Editorial

Interdisciplinary Approaches for Neuropathology

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The brain is unarguably the most complex and quite possibly the most fascinating organ in the body. It has inspired many generations of scientists to commit their own brain power to studying nervous system development, structure, and function. Unfortunately, the mysteries of the human nervous system defy easy exploration, but this has not deterred research in understanding neurological disease pathogenesis. The problem for health posed by brain disorders in the developed world and in many developing societies such as Mediterranean countries is demanding major important changes regarding the approach, efficiency, and solvency of governments, health systems, and the medical community. Research on brain function in health and disease is among the priorities of today's societies, and several indicators put the Mediterranean research area among strategic issues for the European Union (EU).

The Mediterranean Neuroscience Society (MNS) (https://mnsociety.live/), a member of IBRO, is highly active in this field and works towards three main objectives: i) strengthening exchanges between Mediterranean neuroscientists from more developed countries in the world; ii) promoting education in the neurosciences and increasing public awareness of progress in the field; iii) sustaining scientific, training and networking events, such as, in particular, the biennial Mediterranean Neuroscience Conference.

Many South-North collaborations and networks have emerged in recent years through bilateral and multi-lateral actions, supported by the EU or by international and national actions, whether for setting up teaching curricula (e.g. Tempus programs), or building human potential (e.g. FP7, H2020). Many other initiatives of cooperation (e.g. Neurobridges) have seen the light of day, initiated by groups of motivated individuals who believe in the importance of scientific cooperation as a way to alleviate political distress between cultures.

The main pillar on which a government with an efficient health system has to stand on in dealing with brain disorders is a strong education system and research program with scientists motivated to understand the causes of the disease, implementing early diagnostic procedures, and discovering new and effective

treatments to slow-down the progression of the disease, thereby reducing disability and costs, and increasing the quality of life of the patients and their families. Currently, we are also in a favourable position to enter into two new areas of progress, such as prevention, relying on interesting new findings related to the molecular neuropathology and genetics of brain diseases, and also pharmacogenomics, as the most effective manner of optimizing drug development and therapeutics, increasing efficacy and safety, and reducing side-effects and unnecessary costs.

This special issue of CNS Neuroscience and Therapeutics comprises some of the works presented at the last Mediterranean Conference of Neuroscience that was organized in 2017 in St. Julian's, Malta. The 6th Mediterranean Neuroscience Society Meeting MNS 2017 MALTA was a forum to discuss modern experimental and interdisciplinary approaches that have led to important new insights on the pathogenesis and treatment of diseases of the human central and peripheral nervous systems and explore new avenues for understanding the brain. The international scientific community was represented by scientists from 48 different countries from all over the world. It was a very successful event, both scientifically and socially. The MNS2017 programme included 8 plenary lectures by Giacomo Rizzolatti (IT/MT), Vincenzo Crunelli (UK/MT), Raphael Mechoulam (EL), Michela Matteoli (IT), Pierre J. Magistretti (CH), Rosa Cossart (FR), Carmen Cavada (ES), Ilana Gozes (ES) and the FENS special lecture by Juan Lerma, more than 60 symposia and hundreds of poster presentations which furthered stimulating interactions among participants. This 6th MNS Conference was surely a memorable experience.

This Special Issue starts with the contribution by McCafferty and colleagues on absence seizures (ASs), the most common form of generalized epilepsy [1, 2]. The authors demonstrated that knocking-out the δ subunit of the extra synaptic $GABA_A$ receptors in the stargazer (STG) mouse, via crossbreeding them with δ subunit KO mice, prevented the development of ASs, thus leading to a "genetic rescue" of the STG epilepsy phenotype. This study is the first example of a genetic rescue of an absence seizure

phenotype, confirming the centrality of TC neuron tonic $GABA_A$ current in the mechanisms of rodent ASs, and therefore suggesting that therapeutic interventions for these seizures based on the disruption of this current, specifically via extra synaptic $GABA_A$ receptor containing the δ subunit, hold particular promise.

Apart from regulating excitability and being involved in epilepsy, the GABA system modulates several forebrain functions. As Olucha-Bordonau and colleagues reviewed in their contribution, an important GABAergic projection arises from ascending, subcortical neural projections originating in the nucleus incertus (NI) in the pontine tegmentum and made by large GABA neurons co-expressing neuropeptides including relaxin-3, cholecystokinin, and neuromedin-B. At the behavioural level, activation of the NI promotes locomotor activity, theta oscillations in the hippocampus phase-locked to those in the brainstem, spatial learning, anxiety processes, feeding behaviour and alcohol-seeking. Further knowledge of how this system modulates these processes may offer a new therapeutic perspective on treating malfunctions associated with neuropathology and psychiatric disorders.

Florio and colleagues focus their review on basal ganglia and Parkinson's disease (PD), the most common movement disorder and the second most common neurodegenerative disease after Alzheimer's. The number of people with PD over the age of 50 will at least double by 2030 in the world's most populous countries [3]. Given the global phenomenon of population ageing affecting all nations, the economic burden of PD is expected to grow substantially in the coming decades. Unfortunately, as Florio and colleagues underline in their review, our understanding of the basal ganglia and in general of PD neuropathology is limited and therapy is only symptomatic [4]. Florio et al conclude that basal ganglia are more than just a switching device and suggest that the consequences of bilateral functional coordination loss in the progression of neurodegenerative disorders, such as PD, deserve careful consideration, assuming that they could emerge and develop unilaterally during the early-phase of their staging. Many neurotransmitter systems, apart from the dopaminergic one, seem to be involved in basal

ganglia pathophysiology. One of the most investigated neurotransmitters is serotonin [5, 6] and its 5-HT_{2C} receptors [7]. Lagière et al. show that the 5-HT_{2C} receptor agonist WAY 163909 facilitates the appearance of the late excitatory response (indirect pathway of the basal ganglia) of the substantia nigra pars reticulata neurons connected to the anterior cingulate cortex. This intriguing result might be related to an effect of the 5-HT_{2C} receptor agonist in the cortex rather than in the basal ganglia.

Another disorder that involves the basal ganglia is Tourette's syndrome (TS), characterized by multiple motor and phonic tics, emerging before 18 years of age that are recapitulated by different animal models [8] including the D1CT-7 mouse model. As shown by Santangelo and colleagues, D1CT-7 mouse model is subjected to a behavioral fragmentation, with repercussions going beyond the simple tic-like phenomenon. These phenotypes are strikingly akin to behavioral problems observed in TS patients and further validate the power of this model in summarizing pivotal behavioral aspects of TS.

The following article is on Alzheimer's disease (AD) and dementias that are major public health problems, in part due to the increasing life expectancy of the population. A search for biomarkers has appeared to be essential for the early treatment of this devastating disease. Kiđemet-Piskač and colleagues confirm and extend the evidence that the cerebrospinal fluid (CSF) levels of the tau protein phosphorylated at threonine 231 (p-tau231) reliably differentiate patients with AD and healthy control subjects as they indicate that CSF p-tau231 levels can also be used for differentiating subjects with vascular dementia (VaD) from control subjects. Additionally, in distinguishing between AD and VaD, the authors established that factor score (FS) determined by combination of p-tau231 and Mini-Mental State Examination (MMSE) has a strong potential to offer earlier distinction between these conditions. This finding not only has clinical significance, but also potential to prevent development and complications of VaD at an early stage.

The next article deals with one of the current hot topics in neuroscience i.e., the role of the lateral habenula (LHb) and the serotonergic system in depression. Delicata and co-authors show that 5-HT_{2A}

receptor and 5-HT_{2C} receptor subtypes, that are thought to play a role in the mechanism of action of antidepressant drugs and drug of abuse [11], control the activity of LHb neurons. Most of the published data on 5-HT_2 receptors in the LHb have up until now been interpreted in the light of 5-HT_{2C} receptor subtypes, while Delicata and colleagues' data would suggest a main role of for 5-HT_{2A} receptors that might act also through the activation of the LHb 5-HT2A receptor expressed on the astrocytes.

The selection continues with Carbone and co-authors' behavioral study that sheds light on the role of 5-HT_7 receptor in emotional and motivational regulations as well as in processing of memory and anxiety. The selective agonist LP-211 exhibited a modulatory effect on motivational drives and improved both visuo-spatial and emotional consolidation. On the contrary, in a third experiment, it showed a very slight anxiolytic effect in a dark light task.

The Special Issue ends with two reviews. The first by Rizzolatti and colleagues gives an historical excursus on the major advancements which have characterized system neuroscience since the golden age (1940-2000), through the brain imaging era and up to the modern era. In the latter, the use of multimodal approaches combining different recording techniques and advanced signal processing will hopefully lead to a better understanding of the neural mechanisms underlying neurological and cognitive functions. The authors believe that to this aim, the contribution offered by intracranial recordings will be fundamental, thanks to the possibility of detailing with a millisecond-based temporal resolution the time course of neural activity, and of investigating the causal relationship between the activation of cortical areas and the emergence of specific behavior. In addition, Rizzolatti and co-authors underline that given that patients undergoing stereo-EEG are free to move while being recorded, intracranial recordings should lead to a major step forward in the knowledge about the organization of the human motor system and the spatiotemporal dynamics ruling the motor contribution to cognitive functions.

The last contribution by Khalil et al. briefly outlines the plausibility of the neural interaction between motor control, imitative behaviors and their impact on social decision making in Autism Spectrum

Disorders (ASDs). Khalil and colleagues discuss the methodological approaches (i.e., fMRI and EEG recording as neurophysiological markers) that can be implemented to test the proposed competitive interactions between the mirror neuron system, the BG, and the motor cortex.

In summary, we believe that the articles presented in this special issue provide an important update on the role of neurotransmitters (i.e., GABA and serotonin), brain structure and neural networks in brain physiology and pathology. As noted in many of the articles, brain research continues to evolve as both the acquisition and analyses methods develop and expand, but the existing evidence points to the functional relevance of understanding variations in normal development and the critical importance of their structural and functional brain disruption as a means of understanding pathophysiology and potential pathways for intervention or even prevention. The articles in this special issue are small steps along that path.

Guest Editors

Giuseppe Di Giovanni, Vincenzo Crunelli and Giacomo Rizzolatti were the President and the honorary Presidents, respectively, of the Local Organizing Commette of MNS2017.

Giuseppe Di Giovanni holds a PhD in Neuroscience. He is Professor of Human Physiology at the University of Malta, as well as an Honorary Professor at the Neuroscience Division of the School Biosciences at Cardiff University, UK. He has received grants from national and international grant bodies. His main research interests are in experimental neurology and biological psychiatry. Specifically, he is interested in the pathophysiological role of serotonin in brain disorders, such as epilepsy, depression, drugs of abuse and Parkinson's disease. He is frequently invited to speak at and Chair National and International conferences on serotonin. He is the Coordinator of the Malta Neuroscience Network, and the Vice-President of the Mediterranean Neuroscience Society. He is also the Editor-in-Chief of the Journal of Journal of Neuroscience Methods and he sits on the editorial board of several prestigious international journals. In addition, he is an expert with the intergovernmental framework known as European Cooperation in Science and Technology.

Vincenzo Crunelli is Professor of Neuroscience, at the Neuroscience Research Division, Cardiff University. He is an Affiliate Professor (since 2015) at the University of Malta, Malta. He is a member of Academia Europaea and a Fellow of the Academic of Medical Sciences (UK). He has received major grants from the Wellcome Trust, Medical Research Council and European FP4, FP6 and FP7 (H2020). His research focuses on the cellular and network mechanisms operating in the thalamus and cortex during sleep and absence epilepsy, focussing on both neuronal and astrocytic assemblies. His multi-disciplinary

group uses a combination of electrophysiological, morphological, immunocytochemical and confocal imaging techniques both in normal and transgenic, in vivo and in vitro animal models, as well as a computational approach for simulations of neuronal and astrocytic network activities.

Giacomo Rizzolatti is Emeritus Professor of Human Physiology, University of Parma. Responsible of Parma URT of the CNR Institute of Neuroscience. He is Affiliate Professor (since 2015) at the University of Malta, Malta. He is Member of Academia Europaea, of Accademia dei Lincei, of the Institute de France (Académie des Sciences), and Honorary Foreign Member of the American Academy of Arts and Sciences and Foreign Member of National Academy of Science (USA). He is Honorary member of Italian Society for Neuroscience and Italian Physiological Society. He has received many awards and among which the most recent are: The Brain Prize from Lundbeck Foundation and recently the prestigious "Premio Lombardia è Ricerca" of 1 milion Euros. He has received Honorary Degrees from the University Claude Bernard of Lyon, from the University of St. Petersburg, St. Petersburg, from the University of Sassari, from KU Leuven and University of St. Martin, Buenos Aires. The main focus of his research concerns the motor system and its role in cognitive functions. He is the discoverer of mirror neurons.

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