Preface

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Published online: 6 June 2009
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This collection of research papers is based on an international conference on *Brain Plasticity, Aging and Neuropsychiatric disorders* hosted by the Ramon Areces Foundation and held in Madrid, 13–14 May of 2008. The main idea behind the organization of this scientific meeting was to have the opportunity to present and discuss some new perspectives on brain plasticity in relation to aging and neuropsychiatric disorders including drug addiction.

Today we know that the brain is a plastic organ which changes constantly as a result of its interaction with the environment through physical, emotional or social stimuli. Drs. Agnati, Fuxe and colleagues in their paper use the “*Energide*” concept to point out the existence of a private *Internal Milieu* (the cytosol) as the environment where the integration of several molecular networks occurs either activated at membrane level or at intracellular level. On this basis, a new understanding of communication and information handling and thus of brain plasticity is proposed. This view could also shed light on recent research, which has shown that the expression of gene–environment interactions modulates the brain not only during development and adulthood but also during aging, and in neuropsychiatric diseases and drug addiction. The role of aging

in an animal model of extinction-induced depression is discussed in a paper by Dr. Huston and colleagues.

Plasticity in the CNS has a long history. In fact, it was Ramon y Cajal who already in 1894 used the term plasticity in a Congress in Rome, advancing the idea that as a result of training and mental exercise the connections between neurons could be changed and also multiplied. Cajal was possibly the first scientist pointing out, from a structural point of view, the influence of the environment on brain development and function through changes in neural connections. He specifically wrote “such plasticity of the cellular processes probably varies at different ages: greater in the young man, diminished in the adult and almost completely disappearing in the aged”. These ideas of Cajal are today reflected in the results of current research on the influence of an enriched environment on the brain in both young and aged animals. However, Cajal was not right in his observation that plasticity disappeared in the aged brain. Today we know that neural plasticity is still present in the aged brain but possibly the integration of the different signals and molecular networks at membrane or cytosolic levels are less efficient likely due to alterations in the three-dimensional conformations and/or turnover of proteins.

Aging of the brain, which is one of the topics reflected in some of the research papers of this special issue, is a physiological process that occurs asynchronously among different areas of the brain and the rate of that process is very much dependent on the style of life of the individuals. In fact, aging is a process that seems to be specific for each area of the brain (coding for specific functions—one or many-) and related to the neuronal-synaptic-molecular substrates of that area. Papers by Drs. Mudo, and Segovia and colleagues explore these ideas by analyzing the effects of enriched environments and neurotrophic factors on neurogenesis and neurotransmitters.

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Stress is an important topic these days which has been long shown to produce neurochemical and behavioral changes associated with altered function of many areas of the brain and their neurotransmitter activity. Brain areas of special interest include the prefrontal cortex, hippocampus, nucleus accumbens and amygdala. The neurotransmitters include glutamate, monoamines and acetylcholine. In fact, stress is implicated not only in the physiological process of aging but also has a powerful influence to predispose to development of mental diseases and drug addiction since it has been shown to change the dynamics of several neurotransmitters and their receptors and be a potent modulator of learning and memory processes. The study of the neurobiological correlates of stress to different parameters is reflected in the papers by Dr. Segovia and colleagues. Also Dr. Del Arco and colleagues present their research on the prefrontal cortex–nucleus accumbens interactions and dysfunctions as an important substrate for mental diseases such as schizophrenia and Dr. Lopez-Barneo and colleagues discuss Parkinson's disease and cell therapy. Drs. Agnati and Fuxe on the basis of their previous Red Queen Theory postulates that the aged brain has to overblow potentially dangerous mechanisms like glutamate neurotransmission in an attempt to maintain a certain degree of neuronal plasticity. Thus, they introduce the view that the same common plasticity-favouring signals like glutamate are used in learning which may cause neurodegeneration especially in the presence of reduced neurotrophic support. Dr. Ferraro and colleagues focus their paper on a different perspective, namely the effects of an early exposure to cannabinoid drugs on glutamate mechanisms and its relevance for cognitive functions.

A new perspective on receptors are given in the papers by Drs. Agnati, Fuxe and Franco and colleagues. Their papers analyze the heterodimers and receptor mosaics of different types of receptors (more than two receptors), their receptor–receptor interactions and their implications in neural plasticity, neuropsychiatric disorders and neurodegeneration. Within heterodimers and receptor mosaics

direct interactions between the receptors occur (receptor–receptor interactions) via allosteric mechanisms leading to changes in receptor recognition, signalling and trafficking resulting in an integrated response and plasticity at the molecular level in the plasma membrane. Drs. Agnati, Fuxe and Franco and their colleagues have *inter alia* investigated putative receptor mosaics built of adenosine A2A, dopamine D2, and metabotropic mGluR5 receptors. The results suggest that the differential stimulation of the participating receptors determines the major signalling pathway to be selected leading to adaptive changes in neuronal excitability and gene expression. This research offers a new perspective on neurochemistry and neuropharmacology and opens up a new window to understand the integrated actions of neurotransmitters in complex functions such as learning and memory. This molecular integration of receptors in receptor mosaics is also of crucial importance to understand the neurochemical substrates of mental diseases such as schizophrenia and neurological diseases such as Parkinson's disease. Tarakanov and colleagues in their paper also importantly suggest a role for receptor heteromers in multiple sclerosis.

As a conclusion, we would like to highlight the idea that all these changes occurring during aging and during the clinical expression of neuropsychiatric disorders and also neurodegenerative diseases are dependent on the genome–ambiome interaction. Ambioime is defined as “the set of non-genetic influences from conception to death (physical, psychological, social and cultural factors) that changes the biochemistry, anatomy and physiology of the brain or could determine the clinical expression of a disease”.

We feel very grateful to the contributors and their collaborators for making this special issue possible presenting a novel view for understanding brain aging and psychiatric and neurological disorders. Also we would like to express our sincere thanks to the Ramon Areces Foundation and to Prof. P. F. Riederer for accepting to publish the manuscripts after the regular reviewing process in this special issue.