ERA-NET NEURON

Neurodevelopment, boost for new interplays.

Figure legend: Speaker and ERA-NET NEURON members at the symposium in Rekyjavik, Iceland, May 2013

By Hella Lichtenberg and Marlies Dorlöchter. MD is the coordinator of ERA-NET NEURON at PT-DLR on behalf of the German Ministry for Education and Research (BMBF)

One of the key-elements of the ERA-NET NEURON is the support of excellent research in the area of disease-related neuroscience. ERA-NETs are projects funded by the European Commission in various research fields that offer new types of co-operation between European ministries and funding agencies. By co-operation and co-ordination on a national or regional level between funding bodies, a European Research Area is created in which cross border research is funded, allowing research groups to jointly work on specific problems, exchange ideas, and benefit from interdisciplinary expertise. Twenty-one funding organisations from 16 EU Member States, Associated Countries, and Canada participate in ERA-NET NEURON for disease-related neuroscience.

Within the multitude of activities of the EUROPEAN MONTH OF THE BRAIN in May 2013, the ERA-NET NEURON organised a symposium on 'NEURODEVELOPMENT AND RELATED DISORDERS' on May 16th, 2013 in Reykjavik, Iceland. The symposium was hosted by RANNIS, the Icelandic Centre for Research and well attended by over 150 visitors.
The topic is hot because the dogma of brain diseases as – though complex - traits of certain life times is currently under debate. Instead, many researchers now think (and experiment) on the influence and variations of brain development during the lifespan. Like any tissue, the development of the brain and its functions occurs as a result of coordinated influences that include heritable variations in genomic sequence. A neurodevelopmental disorder can thus be described as a disorder that alters development of the brain,
interfering with growth and function over time. Or, as Etienne Hirsch, the organiser of the ERA-NET NEURON symposium put it "The topic of this symposium represents one of the most important and challenging aspects of sciences. Indeed, the development of our brain influences our entire life and thus, if this process is impaired, the consequences may last for years and may be associated with a lot of suffering."

The first part of the symposium was a 'General overview of nervous system development' by Amparo Acker-Palmer and a talk by Klaus-Armin Nave on 'Myelin and Glial cells in nervous system development'. They focused on how the billions of neurons (transmitting nerve impulses) and glial cells ('mother's little helpers', not conducting nerve impulses) orchestrate the brain development to set up complex behaviors such as cognition, learning, hearing, vision, dreams, consciousness.

Dr. Amparo Acker-Palmer

Acker-Palmer leads the Molecular and Cellular Neuroscience Research at Goethe University Frankfurt, Germany, that centres around the molecular basis of synaptic plasticity and development of the nervous system. Synapses are specialized, mushroom cap like projections at neuronal cells and crucial for information transmission. Acker-Palmer deciphered a special molecule, Ephrin B, as essential component in the modulation of synapse formation and of a certain pathway that controls neuronal migration. Some severe brain diseases like epilepsy, ataxia, schizophrenia and Alzheimer's disease are - among other features – characterized by a lack of migration. Recent scientific curiosity directs towards the Blood Brain Barrier (BBB), that is a most highly regulated interface between the peripheral blood circulation and the central nervous system that prevents the passage to the brain of most (harmful) molecules while allowing entry to other (useful) molecules. Several BBB dysfunctions are known and new treatments could possibly benefit from its modification in the early developmental stage.

Dr. Klaus Nave

Nave heads the Department of Neurogenetics at the Max-Planck-Institute of Experimental Medicine in Göttingen, Germany. In his talk he explained that myelinating glia (those that form a thick insulator around conducting nerve fibers thereby promoting high-speed electrical signaling) are only found in higher vertebrates, building the 'white' impression of the so called white brain matter. White matter abnormalities in neuro-psychiatric diseases are observed e.g. in multiple sclerosis. A major goal of his research is to better understand the molecular mechanisms by which nerve cells instruct associated glial cells to wrap axons (signal conducting projections) and to support nerve fiber integrity. Long-term integrity, and thus function and survival require myelin maintenance by other metabolically active specialized glial cells. Nave hypothesises that "Such neuro-protective function may have been the primary role of axon-associated glial cells in nervous system evolution. Perturbations of this glial support of axonal energy metabolisms are a likely cause of reduced connectivity in the brain and the loss of higher brain functions."

In the second part of the symposium, a special emphasis was put on the diseases characterised by abnormal development of the brain, such as autism, mental retardation, attention deficit hyperactivity disorder (ADHD), language disorders, learning disorders, motor disorders, and others.

Dr. Wendy S. Roberts

In her contribution 'Focus on Autism and Neurodevelopmental Disorders' Wendy Roberts, head of the Department of Paediatrics at the University of Toronto, Canada explained that the term autism has rather been exchanged for Autism Spectrum Disorders (ASD), because the latter better reflects the heterogeneous 'spectrum' involving impairments in three domains of function: social communication, language, and preference for repetitive, solitary and stereotyped behavior. Roberts says that only approximately 20% of ASD can currently be explained by known genes. The average age of the children is ~4.5 years when a clinical diagnosis is made, but the optimal age of intervention should be much earlier. Families experience a 'Diagnostic Odyssey' and can go years without a focused management plan. Other complications are the many medical co-morbidities like e.g. seizures (convulsions), gastrointestinal and sleep problems. She is confident that a better understanding of the causes of autism will benefit medical management and improve health and mental health outcomes for all neurodevelopmental disorders.

Dr. Karen B. Avraham

Karen B. Avraham, head of the Department of Human Molecular Genetics and Biochemistry at Tel Aviv University, Isreal talked about 'Developmental disorders of sensory systems: the example of deafness'. Deafness may have been overlooked as developmental disease but a severe to profoundly deaf child is born every 1,000 births, with hearing loss in 4% of people below age 45 and reaching 50% by age 80. She explained that while this sensory defect is quite common, it is genetically heterogeneous with many genetic forms of deafness, and each in themselves is rare. It is thus not surprising that many rare forms of deafness are represented by 61 genes. Because hearing loss can manifest in complex forms studies are directed to a better understanding of the genetic regulation of the development and function of the ear including large scale genetics. It is thus important to identify genes associated with deafness in order to detect genetic mutations in patients for genetic counseling and rehabilitation, and to discover new mechanisms for deafness that may help

develop therapies.

Dr. Yehezkel Ben-Ari

The thought-provoking concept that some disease of the elderly may even start early during life was by Yehezkel Ben-Ari, honorary head of the 'Institut de Neurobiologie de la Méditerranée' in Marseille, France in his presentation on 'Neurodegenerative disorders of aging are neurodevelopmental disorders'. This is reasoned by the fact that ionic currents, which are responsible for the electrical signaling in nerve impulse transmission, follow developmental sequences and are very different in immature and adult neurons. His research focuses on a particular molecule, GABA (a chemical substance and so called neurotransmitter) which is the main inhibitory neurotransmitter in adult brain. However, it excites immature neurons and its actions are thought to exert an important role in developmental processes. Because spatial and temporal organisation are crucial for the correct cortical networks formation, it is not surprising that alterations of these – normally highly fine-tuned - sequences play a central role in developmental malformations, notably migration disorders and associated neurological complications.

Dr. Ragnhildur T. Karadottir

The symposium was concluded by a special lay audience presentation: "The bright side of the brain: the role of white matter in brain function and dysfunction" by Ragnhildur Thora Karadottir. She explained that the human brain is equally segregated into grey and white matter. The white matter actively affects how the brain learns and functions and provides a data superhighway that links ~100 billion neurons situated in the grey matter - the brain's computational area. Thus, the grey matter is primarily associated with processing and cognition while the white matter modulates the distribution of electrical signals (action potentials), and is essential to coordinate fast communication between different brain regions indispensable for us to be able to think, move, sense our environment, and see. The cells in the brain communicate between each other utilising electrical signals that are converted into chemical signals at specific cell junctions. Karadottir, researching at the Cambridge Centre for Brain Repair and Cambridge Stem Cell Initiative, UK, detailed that in the last decades neuroscience research has focused on understanding these signals between neurons. In disease, where either the neurons die, or the supporting cells or the white matter are damaged leading to mental and/or physical disability. Different to the grey matter the white matter has the capability of repair.

Conclusions:

As Etienne Hirsch summarized it: "Altogether, this symposium emphasised the role of developmental alteration during the whole lifespan. It stresses also the need for understanding the role of genes in brain development, how genetically predisposed events may be altered by environment and what determines brain normal functioning and dysfunction." We are witnessing a paradigm shift: when 15 years ago a genotype was thought to be a more or less invariable determinant of a phenotype, the question is now how the environment impacts on the genotype. It is for instance known that maternal stress poses enduring effects on gene expression in the child. Current research will thus increasingly focus - besides ongoing gene identification - on the epigenetic (chemical modifications on the DNA sequence) characteristics of a particular phenotype. Such efforts are directed towards a personalised medicine including, but not limited to, the search for preventive interventions that also comprise measures for family stress and consideration of economic implications of ineffective or insufficient interventions.

During the 'after work' reception lively discussions took place. It was highly appreciated that this symposium brought scientists from very different areas together with ministry and funding agency representatives and the general audience. As Amparo Acker-Palmer said: "This is a new concept of interaction, with efficient contact and important exchange".