the genome and direct CNS injury are probably the main mechanisms to mediate prenatal environmental effects, whereas postnatal risk factors (e.g., stress, cannabis use) may also affect risk via use-based potentiation of vulnerable CNS pathways implicated in schizophrenia [22].

Three epigenetic modifications, DNA methylation, histone modification, and regulation by noncoding RNA, have been described, but the most used epigenetic mechanism in animal models of schizophrenia is DNA methylation. In mammalian cells, DNA methylation occurs in the 5′ position of the cytosine residues that precedes a guanosine in the DNA sequence, called the CpG dinucleotide which are mainly present of the gene

promoter; in general CpG islands are hypo- or unmethylated in normal cells and allow for the active gene transcription. DNA methylation is a crucial step to gene expression or gene silencing preventing or promoting the recruitment of regulatory proteins, such as nuclear co-regulators and transcriptional factors. L-Methionine (MET) administration to patients produces the worsening of psychotic symptoms, which were reproduced in MET-induced mice [23]. L-Methionine supplementation in rats induces epigenetic variations including reelin promoter hypermethylation in offspring [24]. Schizophrenia has also been associated with a global increase in microRNAs (miRNAs) biogenesis and expression in the cerebral cortex [25].

## CNS Areas and Neurotransmission Systems Involved in Schizophrenia

Anatomical and functional modifications were studied by magnetic resonance imaging performed for patients at the onset and chronic stage of the disease. The results indicated that there was no correlation since these modifications have been occurring in different brain regions. The antipsychotic treatment produces a clinical improvement, but the functional modifications are maintained throughout the patient's lifetime.

A recent research has focused on changes in neuronal connectivity and microcircuits of cortical layers that show an increase in clustered neuronal groups and a decrease in the density of neurophil and dendritic spines in the pyramidal neurons of the prefrontal cortex [26]. The prefrontal cortex is a cerebral region involved in the executive function's performance, being deregulated in schizophrenia [27, 28]. For this reason, working memory tests and imaging studies in simultaneous was used to demonstrate that schizophrenics were unable to complete these tasks, whose results were interpreted as a deficit in the prefrontal cortical activity or hypofrontality [29]. Dopaminergic transmission in the prefrontal cortex is mainly mediated by D1 receptors; thus D1 dysfunction has been linked to cognitive impairment and negative symptom of schizophrenia [30]. Additional researches have proved that prefrontal cortex remains hyperactive, not resulting in a possible further activated [31]. The hippocampus is another area that remains hyperactive [32–34], and this hippocampal hyperactivity has perfectly correlated with psychosis [35]. Therefore, the psychotic features of schizophrenia can be driven by abnormally heightened hippocampal activity.

In fact, basic studies have reported that the activated hippocampus leads to a hyperdopaminergic state [36]. Initial evidence for GABAergic hyppocampal abnormalities came from studies that showed a decrease in the number of GABAergic interneuron in schizophrenia. Furthermore, it has been disclosed a reduction in gene and protein expression of somatostatin-positive and parvalbumin-positive interneurons involving to GABAergic system [37].

The basal ganglia associated with the prefrontal cortex are implicated in the motivation, emotion, and reward. The striatum is part of a motor circuit, its association with premotor cortex, motor cortex and other brain areas is involved in regulation of the motor and sensitive information. The afferent nerve fibers that come from the prefrontal cortex, the amygdala, the thalamus, the ventral tegmental area, and the substance nigra pars compacta arrive at the basal ganglia, whereas the efferent nerve fibers go to Globus pallidus and substantia nigra pars reticulata which are GABAergic structures and to the glutamatergic subthalamic nucleus that projects to the thalamus [38].

The cerebellar system is also implicated in schizophrenia because it is behaving like an adaptive regulatory system of the cerebral cortex and the brainstem. Normal subjects and patients have been subjected to memory tasks and positron-emission tomography (PET) studies that provide an accurate description of a memory circuit, which is made up to the prefrontal cortex, thalamus and cerebellum. In addition, these studies have proved that the brain areas involved in the circuit remain inactive in the schizophrenic patients [39]. The thalamus receives inputs of the reticular system, cortical areas, and the amygdala. Thus, impulses generated in the amygdala toward the frontal cortex come from the ascending pathway which is the inferior thalamic peduncle. The hyperdopaminergic state inhibits

to the thalamus, which leads to an increase in stimuli reaching the cerebral cortex producing the characteristic symptoms of schizophrenia [40]. Daniel R. Weinberger described a feedback of the cortico-subcortical circuit, highlighting the importance of dopaminergic activity of mesolimbic and mesocortical pathways [41].

The most accepted theory has been the dopamine hypothesis, although supporting evidence was indirect such as psychotic effect produced by dopaminergic agonists [42]. Over time, dopaminergic theory has been modified based on experimental tests that provide new data on the molecular mechanisms involved in the disease. Firstly, the dopamine receptor was involved; this idea arose from the discovery that antipsychotic drugs act as dopamine receptor antagonists [43] demonstrating the requirement for a dopamine receptor blockade to treat the disease [44, 45]. In a subsequent revised version, the main idea was that schizophrenia would be associated with a deregulation of dopamine transmission since it would be observed as a hyperfunction of the mesolimbic dopaminergic subcortical projections leading to D2 receptor hyperstimulation with the occurrence of positive symptoms. Then, coexistence of hyperdopaminergic and hypodopaminergic states due to an alteration of modulation of dopamine activity has been raised [46, 47]. This modulation depends on dopamine receptor interactions due to the existence of homeostatic regulatory mechanisms, which are involved in decreasing or increasing the number of dopamine receptors depending on the dopamine levels. Thus, an excess of dopamine concentrations into the synaptic cleft produces a dopamine receptor reduction, but the opposite occurs when dopamine concentrations are decreased. In normal conditions, certain stimuli such as stress produce a phasic dopamine release and a rapid uptake without the presence of the homeostatic mechanism described. However, during the rest the dopamine is released into the synaptic cleft in a tonic and sustained manner, activating the homeostatic mechanism and regulating dopamine receptor density. This tonic dopamine release would be maintained by cerebral cortex activity through cortico-subcortical glutamatergic projections, which lead to a suitable dopaminergic tone [47]. Subcortical dopamine deregulation observed in schizophrenia could be secondary to a prefrontal cortex failure [47–49]. Thus, Arvid Carlsson has described a model in which the prefrontal cortex modulates the midbrain activity by an activating pathway, which consists of glutamatergic projections toward dopamine neurons and the other inhibitory pathway constituted by glutamatergic projections toward GABAergic interneurons [43]. According to Grace's model, in schizophrenia exists a cortico-subcortical hypoglutamatergia with the diminish of tonic dopamine release resulting in a dopamine decrease in the synaptic cleft, and then a homeostatic mechanism of dopaminergic hypersensitivity is activated, producing the postsynaptic dopaminergic hyperactivity in response to a phasic dopaminergic activity [47].

Recently, Oliver Howes and Shitij Kapur (2009) have reported the version III of the dopamine hypothesis whose name is "the final common pathway" where the authors have hypothesized that multiple "hits" interact to result in dopamine deregulation at the presynaptic level. In addition, the dopamine deregulation is linked to "psychosis" rather than schizophrenia, and perhaps in the course of time, it will be about "psychosis proneness" [17]. Another neurotransmitter system involved has been the serotoninergic system, since hyperfunction of serotonin 5-HT2A receptors in schizophrenia has been reduced by the blockade of clozapine, an atypical antipsychotic agent which is effective to control negative symptoms [50].

Several neurochemical studies have demonstrated the existence of abnormalities in the cerebral glutamatergic transmission of schizophrenic patients, ranging from the reduction of glutamate levels in the cerebral cortex to modifications in NMDA, AMPA, and kainate receptor subunits located in the hippocampus, the medial temporal lobe, and the thalamocortical circuits. The hypothesis that glutamatergic system hyperactivity occurs in schizophrenia arises from the observation of psychotic states induced by NMDA antagonists such as phencyclidine (PCP) or ketamine. Thus, NMDA receptor inhibition predominately decreases the activity of putative GABA neurons but, at a delayed rate, increases the firing rate of the majority of pyramidal neurons.

NMDA receptors preferentially drive the activity of cortical inhibitory interneurons suggesting that NMDA receptor inhibition causes cortical excitation by disinhibition of pyramidal neurons. These findings support the hypothesis of NMDA receptor hypofunction, which has been implicated in the pathophysiology of schizophrenia, diminishing the inhibitory control of prefrontal cortex output neurons [51]. Dopamine D2 receptors can regulate glutamate release from cortico-limbic and cortical-striatal terminals due to their presynaptic location in these terminals. D2 antagonist can modulate the fine tune in the release of glutamate from key neurons in the cortical and limbic regions [52].

Several lines of evidence suggest that brain cholinergic neurons play an important role in schizophrenia, so modulation of cholinergic activity may represent a therapeutic benefit [53]. In particular, cholinergic neurotransmission has been involved in cognitive deficits associated with schizophrenia [54]. Several researches have shown that muscarinic acetylcholine receptor density is reduced in the prefrontal cortex, hippocampus, and basal ganglia [55]. Muscarinic antagonists produce psychotomimetic effects in schizophrenic patients, supporting the idea that the cholinergic system would be involved in the genesis of psychosis [56]. M1 acetylcholine receptors have an important role in regulating brain regions that are altered in schizophrenia. In this regard a single-nucleotide polymorphism in the M1 acetylcholine gene has been associated with prefrontal cortical dysfunction in schizophrenia. M1 acetylcholine receptors possess an allosteric site that can be activated by selective agonists producing certain cognitive benefits in schizophrenia [57]. AC42 is a small molecule that behaves as a selective agonist of the M1 receptor, since it binds to the ectopic/allosteric site and has no affinity for other muscarinic receptor subtypes. The alkaloid brucine is other example of M1 allosteric modulators. The M2 acetylcholine receptor is another attractive target since it has been involved in neuronal plasticity and cognitive process, but new agonist development is limited because the M2 receptor takes part both in central as in cardiac effects [58]. M4 acetylcholine presynaptic receptors are found in midbrain cholinergic neurons, which originate in the laterodorsal and the subpeduncular tegmental nucleus as well as pedunculepontine tegmental nuclei. Thus, they control acetylcholine release in the dopaminergic afferents that project to the nucleus accumbens controlling the hyperactivity of the dopaminergic mesolimbic pathway [53]. Acethylcholinesterase inhibitors produce an increase in endogenous acetylcholine, which can interact with muscarinic and nicotinic receptors. Canadian families of schizophrenic patients have shown that the M5 receptor gene in combination with α7 nicotinic acetylcholine receptor gene located in the cromosoma15q13 would be related to schizophrenia [59]. Single-nucleotide polymorphism of α7 nicotinic acetylcholine receptor gene [60] has been disclosed. The α7 nicotinic acetylcholine receptor is reduced in the hippocampus and dorsolateral prefrontal cortex in schizophrenic patients [61]. This reduction is relevant since α7 nicotinic acetylcholine receptor is densely expressed in parvalbumin GABAergic interneurons where it provides rapid cholinergic excitatory transmission. This suggests that any alteration in glutamate and acetylcholine transmission could lead to modifications in the effectiveness of the GABAergic neurotransmission [62].

Regarding neuropeptide systems, cholecystokinin (CCK) reduction is observed in the temporal cortex, the hippocampus, and the amygdala of schizophrenic brain. The somatostatin reduction in the hippocampus and substance P and vasoactive intestinal peptide (VIP) reduction in the amygdala and hippocampus of patients' brain are observed. It should be noted that CCK behaves as a co-transmitter that inhibits the dopamine release; thus in schizophrenia a reduced CCK level produces an increase in dopamine activity. Opioid peptides are related to the development of schizophrenia symptoms, such as auditory hallucinations, but the administration of opioid agonist or antagonist does not produce any clinical outcome [63].

Finally, neurotensin is found in rich areas of neuronal bodies and terminals on the dopaminergic system where neurotensin exerts the regulation of dopamine activity [64]. The effects of neurotensin occur when the peptide binds to receptors termed NTR1, NTR2, and NTR3; the NTR1 and NTR2 are receptors coupled to G

proteins and participate in the regulation of $Na^+$, $K^+$-ATPase, an enzyme involved in neurotransmission. However, neurotensin inhibitory effect on $Na^+$, $K^+$-ATPase has not been recorded in an animal model of schizophrenia, which is obtained by the administration of a nitric oxide synthase inhibitor during the postnatal period [65, 66].

It is known that dopamine receptors also belong to G-protein-coupled receptor (GPCR) family. These receptors can exist as monomers, dimmers, or higher-order oligomers which conform assembles with their peers (D1/D2 or D2/D3) and other GPCRs, ion channel receptors, tyrosine kinases receptors, scaffolding proteins, and transporters [67]. Neurotensin can reduce the affinity of dopamine D2 receptor (D2R) agonist binding sites, which correlated with its ability to counteract the DA agonist-induced inhibition of striatal DA and GABA release and to induce neuroleptic actions. NT produces via an antagonistic allosteric NTR1-D2R receptor-receptor interaction, a reduction in the D2R agonist-induced activation of Gi/o proteins, and β-arrestin-mediated internalization due to a biased modulation of the dopamine D2 receptor protomer [68]. These results have a therapeutic relevance for treatment of schizophrenia since they have indicated that NTR1 protomer in the D2R-NTR1 heteroreceptor complex can reduce D2R protomer signaling. Therefore, the development of NTR1 agonists and positive allosteric modulators would be considered as a relevant strategy for the design of new therapeutic drugs [69].

## Schizophrenia Treatments

Drug treatments for schizophrenia are based on the dopamine hypothesis concerning the symptoms of this disorder. Typical antipsychotic agents induce a nonselective dopamine D2 receptor blockade which produces side effects such as involuntary movements known as extrapyramidal effects and the increase of prolactin levels [70]. Atypical antipsychotic agents are better tolerable than typical antipsychotic agents, especially in relation to extrapyramidal side effects [71]. Iloperidone is a new atypical antipsychotic that received marketing approval for the acute treatment of schizophrenia [72]. Lurasidone is an antagonist of dopamine D2 receptor and serotonin 5-HT2A and 5-HT7 receptors and is a partial agonist of serotonin 5-HT1A receptor, reducing the risk of relapse after a long-term treatment [73]. Both aripiprazole and brexpiprazole are partial agonists of 5HT1A, D2, and D3 receptor and an antagonist of 5HT2A that produces a lower risk of extrapyramidal effects [74]. Paliperidone palmitate is a long-acting injection that can be used as an acute treatment even in an outpatient setting [75]. Asenapine is a new sublingual atypical antipsychotic drug that behaves as an antagonist at several dopamine, serotonin (5HT2A, 5HT2B, 5HT2C, 5HT6, and 5HT7), and alpha adrenergic receptors (α1 and α2). Asenapine has no activity at muscarinic receptors in the therapeutic dose range. Hence, it does not cause any anticholinergic adverse effects and metabolic syndrome but may produce weight gain and sedation due to histamine H1 receptor antagonist [76].

D3 dopamine receptor (D3R) is another pharmacological target that appears to play a role in the schizophrenia; hence, cariprazine is a partial D3R agonist that produces antipsychotic-like effects in preclinical animal models. Cariprazine was approved in 2015 by the US Food and Drug Administration for the treatment of schizophrenia. Cariprazine may also reduce the risk of dopamine-related adverse effects further due to its partial agonist effect on 5HT1A, which may reduce extrapyramidal symptoms and improve mood and cognition [71]. ALKS 3831 is a fixed-dose combination of samidorphan, a mu-opioid receptor antagonist, and the atypical antipsychotic drug olanzapine. The combination treatment uses the action of samidorphan to reduce the weight gain and metabolic adverse events associated with olanzapine while maintaining olanzapine's antipsychotic efficacy. MIN-101 is a first-in-class 5-HT2A and sigma-2 receptor antagonist in the same molecule. The blockade of serotonin 5-HT2A receptors reduces hallucinations, delusions, and movement disorders associated with schizophrenia. Moreover, sigma-2 receptor antagonism modulates dopamine transmission and improves the negative symptom control [77]. Recently, the N-methyl-D-aspartate (NMDA) receptor hypothesis of schizophrenia

has been validated in animal models and patients [71]. Phencyclidine (PCP) animal model of schizophrenia has been useful to study the disruption of the dopamine D4 receptor interaction in the prefrontal cortex where clozapine restored D4 receptor regulation of NMDA receptor in this animal model. New antipsychotic agents that are mGluR2/3 receptor activity modulators have been developed by schizophrenia treatment at an early stage. However, they failed to demonstrate clinical efficacy in this condition, and some of them produced centrally mediated side effects, limiting their routine use [78]. Lately, new generations of glutamate-enhancing compounds that allosterically enhance the functionality of mGluR2 have been discovered, and their effects are being evaluated [79].

The heavy users of cannabis as well as individuals who abuse with highly potent preparations of cannabis, which contain roughly 15% delta-9-tetrahydrocannabinol (THC), have an increased risk of schizophrenia. Differently, cannabidiol is a negative allosteric modulator of the cannabinoid 1 (CB1) receptor that reduces the psychogenic effect of THC and may possess antipsychotic properties [71].

## Conclusion

The study of anatomical, functional, and neurotransmission system modifications has been extensively performed to achieve a better understanding of schizophrenia and the possibility of developing new treatments.

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# 34 Melatonin and Benzodiazepine/Z-Drug Abuse

Daniel E. Vigo and Daniel P. Cardinali

**Key Points**

- The efficacy of BZD/Z-drugs in treating insomnia is hampered by adverse effects including dependence, and BZD/Z-drug abuse is becoming a public health problem.
- A limited number of studies support the efficacy of melatonin to curtail chronic BZD/Z--drug use in insomnia patients.
- A major advantage is that melatonin has a very safe profile and is usually remarkably well tolerated.
- Further studies on this application of melatonin are warranted.

## Introduction

Insomnia is a common disorder that includes unsatisfactory sleep, either in terms of sleep onset, sleep maintenance, or early waking. It is also a disorder that affects the day and subjective well-being, skills, and performance. Like pain, insomnia is a subjective disorder amenable of diagnosis through clinical observations rather than through objective measurements [1, 2]. Insomnia occurs despite having adequate opportunity for sleep, and it is associated with clinically significant distress or impairments of daytime functioning involving fatigue, decreased energy, mood disturbances, and reduced cognitive functions (e.g., attention, concentration, memory).

Factors influencing the persistence of insomnia include iteration of precipitating stress, anxiety about sleep, maladaptive sleep habits, or an intrinsic vulnerability of the neural mechanism for regulating sleep [3]. The diagnosis of insomnia is made when sleep difficulties are present three nights or more per week and last for more than three months. The diagnostic procedure for insomnia, and its comorbidities, should include a clinical interview consisting of a sleep history (sleep habits, sleep environment, work schedules, circadian factors), the use of sleep questionnaires and sleep diaries, questions about somatic and mental health, a physical examination, and additional measures if indicated (i.e., blood tests, electrocardiogram, electroencephalogram). Polysomnography can be only used to evaluate

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other sleep disorders if suspected (i.e., periodic limb movement disorder, sleep-related breathing disorders), in treatment-resistant insomnia, for professional at-risk populations, and when substantial sleep state misperception is suspected. Cognitive behavioral therapy for insomnia is recommended as the first-line treatment for chronic insomnia in adults of any age [2].

The general detrimental effect of insomnia on health has long been established. Epidemiological studies have shown that disturbed sleep – comprising short, low-quality, and mistimed sleep – increases the risk of metabolic diseases, especially obesity and type 2 diabetes mellitus [4] as well as neurodegenerative disorders [5]. Epidemiological studies have also identified an association between insomnia, especially with reduced or fragmented sleep, and increased rates of accidents [6] and falls in the elderly [7].

Epidemiological surveys indicate that up to 40% of individuals over 65 years of age are not satisfied with their sleep or report problems initiating and maintaining sleep and that 12–20% complain of persistent insomnia [8–10]. This leads to increased use of hypnotics for the elderly, which is a cause for concern [11]. Up to 30–40% of older people use sedative hypnotic benzodiazepines (BZD) and related Z-drugs and often show side effects of hypnotics due to both a greater sensitivity of the nervous system and decreased serum albumin that binds the drug. Thus, the older population responds to hypnotic drugs differently and less predictable than their younger counterparts [12, 13].

Many aged patients are treated for longer periods or with higher doses of hypnotic BZD/Z-drugs than those generally recommended. The failure to adjust the individual dose to the pharmacokinetic and pharmacodynamic changes caused by the progressive aging and comorbid medical problems can make treatment more difficult and potentially risky [14]. Thus, the chronic and widespread use of BZD/Z-drugs has become a public health problem which has led to campaigns to reduce their prescription, especially in Europe [15].

Several studies have shown the importance of melatonin both for the initiation and for maintenance of sleep [16–18]. In human beings the onset of melatonin secretion coincides with the timing of increase in nocturnal sleep propensity [19]. Since melatonin and BZD shared some neurochemical, i.e., interaction with γ-aminobutyric acid (GABA)-mediated mechanisms in the brain [20] and behavioral properties, e.g., a similar day-dependent anxiolytic activity [21], melatonin therapy has been postulated as a possible tool to decrease the dose of BZD needed in patients [22].

This chapter discusses available data on the efficacy of melatonin to curtail chronic BZD use in insomnia patients. Medical literature was identified by searching databases including (MEDLINE, EMBASE), bibliographies from published literature and clinical trial registries/databases. Searches were last updated January 6, 2018.

## BZD and Related Drugs in Insomnia

BZD are a group of compounds that exert their therapeutic effect on sleep through allosteric modulation of the $GABA_A$ receptor complex [23]. BZD exert broad inhibitory effects on brain function including sleep promotion, anxiolysis, anticonvulsant effects, cognitive and motor impairment, and reinforcing effects [24]. BZD exert their actions through activation of $BZ_1$ and $BZ_2$ receptor subtypes of the $GABA_A$ complex, the activation of $BZ_1$ accounting for their specific hypno-sedative, anxiolytic, and anticonvulsant activities [25]. The $\alpha_1$-subunit of the $GABA_A$ receptor mediates the sedative and anxiolytic effects of BZD [24] (Fig. 34.1).

The efficacy of BZD in treating insomnia is supported by several meta-analyses, e.g., [26], but significant adverse effects like cognitive and psychomotor impairment, anterograde amnesia, next-day hangover, rebound insomnia, and dependence have also been documented. Because of their adverse effects, the use of BZD for treatment of insomnia in the elderly has become controversial [27, 28].

Z-drugs are a group of agents that are not part of the BZD chemical class but act via the same mechanism – they enhance GABA-mediated inhibition through allosteric modulation of the GABA-A receptor [23, 24]. This group includes drugs like

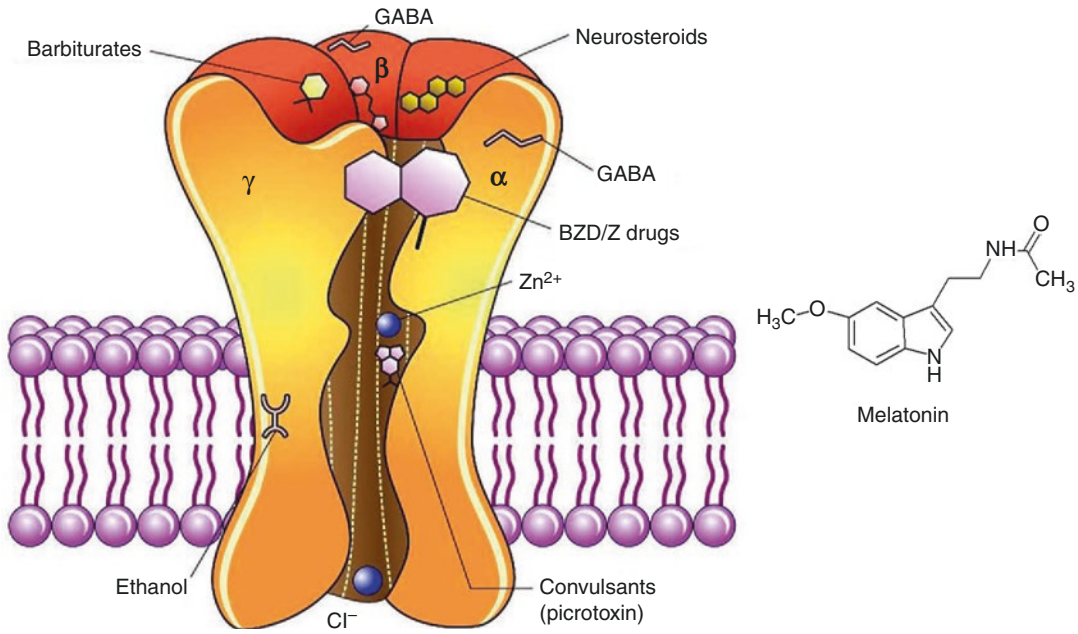


**Fig. 34.1** Schematic representation of the GABA type A receptor

zolpidem, zaleplon, and zopiclone all having high affinity and selectivity for the $\alpha_1$-subunit of the $GABA_A$ receptor complex. Zolpidem improves sleep maintenance shortly after administration, but the effect disappears at later in the night [1]. It may cause adverse effects like daytime drowsiness, dizziness, headache, and nausea. The pyrazolopyrimidine derivative zaleplon is effective to decrease sleep latency and to improve sleep quality. Zopiclone and its active stereoisomer eszopiclone have both been shown effective and safe in patients with primary insomnia. In general Z-drug sedative hypnotics, although effective in reducing sleep latency, are only moderately effective in increasing sleep efficiency and total sleep time [29]. These agents are problematic in those prone to abuse potential [27, 28].

International studies indicate that 50–80% of nursing home residents have at least one prescription for psychotropic medication. The most commonly prescribed medications for sleep are BZD and Z-drugs. Utilization rates vary dramatically from country to country and from institution to institution. In general, recommendations for the pharmacotherapy of insomnia in elderly patients include using a reduced dosage. For some substances (e.g., zolpidem, zopiclone, zaleplon, temazepam, and triazolam), the recommended dosage is half that recommended for younger patients. The vast majority of studies of these medications are short term, i.e., < or = 2 weeks. Clinicians are advised to avoid long-acting BZD and to use hypnotics for as brief a period as possible, in most cases not exceeding 2–3 weeks of treatment [24, 27, 28].

Can we define the characteristics of the ideal hypnotic? It clearly should not only decrease sleep latency but should also increase total sleep time and sleep efficiency [1]. In addition, the ideal hypnotic drug should not produce undesired side effects such as impairment of memory, cognition, psychomotor retardation, and next-day hangover effects or potentiality of abuse (Fig. 34.2).

Melatonin fulfills many of these requirements as recognized in several consensus statements [1, 30–33]. Meta-analysis publications also support such a conclusion [34, 35] although not unanimously [36].

Controlled-release melatonin is recommended as a first-line agent in older insomniacs [1]; the Z-drugs (zolpidem, eszopiclone, and zaleplon) should be reserved for use if the first-line agents are ineffective. BZD are not recommended because of their high abuse potential and the availability

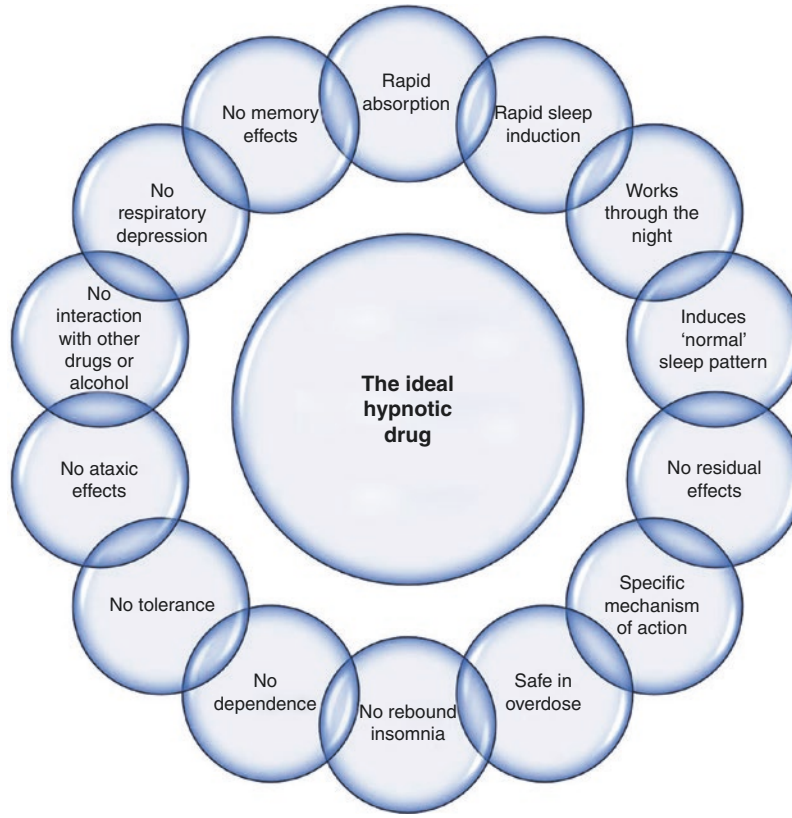


**Fig. 34.2** Theoretical properties of the ideal hypnotic drug

of better alternatives. Although the orexin receptor antagonist suvorexant appears to be relatively effective, it is no more effective than the Z-drugs and much more expensive [37]. However, further studies on melatonin and its analogs are needed as indicated in the recent guidelines for the treatment of insomnia developed by the European Sleep Research Society [2] and by the American Academy of Sleep Medicine [27].

## Basic Studies on Melatonin Relevant to Sleep Regulation

The discoverer of melatonin, Aaron Lerner, initially reported soporific effects of melatonin, noting that drowsiness and sleep enhancement followed administration of doses of 200 mg and 1 g of melatonin [38]. Since then numerous studies have demonstrated melatonin's value as a hypnotic agent. In low doses (such as 0.5–3 mg), administered melatonin can function as a cue for the sleep/wake cycle acting in the opposite manner to light so that when given prior to sleep onset, it advances the timing of sleep onset, but when given after waking, it can lead to a delay in sleep timing. Phase response curves for both melatonin and light have been obtained [39].

Melatonin regulates circadian rhythms in both brain and periphery. Administration of melatonin will cue the circadian phase in a variety of disorders including jet lag problems, shift work maladaptation, advanced and delayed sleep phase disorders, major affective disorder, seasonal affective disorder, and disrupted rhythms in attention deficit hyperactivity disorder, autism, and schizophrenia. Preclinical studies have established that melatonin has significant neuroprotective effects, and clinical trials have been proposed for preventive treatment of neurodegenerative diseases [39].

Melatonin blood levels normally increase during darkness rising to a peak around 2–3 AM and then decreasing with virtually no melatonin

detectable during light. Although produced in many tissues of the body, serum melatonin originates almost exclusively from the pineal gland where production is driven by neural inputs from the suprachiasmatic nucleus (SCN) functioning as the master body clock [40]. The inherent rhythm of the SCN is synchronized both by the light/dark cycle via neural inputs from the retina and by melatonin acting via two protein-linked melatonin receptors $MT_1$ and $MT_2$. In many laboratory animals, melatonin's phase shifting (chronobiotic) effects are mainly produced by $MT_2$ receptors. However, $MT_2$ receptors are poorly expressed in the human SCN, so that phase shifting may be ascribed to $MT_1$ receptors.

Binding sites for melatonin were initially identified in a wide variety of central and peripheral tissues using $^3$H-melatonin [41–43] and later 2-$I^{125}$-iodomelatonin [44]. Molecular cloning of the first high-affinity membrane melatonin receptor ($MT_1$) was accomplished using a cDNA library from a dermal cell line of amphibian melanophores [45]. This initial finding led to the discovery that there are at least two $G_i$-protein-coupled membrane melatonin receptors in humans. The second receptor ($MT_2$) [46] is 60% identical in amino acid sequence to the $MT_1$ receptor. Additionally, a third receptor, now called GPR50, shares 45% of the amino acid sequence with $MT_1$ and $MT_2$ but does not bind melatonin [47].

In the mammalian brain, $MT_1$ and $MT_2$ receptors have been reported in the SCN, prefrontal cortex, cerebellar cortex, hippocampus, basal ganglia, substantia nigra, ventral tegmental area, nucleus accumbens and in retinal horizontal, amacrine and ganglion cells, and choroid plexus (summarized by [48]). The $MT_1$ receptor is highly expressed in the human SCN [49] and mainly in vasopressinergic neurons. $MT_2$ was not detected in an earlier investigation of the human SCN [49]. This receptor subtype is expressed in the SCN of numerous mammals and, where present, is particularly important for circadian phase shifting [50, 51]. Since circadian clock reset does occur in humans after administering melatonin [52, 53], these changes must be ascribed to $MT_1$ signaling.

Since melatonin is a lipophilic substance, once it is synthesized in the pineal gland, it diffuses readily into the bloodstream, where it is bound to albumin [54]. Melatonin rapidly disappears from the blood with a half-life that is biexponential, with a first distribution half-life of 2 min and a second of 20 min [55]. Circulating melatonin is metabolized mainly in the liver which clears 92–97% of circulating melatonin in a single pass [56]. Melatonin is first hydroxylated in the C6-position by cytochrome $P_{450}$ monooxygenases (isoenzymes CYP1A1, CYP1A2, and to a lesser extent CYP1B1) and thereafter conjugated with sulfate to be excreted as 6-sulphatoxymelatonin, glucuronide conjugation being extremely limited [55]. CYP1A2 and to a greater extent CYP2C19 also demethylate melatonin to its precursor *N*-acetylserotonin [57]. Specific melatonin deacetylases or less specific aryl acylamidases [40] are also present in the brain.

Because melatonin has a relatively short half-life (30–45 min), prolonged-release melatonin and several synthetic melatonin analogs which are agonists of $MT_1/MT_2$ receptors and have a longer half-life have been developed. Circadin, a prolonged-release form of melatonin (2 mg), has been approved by the European Medicines Agency (EMA) as monotherapy for insomnia in 55-year-old patients and over. It is formulated to provide peak levels 3 h after dosing, plateauing at 3.5 h, and then gradually falling [58]. Blood levels thus approximate physiologic nocturnal patterns of melatonin.

Available evidence tends to indicate that melatonin has a more potent sleep-inducing action at a higher dose than the low doses typically used as a chronobiotic to trigger sleep onset. Sleep latency is significantly shortened, and sleep quality and morning alertness are improved following treatment of affected patients in that age group. In contrast, effects on sleep maintenance and duration do not show significant changes [59].

In several consensus statements [1, 30–32], melatonin was recognized as fulfilling the properties of a useful sleep-promoting agent. For example, the consensus of the British Association for Psychopharmacology on evidence-based treatment of insomnia, parasomnia, and circadian

rhythm sleep disorders concluded that melatonin is the first-choice treatment when a hypnotic is indicated in patients over 55 years [1]. Similar conclusions were put forth by Canadian and European pediatrics consensuses [1, 30–32]. Brain imaging studies in wake subjects have revealed that melatonin modulates brain activity pattern to one resembling that of actual sleep [60].

The melatonergic agonist ramelteon is effective in helping initiate and thus improving sleep in insomniacs with minimal side effects. Several reports indicate that ramelteon can both prevent and treat delirium [61]. The melatonin agonist, tasimelteon, has been approved to treat non-24 h sleep-wake disorders, often caused by blindness [62]. For major affective disorder, the melatonergic agonist agomelatine which also has 5-$HT_{2C}$ antagonistic properties ameliorates not only the symptoms of depression but also the quality and efficiency of sleep [63]. In common with other naphthalenic drugs, there is a risk of severe hepatotoxicity and is contraindicated in those with liver disease. Another melatonin agonist, TIK-301, is under development; TIK-301 also has 5-$HT_{2C}$ and 5-$HT_{2B}$ receptor antagonism and potentially has antidepressant properties.

## Melatonin and Brain GABAergic Mechanisms

GABA-containing neurons are mostly interneurons in the majority of central neuronal circuits including the SCN [64]. GABAergic neurons are also important in other components of the circadian timing system, e.g., GABA coexists with neuropeptide Y in the intergeniculate leaflet of the thalamic lateral geniculate complex as well as in certain horizontal cell interneurons and ganglion cells of the retina [65]. Because of this key distribution, it was thus logical to postulate GABA as the principal neurotransmitter of the circadian timing system [64].

Through activation of $GABA_A$ receptors, GABA inhibits neuronal firing by increasing $Cl^-$ conductance (Fig. 34.1). Blockade of $GABA_A$ receptors by bicuculline generates neuronal epileptic activity. The receptor-channel complex, which has been sequenced, is allosterically modulated by drugs like BZD or barbiturates. In addition to its effect on $Cl^-$ channels, GABA also inhibits neuronal activity by activating $GABA_B$ receptors coupled to $K^+$ channels. A third type of receptor ($GABA_C$ receptor) is associated, as the $GABA_A$ receptor, to a chloride ionophore through binding sites which are insensitive to bicuculline antagonism.

The pineal gland exerts a depressive influence on CNS excitability [66]. This activity is attributed to melatonin, since pharmacological doses of the hormone prevent pinealectomy (Px)-induced seizures in gerbils [67] as well as kindled convulsions in rats [68]. In murine seizure models, melatonin has been documented to potentiate the anticonvulsant action of phenobarbital and carbamazepine against electroshock seizures in adult animals [69, 70]. Melatonin has also been reported to exert an anticonvulsant action when given alone to adult rats, mice, hamsters, guinea pigs, cats, and baboons (for ref. see [70]).

Both $MT_1$ and $MT_2$ receptors appear to be involved in sedative and antiexcitatory effects of melatonin. This has been mainly studied in relation to anticonvulsant actions [21, 71–75]. The anticonvulsant activity of melatonergic agents seems to be mediated by $MT_1$ and/or $MT_2$ membrane receptors since similar effects were observed with the $MT_1/MT_2$ agonist ramelteon [76]. These antiexcitatory actions may be also related to additional anxiolytic, antihyperalgesic, and antinociceptive effects of melatonergic agents [77–83].

The first indication of a possible link between the pineal and brain GABAergic neurons was provided by Anton Tay et al. [84] who reported increased GABA levels in rat brain following Px and depressed levels after melatonin injection. Exogenously administered melatonin increases pyridoxal phosphokinase activity in rat brain [84]. Results in rats indicate that central synapses employing GABA as an inhibitory transmitter are a target for pineal melatonin activity because:

(a) Px disrupts circadian rhythmicity of brain GABA and BZD binding [85, 86].

(b) Low doses of melatonin counteract Px-induced modifications of BZD and GABA binding [87].
(c) Chronic melatonin treatment increases brain BZD and GABA binding [85, 86, 88].
(d) Melatonin administration accelerates brain GABA turnover rate [89].
(e) Melatonin increases glutamic acid decarboxylase activity and $Cl^-$ ion conductance in the medial basal hypothalamus-preoptic area, with maximal activity in the evening [90].

Melatonin competes for diazepam binding sites in rat, human, and bovine brain membranes with micromolar affinity [91]. Similarly, pharmacological doses of melatonin act on BZD-$GABA_A$ receptors to enhance both in vitro and in vivo binding of GABA and to inhibit allosterically the binding of the caged convulsant t-butyl bicyclophosphorothionate on GABA-gated chloride channels in rat brain [92]. The binding site for melatonin on the BZD-$GABA_A$ receptor complex is not known, but its ability to competitively inhibit diazepam binding suggests a direct interaction within the BZ binding pocket, which is located at the α/γ subunit interface of the BZD-$GABA_A$ receptor complex.

There is in vivo electrophysiological evidence that nanomolar concentrations of melatonin can potentiate GABAergic inhibition of neuronal activity in the mammalian cortex [93]. In vitro electrophysiological studies have indicated that the $MT_1$ receptor is coupled to stimulation of GABAergic activity in the hypothalamus, whereas the $MT_2$ receptor mediates an opposite effect in the hippocampus [94]. The primary effect of melatonin in the rat SCN appears to be inhibition of neuronal activity [95], which is consistent with the relatively high expression of the $MT_1$ subtype in the circadian clock and the fact that this receptor is linked to enhancement of GABAergic activity [94]. $GABA_A$ receptor currents are also modulated by melatonin in neurons of chick spinal cord [96] and carp retina [97]. In a study aiming at assessing the effect of melatonin on the GABA-induced current and GABAergic miniature inhibitory postsynaptic currents in cultured rat hippocampal neurons, melatonin was effective only when GABA and melatonin were applied together [98]. This enhancement was mediated via high-affinity BZD sites as BZD receptor antagonist flumazenil inhibited it.

In principle, to demonstrate that a neurotransmitter system is involved in the mediation of a given melatonin effect, two requirements should be fulfilled: (a) the neurotransmitter system should show dynamic changes because of melatonin injection; (b) functional obliteration of the neurotransmitter system should significantly modify the melatonin effect. It should be stressed that monoamine pathways within the brain seem not to be important for melatonin entrainment of circadian rhythmicity in rodents, since the intraventricular injection of 6-hydroxydopamine and 5,7-dihydroxytryptamine, which deplete catecholamines and indoleamines, failed to alter entrainment [99].

To achieve an effective inhibition of $GABA_A$-mediated mechanisms, a rather indirect procedure had to be employed, because the use of $GABA_A$ antagonists, like bicuculline or picrotoxin, was precluded due to the convulsive state produced in the animals. The central-type BZD antagonist flumazenil was thus employed. In a study aiming to determine whether melatonin-induced analgesia in rats could be inhibited by flumazenil, melatonin exhibited maximal analgesic effects at late evening and the administration of fIumazenil, although unable by itself to modify pain threshold, blunted the analgesic response. This indicated that the time-dependent melatonin analgesia was sensitive to impairment of $GABA_A$-mediated mechanisms [78]. In subsequent studies, the inhibitory effects of flumazenil on melatonin-induced depression of locomotor behavior and 3-mercaptopropionic acid seizures were analyzed [72, 100]. The administration of fIumazenil, although unable by itself to modify locomotor activity or seizures, significantly attenuated the inhibitory effects of melatonin. A similar result was observed when the anxiolytic and pro-exploratory melatonin properties were assessed in rats using a plus-maze procedure [77]. Melatonin displayed maximal effects at night, with the absence of effects at noon and a weak activity at the beginning of the light phase,

an effect also blunted by administration of flumazenil. Other studies also supported the link of melatonin and GABA-mediated mechanisms in the brain [101, 102].

In view of the importance of GABAergic mechanisms in sleep modulation, it is likely that the sedative effects of pharmacological doses of melatonin involve its allosteric interaction with BZD-$GABA_A$ receptors (Fig. 34.1). This view is supported by evidence that BZD/$GABA_A$ antagonists block the sleep inducing effect of pharmacological doses of melatonin in experimental animals [103]. The ability of pharmacological concentrations of melatonin or BZDs to inhibit the cAMP pathway via putative G protein-coupled BZ receptors [104] suggests yet another neuropharmacological mechanism for modulation of GABAergic activity. In a recent study the relationship of nocturnal concentrations of melatonin and GABA with insomnia after stroke was examined in insomniac and non-insomniac patients recruited during rehabilitation phase. Nocturnal concentrations of melatonin and GABA were lower, and the severity of stroke was higher, in the insomnia group. Correlation analysis demonstrated that the nocturnal concentrations of melatonin and GABA were associated with insomnia after stroke [105].

## Melatonin and BZD Use in Insomnia Disorder Patients

Tables 34.1 and 34.2 summarize published data on melatonin/BZD interactions in clinical studies. Table 34.1 reports data on the comparison of melatonin with BZD/Z-drugs in their effects on sleep. Table 34.2 summarizes the efficacy of melatonin to curtail BZD.

Several studies compared melatonin and BZD/Z-drug efficacy (Table 34.1). In a study aimed to assess subjective sleepiness and cognitive performance after administering 5 mg melatonin, 10 mg temazepam, or placebo, greater changes in performance were evident following temazepam administration than melatonin administration, relative to placebo. Administration of melatonin or temazepam significantly elevated subjective sleepiness levels. The authors concluded that melatonin administration induced a smaller deficit in performance on a range of neurobehavioral tasks than temazepam, indicating that melatonin is preferable to BZD in the management of circadian and sleep disorders [106].

Two studies have undertaken in healthy volunteers to compare the effect of controlled-release melatonin with that of zolpidem. In one of those studies, 16 healthy volunteers were randomized for a double-blind, placebo-controlled, single-dose, four-way crossover study of controlled-release melatonin and zolpidem (10 mg) or their combination [107]. Subjects were tested 1 h, 4 h, and next morning after dosing. Psychomotor functions, memory recall, and driving skills were assessed. No impairment of performance after melatonin was detected, whereas zolpidem impaired psychomotor and driving performance 1 h and 4 h post-dosing as well as early memory recall. Melatonin co-administration exacerbated the zolpidem effect [107].

In another study, effects of controlled-release melatonin and zolpidem on postural stability were assessed in healthy older adults [108]. Twenty-four volunteers, aged 55–64 years, were randomized for a double-blind, placebo-controlled, single-dose, three-way crossover study. Body sway was tested by the area of the 95% confidence ellipse enclosing the center of pressure (A95) and its path length. No effect of melatonin on A95 was detected. In contrast, zolpidem significantly increased the A95 and path length pointing out to the feasible disturbance of postural stability caused by the drug [108].

To establish whether the effects of controlled-release melatonin (2 mg) on the nocturnal sleep EEG were different to those of temazepam (20 mg) and zolpidem (10 mg), 16 healthy men and women aged 55–64 years participated in a double-blind, placebo-controlled, four-way crossover trial. Nocturnal sleep was assessed with polysomnography and spectral analysis of the EEG. In an entire night analysis, controlled-release melatonin did not affect slow wave activity (SWA), whereas temazepam and zolpidem significantly reduced SWA compared with placebo. Melatonin only reduced SWA during the first third of the

**Table 34.1** Clinical studies comparing melatonin vs. BZP/Z-drugs

| Subjects | Design | Study's duration | Treatment | Measured | Results | Reference(s) |
|---|---|---|---|---|---|---|
| 16 healthy, young subjects (10 females; mean age, 21.4 ± 6 years) | Randomized, double-blind crossover study | 3 days | Subjective sleepiness was measured at hourly intervals using a visual analogue scale. At 12:00 h subjects were administered a capsule containing 5 mg melatonin, 10 mg temazepam, or placebo | After sleeping overnight in the laboratory, subjects completed a battery of tests at hourly intervals between 08:00 and 11:00 h and at 2-hourly intervals between 13:00 and 17:00 h | A significant drug x time interaction was evident on the unpredictable tracking, spatial memory, and vigilance tasks. Greater changes in performance were evident following temazepam administration than melatonin administration, relative to placebo. Administration of melatonin or temazepam significantly elevated subjective sleepiness levels, relative to placebo. The findings demonstrated that melatonin administration induces a smaller deficit in performance on a range of neurobehavioral tasks than temazepam | [106] |
| 16 healthy volunteers aged ≥55 years | Randomized, double-blind, placebo-controlled, single-dose, four-way crossover study | 1 day | Melatonin controlled release (2 mg p.o.), zolpidem (10 mg p.o.) or their combination | Psychomotor functions, memory recall, and driving skills. Subjects were tested 1 h and 4 h and next morning after dosing | No impairment of performance after melatonin. Zolpidem impaired psychomotor and driving performance 1 h and 4 h post-dosing, and early memory recall. Melatonin co-administration exacerbated zolpidem effect | [107] |
| 24 healthy volunteers, aged 55–64 years) | Randomized, double-blind, placebo-controlled, single-dose, three-way crossover study | 1 day | Melatonin controlled release (2 mg p.o.), zolpidem (10 mg p.o.) or their combination | Body sway tested by the area of the 95% confidence ellipse enclosing the center of pressure (A95) and its path length. Subjects were tested 30 min before, 1.5 and 4 h after dosing | No effect of melatonin on A95. It increased path length at 4 h post-dose in open but not closed eyes condition. Zolpidem significantly increased the A95 and path length | [108] |

(continued)

**Table 34.1** (continued)

| Subjects | Design | Study's duration | Treatment | Measured | Results | Reference(s) |
|---|---|---|---|---|---|---|
| 38 patients with Parkinson's disease with complaints on sleep disorders (mean age, 67.3 ± 4.8 years; 15 males) | Open-label study | 6 weeks | Melatonin (3 mg p.o.) vs. clonazepam (2 mg p.o.) | Quality of sleep was assessed with the Parkinson's disease sleep scale (PDSS) and the Epworth sleepiness scale as well as with overnight polysomnographic study at baseline and at the end of the trial. All patients underwent neuropsychological testing using MMSE, five-word test, digit span and the Hamilton scale | Compared to baseline, melatonin and clonazepam reduced sleep disorders in patients. However, the daytime sleepiness was increased in the clonazepam group. Patients treated with melatonin had better scores on the MMSE, five-word test, Hamilton scale at the end of the study period as compared with the clonazepam group. The number of REM sleep epochs remained lower in patients treated with clonazepam | [109] |
| Randomly assigned 80 adult patients (ASA 1&2, American Society of Anesthesiologists physical status classification) with a visual analogue score (VAS) for anxiety >3 | Prospective, double-blind placebo-controlled trial | 24 h | A tablet containing a combination of alprazolam 0.5 mg and melatonin 3 mg, alprazolam 0.5 mg, melatonin 3 mg, or placebo orally 90 min before a standard anesthetic | Primary end points were change in anxiety and sedation score at 15, 30, and 60 min after premedication, and the number of patients with loss of memory for the five pictures shown at various time points when assessed after 24 h | Combination drug produced the maximum reduction in anxiety VAS from baseline at 60 min. Sedation scores at various time points and a number of patients not recognizing the picture shown at 60 min after premedication were comparable between combination drug and alprazolam alone. Addition of melatonin to alprazolam had superior anxiolysis compared with either drugs alone or placebo | [110] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 15 healthy men and women aged 55–64 years | Double-blind, placebo-controlled, four-way crossover trial | 4 weeks | Controlled-release melatonin (2 mg p.o.), temazepam (20 mg p.o.), zolpidem (10 mg p.o.) | Polysomnography and spectral analysis of the EEG | Temazepam and zolpidem significantly reduced slow wave activity (SWA) as compared to placebo. Temazepam significantly reduced SWA compared with melatonin. Melatonin only reduced SWA during the first third of the night compared with placebo | [111] |
| 82 critically ill with mechanical ventilation >48 h and simplified acute physiology score II >32 points were examined | Double-blind randomized placebo-controlled trial | | Patients were randomized 1:1 to receive, at 8 p.m. and midnight, melatonin (3 + 3 mg) or placebo p.o., from the third ICU day until ICU discharge | Primary outcome was total amount of enteral hydroxyzine administered | Melatonin-treated patients received lower amount of enteral hydroxyzine. Other neurological indicators (amount of some neuroactive drugs, pain, agitation, anxiety, sleep observed by nurses, need for restraints, need for extra sedation, nurse evaluation of sedation adequacy) improved, with reduced cost for neuroactive drugs | [112] |
| 92 children aged 5–14 years, scheduled for elective surgery, were randomly assigned to two premedication groups | Prospective, randomized, double-blind study | | Oral melatonin (0.5 mg/kg) or oral midazolam (0.5 mg/kg) premedication before induction of anesthesia with propofol | The effect of premedication on the required infusion of propofol was assessed. As a secondary outcome, the effect of premedication on the preoperative sedation level and on the postanesthesia recovery score was evaluated | Oral administration of melatonin significantly reduced doses of propofol required for induction of anesthesia, more than midazolam ($P < 0.001$). No statistically significant differences were found in the pre- and postanesthesia sedation score ($P = 0.387$ and $P = 0.525$, respectively) between the two groups | [113] |

**Table 34.2** Clinical studies on the efficacy of melatonin to curtail BZP/Z-drug use

| Subjects | Design | Study's duration | Treatment | Measured | Results | Reference(s) |
|---|---|---|---|---|---|---|
| 41 patients (28 women, mean age 74 ± 12 year) with sleep disturbance including 22 insomniacs, 9 depressed, and 10 demented patients | Open-label study | 3 weeks | 3 mg melatonin p.o./daily at bedtime | Daily logs of sleep and wake quality completed by the patients or their caretakers | Four (31%) of the 13 insomniac patients who were receiving BZP reduced BZP use by 50–75% and 4 (31%) discontinued it. Of the 7 depressed and 7 demented patients who were receiving BZP, 2 (29%) in each group reduced BZP use by up to 50% | [114] |
| A 43-year-old woman who had suffered from insomnia for the past 11 years | Case report | 1 year | 1 mg of controlled-release melatonin p.o./daily at bedtime | Subjective evaluation of sleep quality. Urinary 6-sulphatoxymelatonin measurement | Treatment with melatonin enabled the patient to completely cease any BZP use within 2 days, with an improvement in sleep quality and no side effects. Examination of urinary 6-sulphatoxymelatonin levels before the melatonin treatment indicated that the levels were very low and lacked the typical circadian rhythm of excretion. Reexamination of 6-sulphatoxymelatonin levels during melatonin treatment revealed the existence of a normal circadian rhythm of excretion | [115] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 34 primary insomnia outpatients aged 40–90 years who took BZP and had low urinary 6-sulphatoxymelatonin levels | Randomized, double-blind, placebo-controlled study followed by a single-blind period | 18 months | Patients received melatonin (2 mg controlled release p.o.) or placebo for 6 weeks. They were encouraged to reduce BZP dosage 50% during week 2, 75% during weeks 3 and 4, and to discontinue BZP during weeks 5 and 6. Then melatonin was administered (single blind) for 6 weeks and attempts to discontinue BZP therapy were resumed. Follow-up reassessment was performed 6 months later | Sleep diary and recording of BZP use | 14 of 18 subjects who had received melatonin, but only 4 of 16 in the placebo group discontinued BZP therapy. Sleep quality scores were higher in the melatonin group. Six additional subjects in the placebo group discontinued BZP after 6 months of treatment. At the follow-up, 19 out of 24 patients who discontinued BZP kept good sleep quality | [116] |
| 41 insomniac patients (28 females), mean age 60 ± 9.5 year. Twenty of 22 patients were on BZP treatment | Open-label study | 6 months | 3 mg melatonin p.o./daily at bedtime | Sleep diary and recording of BZP use. Serum concentrations of prolactin, TSH, FSH, and estradiol and urinary 6-sulphatoxymelatonin excretion were measured by RIA | In 13 of 20 patients taking BZP together with melatonin, BZP use could be stopped, and in another 4 patients, BZP dose could be decreased to 25–66% of the initial dose. Serum hormone concentration did not change, nor were any indications of hematologic or blood biochemistry alteration found. Urinary 6-sulphatoxymelatonin correlated negatively with age, but not with the intensity of sleep the disorder or the outcome of treatment | [117] |

(continued)

**Table 34.2** (continued)

| Subjects | Design | Study's duration | Treatment | Measured | Results | Reference(s) |
|---|---|---|---|---|---|---|
| 45 patients (36 females, 70.5 ± 13.1 years old) regularly taking anxiolytic BZP in low doses were studied | Randomized, double-blind, placebo-controlled study | 6 weeks | 3 mg melatonin p.o./daily at bedtime. On day 14 of treatment, BZP dose was reduced by half, and on day 28, it was halted | Sleep diary and recording of BZP use. Urinary 6-sulphatoxymelatonin measurement | No significant modifications of sleep or wakefulness were detected after BZP withdrawal. As compared to basal, there was a general lack of changes in quality of wakefulness or sleep in patients taking melatonin or placebo. Melatonin advanced sleep onset by 27.9 ± 11.9 min and decreased significantly the variability of sleep-onset time. The urinary concentration of 6-sulphatoxymelatonin prior to the study did not correlate with any parameter examined | [118] |
| Of 503 long-term users of BZP asked to participate in a discontinuation program, 38 patients (22 females) agreed to participate | Placebo-controlled trial | 1 year | 5 mg melatonin or placebo which had to be taken p.o. 4 h before patients went to bed | During this period participants received four questionnaires about their use of BZP medication. The urine of all participants was tested for the presence of BZP | After 1 year 40% had stopped their BZP use, both in the intervention group on melatonin and in the placebo-control group. Comparing stoppers and nonstoppers did not reveal significant differences in BZP use or awareness of problematic use | [119] |
| 60 mild cognitive impairment (MCI) out patients | Open-label, retrospective study | 9–24 months | 35 patients received daily 3–9 mg of a fast-release melatonin preparation p.o. at bedtime. Melatonin was given in addition to the standard medication | Daily logs of sleep and wake quality. Initial and final neuropsychological assessment | Beck Depression Inventory score improved in melatonin-treated patients, concomitantly with an improvement in wakefulness, sleep quality, and neuropsychological assessment. Twenty-one out of 25 MCI patients not treated with melatonin received BZP treatment vs. 6 out 25 patients in the melatonin group | [120] |

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| 80 patients enrolled at a community methadone maintenance clinic recruited to a BDZ withdrawal program | Double-blind crossover control study to evaluate the effectiveness of melatonin in attenuating sleep difficulties during BZP withdrawal | 13 weeks | Melatonin (5 mg/day, p.o.) or placebo: 6 weeks one arm, 1-week washout, 6 weeks another arm | Urine BZP; self-reported Pittsburgh Sleep Quality Index and the Center for Epidemiologic Studies Depression questionnaires administered at baseline and at 6, 7, and 13 weeks | Sixty-one patients (77.5% in the "melatonin-first" condition and 75% in the "placebo-first" condition) completed 6 weeks of treatment, showing a similar BZP discontinuation rate. Sleep quality in patients who continued abusing BZP improved more in the "melatonin-first" group than in the "placebo-first" group, with no differences in sleep quality improvement in patients who stopped BZP. The data indicated that most improvement in sleep quality was attributed to BZP discontinuation. Although melatonin did not enhance BDZ discontinuation, it improved sleep quality, especially in patients who did not stop BDZ | [121] |
| 22 older adults (7 men, 15 women over 65) with a history of sleep disorder complaints 14 of these subjects were receiving hypnotic drug therapy | Prospective, randomized, double-blind, placebo-controlled, crossover trial | 4 months | Participants received 2 months of melatonin (5 mg/day p.o.) and 2 months of placebo | Sleep disorders were evaluated with the Northside Hospital Sleep Medicine Institute (NHSMI) test, discarding secondary insomnia and evaluating sleep quality. Behavioral disorders were evaluated with the Yesavage Geriatric Depression Scale (GDS) and Goldberg Anxiety Scale (GAS). Patients discontinuing hypnotic drugs were also recorded | Melatonin treatment improved sleep quality scores. Depression and anxiety also improved significantly after melatonin administration. Nine out of 14 subjects receiving hypnotic drugs were able to discontinue this treatment during melatonin but not placebo administration, one discontinued hypnotic drugs during both melatonin and placebo administration, and four were unable to discontinue hypnotic therapy | [122] |

(continued)

**Table 34.2** (continued)

| Subjects | Design | Study's duration | Treatment | Measured | Results | Reference(s) |
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| 96 MCI outpatients | Open-label, retrospective study | 15–60 months | 61 patients received daily 3–24 mg of a fast-release melatonin preparation p.o. at bedtime. Melatonin was given in addition to the standard medication | Daily logs of sleep and wake quality. Initial and final neuropsychological assessment | Beck Depression Inventory score improved in melatonin-treated patients, concomitantly with an improvement in wakefulness, sleep quality, and neuropsychological assessment. Only 6 out of 61 patients treated with melatonin needed concomitant BZP treatment vs. 22 out of 35 MCI patients not receiving melatonin | [123] |
| 112 insomniac outpatients classified according to their use of hypnotic BZP or BZP-like drugs | Retrospective study from a longitudinal database | Varied intervals | Melatonin (2 mg controlled release) p.o. | Discontinuation rate of BZP | 31% of patients discontinued BZP after melatonin initiation. The discontinuation rate was higher in patients receiving two or three melatonin prescriptions | [124] |
| Pharmacoepidemiologic analysis and evaluation of the impact of anti-BZD/Z-drugs campaigns in face of the availability of alternative pharmacotherapy (melatonin) | | Varied intervals | Annual sales data from 9 European countries were extracted from the IMS sales database | To determine whether trends in use of treatment options were attributed to campaigns and/or availability and affordability of safer alternatives on the market | Campaigns aiming to reduce the use of BZP/Z-drugs failed when they were not associated with the availability and market uptake of melatonin. The reimbursement of melatonin supports better penetration rates and a higher reduction in sales for BZD/Z-drugs | [15] |
| 597 insomniac outpatients classified according to their use of hypnotic BZP or BZP-like drugs (mean age 62.7 year, 68% previously treated with hypnotics, 65% women) | Post-marketing surveillance study in Germany | 3 weeks | Melatonin (2 mg controlled release) p.o. | Sleep diary and recording of BZP use | Most of the patients (77%) who used traditional hypnotics before melatonin treatment had stopped using them, and only 5.6% of naive patients started such drugs after melatonin discontinuation | [125] |

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| 86 patients with schizophrenia or bipolar disorder (21–74 years) | Randomized, placebo-controlled, blinded, trial | 24 weeks | Controlled-release melatonin (2 mg p.o.) | The primary outcome was mean benzodiazepine daily dosage at 24 weeks. Secondary outcomes included pattern of benzodiazepine dosage over time, benzodiazepine cessation proportion, and benzodiazepine withdrawal symptoms | BZP cessation proportion was 38.1% (16/42) in the melatonin group versus 47.7% (21/44) in the placebo group (OR 0.64, 95% CI 0.26–1.56, $P = 0.32$). Prolonged-release melatonin had no effect on BZP withdrawal symptoms | [126] |
| 48 patients with schizophrenia or bipolar disorder were studied | Randomized, double-blind study | 24 weeks | Prolonged-release melatonin (2 mg) or placebo p.o. once daily. All participants gradually tapered usual benzodiazepine dosage | 72 h of actigraphic assessment of activity-rest cycles performed pre- and post- tapering | Melatonin significantly increased the interdaily stability, and at a trend level decreased the intradaily variability compared with placebo | [127] |
| 78 patients with schizophrenia or bipolar disorder were studied | Randomized, double-blind study | 24 weeks | Prolonged-release melatonin (2 mg) or placebo p.o. once daily. All participants gradually tapered usual benzodiazepine dosage | 23 patients underwent sleep recordings (one-night polysomnography), while 55 patients were assessed by subjective sleep quality ratings | Melatonin had no effect on objective sleep efficiency but significantly improved self-reported sleep quality. Reduced benzodiazepine dosage at the 24-week follow-up was associated with a significantly decreased proportion of stage 2 sleep | [128] |
| 80 patients with schizophrenia or bipolar disorder were studied | Randomized, double-blind study | 24 weeks | Prolonged-release melatonin (2 mg) or placebo p. o. Once daily. All participants gradually tapered usual benzodiazepine dosage | Brief Assessment of Cognition in Schizophrenia (BACS) was used to assess neurocognitive performance with additional assessments of subjective well-being and psychosocial functioning | BACS composite and subscale scores (except motor speed) significantly improved in parallel with benzodiazepine dose reduction, but there was no additional effect of melatonin. Cognitive performance was still markedly impaired post-tapering compared with normative data. Neither benzodiazepine withdrawal nor treatment group affected subjective well-being or psychosocial functioning | [129] |

night compared with placebo. The authors concluded that the effects of melatonin on the nocturnal sleep EEG are minor and are different from those of temazepam and zolpidem [111].

A study of 38 patients with Parkinson's disease without dementia with complaints on sleep disorders, both melatonin (3 mg) and clonazepam (2 mg) reduced sleep disorders. However, the daytime sleepiness was significantly increased in the clonazepam group and not affected by melatonin. The authors underlined the treatment efficacy of melatonin in the treatment of sleep disorders in Parkinson's disease [109].

To evaluate whether the addition of melatonin to alprazolam had superior premedication effects compared to either drug alone, a prospective, double-blind placebo-controlled trial randomly assigned 80 adult patients (ASA 1&2, American Society of Anesthesiologists physical status classification) with a visual analogue score for anxiety ≥3 to receive a tablet containing a combination of alprazolam 0.5 mg and melatonin 3 mg, alprazolam 0.5 mg, melatonin 3 mg, or placebo orally 90 min before a standard anesthetic [110]. Primary end points were changed in anxiety and sedation score at 15, 30, and 60 min after premedication and number of patients with loss of memory for the five pictures shown at various time points when assessed after 24 h. Addition of melatonin to alprazolam had superior anxiolysis compared with either drug alone or placebo. Adding melatonin neither worsened sedation score nor the amnesic effect of alprazolam alone [110].

As early as in 1997 two observations pointed to the possible beneficial effect of melatonin to decrease the dose of BZD used by patients (Table 34.2). Fainstein et al. [114] reported that in a short-term (3-week) open-label treatment with fast-release melatonin (3 mg) that included 22 insomniacs, 9 depressed, and 10 demented patients, 4 (31%) of the 13 insomniac patients who were receiving BZD reduced BZD use by 50–75% and 4 (31%) discontinued it. Of the seven depressed and seven demented patients who were receiving BZD, two (29%) in each group reduced BZD use by up to 50% [114].

Dagan et al. published a case report on the efficacy of 1 mg of controlled-release melatonin to completely cease any BZD use in a 43-year-old woman who had suffered from insomnia for the past 11 years [115]. All previous attempts to stop BZD treatment in this patient had resulted in withdrawal symptoms and a renewal of the insomnia. Treatment with melatonin enabled the patient to completely cease any BZD use within 2 days, with an improvement in sleep quality and no side effects.

In a double-blind, placebo-controlled study followed by a single-blind period, of 34 primary insomnia outpatients aged 40–90 years who took BZD and had low urinary 6-sulphatoxymelatonin levels, 14 out of 18 subjects who had received controlled-release melatonin, but only 4 out of 16 in the placebo group, discontinued BZD therapy [116]. An open-label study further supported the efficacy of fast-release melatonin in decreasing BZD use, i.e., 13 out of 20 insomnia patients taking BZD together with melatonin (3 mg) could stop BZD use, while another 4 patients decreased BZD dose to 25–66% of initial doses [117].

In a study evaluating the effectiveness of melatonin in attenuating sleep difficulties during BZD withdrawal, most improvement in sleep quality was attributed to drug discontinuation. Although melatonin did not enhance BZD discontinuation it improved sleep quality, especially in patients who did not stop BZD [121].

The above reported observations were not supported by the results of a placebo-controlled trial of 38 long-term users of BZD. After 1 year 40% had stopped their BZD use, both in the intervention group on melatonin and in the placebo-control group [119]. It must be noted that many times, old patients with minor sleep disturbance received, on a long-term basis, anxiolytic BZD or sedative-hypnotic BZD in low doses.

To assess the efficacy of melatonin to reduce the use of BZD in low doses, one of us carried out a double-blind placebo-controlled study on 45 patients randomized to receive either fast-release melatonin (3 mg) or placebo for 6 weeks [118]. In two steps BZD was tapered off and stopped after 4 weeks. Several subjective sleep parameters were assessed and found not to be different for both groups. That the patients included in this study were taking BZD on reasons other than

an established sleep disturbance was indicated by the lack of subjective changes in sleep quality after reduction or suppression of BZD dose. Melatonin, however, was not devoid of activity: it advanced sleep onset and decreased significantly variability of sleep-onset time as compared to placebo [118].

Mild cognitive impairment (MCI) is an etiologically heterogeneous syndrome defined by cognitive impairment in advance of dementia. Two retrospective analyses of 60 [120] and 96 MCI outpatients [123], receiving or not daily 3–24 mg of a fast-release melatonin preparation p.o. at bedtime for 9–24 or 15–60 months, were published. In both studies there was a significant improvement of cognitive and emotional performance and daily sleep/wake cycles. The comparison of the medication profile in both groups of MCI patients indicated that about 10% in the melatonin group received BZD vs. 63% in the non-melatonin group, thus supporting administration of fast-release melatonin to decrease BZD use.

A retrospective analysis of a German prescription database identified 512 patients who had initiated treatment with controlled-release melatonin (2 mg) over a 10-month period. From 112 patients in this group who had previously used BZD, 31% discontinued treatment with BZD 3 months after beginning controlled-release melatonin treatment [124].

In a study aimed to analyze and evaluate the impact of anti-BZD/Z-drugs campaigns and the availability of alternative pharmacotherapy (melatonin) on the consumption of BZD and Z-drugs in several European countries, it was reported that campaigns failed when they were not associated with the availability of melatonin in the market [15]. In this pharmacoepidemiologic study the reimbursement of melatonin supports better penetration rates and a higher reduction in sales for BZD/Z-drugs.

A post-marketing surveillance study of controlled-release melatonin (2 mg) was recently performed in Germany. It examined the effect of 3 weeks of treatment on sleep in 597 patients. Most of the patients (77%) who used traditional hypnotics before melatonin treatment had stopped using them, and only 6% of naïve patients started such drugs after melatonin discontinuation [125].

Therefore, most data favor the potential utility of melatonin to reduce BZD/Z-drug consumption in insomniac patients. The number of studies is, however, limited and further data on this application of melatonin are warranted.

A recent meta-analysis was performed to assess whether melatonin offers an atoxic alternative to BZD in ameliorating anxiety in the pre- and postoperative period. Randomized, placebo-controlled, or standard treatment-controlled, or both kind of studies that evaluated the effect of preoperatively administered melatonin on preoperative or postoperative anxiety, were compared. This systematic review identified 12 randomized controlled trials including 774 patients that assessed melatonin for treating preoperative anxiety, postoperative anxiety, or both. The authors concluded that when compared to placebo, melatonin given as premedication (tablets or sublingually) can reduce preoperative anxiety in adults (measured 50–100 min after administration). Melatonin was equally as effective as standard treatment with midazolam in reducing preoperative anxiety in adults [130].

Summarizing the observations shown in Tables 34.1 and 34.2 supports the use of melatonin as a valid alternative for BZD abuse. A major advantage for melatonin use is that it has an excellent safety and tolerability record, showing no difference from placebo. Emergent adverse events including gastrointestinal, cardiovascular, and body weight effects were absent.

Melatonin is usually remarkably well tolerated and, in some studies, it has been administered to patients at very large doses. Melatonin (300 mg/day for up to 3 years) decreased oxidative stress in patients with amyotrophic lateral sclerosis [131]. In children with muscular dystrophy, 70 mg/day of melatonin reduced cytokines and lipid peroxidation [132]. Doses of 80 mg melatonin hourly for 4 h were given to healthy men with no undesirable effects other than drowsiness [133]. In healthy women given 300 mg melatonin/day for 4 months, there were no side effects [134]. A randomized controlled double-blind clinical trial on 50 patients referred for liver surgery indicated that a single preoperative enteral dose of 50 mg/kg melatonin was safe and well tolerated [135]. In a recent case report on a

patient with primary progressive, multiple sclerosis followed for 4 years with the only administration of 50–300 mg of melatonin per day a partial recovery of the disease was documented [136].

## Conclusions

The ultimate goal of antiinsomnia therapy is symptomatic and functional recovery that helps a return to everyday life. However, a large proportion of patients under BZD treatment fail to achieve a complete and sustained recovery and are left with residual symptoms that make relapse or recurrence more likely. Most treatment guidelines recognize a symptom-free state as the best definition of insomnia remission, despite functional recovery often lagging behind symptomatic improvement. Given the importance of all three dimensions of functioning (emotional, cognitive, and social) in everyday activities such as work, and the impact that impaired daily functioning by insomnia may have on a patient's life, it is clear that more attention should be paid to functioning when assessing treatment's response.

The use of BZD anxiolytics and hypnotics continues to excite controversy. Views differ from expert to expert and from country to country as to the extent of the problem, or even whether long-term BZD use actually constitutes a problem. The adverse effects of these drugs have been extensively documented, and their effectiveness is being increasingly questioned. Discontinuation is usually beneficial as it is followed by improved psychomotor and cognitive functioning, particularly in the elderly. The potential for dependence and addiction have also become more apparent.

In this respect most safety concerns with use of hypnotics do not apply to melatonin [1]. Melatonin agonists also show promise in some forms of insomnia. Accordingly, it is now even more imperative that long-term BZD users be reviewed with respect to possible discontinuation. Strategies for discontinuation start with primary care practitioners, who are still the main prescribers.

An important point when dealing with the effects of melatonin on sleep is to understand that they are different from BZD/Z-drugs in that they exert a promoting effect on sleep by amplifying day/night differences in alertness and sleep quality and displaying a modest sleep inducing effect, quite mild as compared to that seen with the BZD. Certainly because of them being in the market for a long time, and due to the lack of new alternatives for the treatment of insomnia, the preconception that the consumer has for a sleeping pill is that of a strong sleep inducer, something that the melatonin family of compounds will hardly accomplish [137]. Therefore, a very important educational goal would be to change this view because of the lack of negative effects (addiction, dependence, etc.) the melatonin analogs have in contrast to the well-known complications of BZD.

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# Correction to: Psychiatry and Neuroscience Update: From Translational Research to a Humanistic Approach - Volume III

Pascual Ángel Gargiulo and Humberto Luis Mesones Arroyo

**Correction to:**
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This book was inadvertently published with incorrect city in the second affiliation of Humberto Luis Mesones Arroyo. His second affiliation "Argentine Association of Psychiatrists (AAP), Mar del Plata, Argentina" was amended to "Argentine Association of Psychiatrists (AAP), Buenos Aires, Argentina".

In addition to this, the heading "Stopped" was deleted in page x since it is redundant.

The updated version of the book can be found at
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