ERA-NET Neuron

NEWSLETTER 34

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If you a first author of an outstanding scientific article in the field of neuroscience published in 2019 - you may be eligible to apply with a chance to win 3000€ and an opportunity for a special lecture at the NEURON midterm symposium!

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NEURON Midterm Symposium of JTC2018 Call on:
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January 26-27th, 2021, Berlin

'Neuroethics and quality management' Workshop
January 26th, 2021, Berlin

Organized on behalf of EBRA

Funded by the European Commission

More information can be found on our website
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From the desk of the coordinator | August 2020

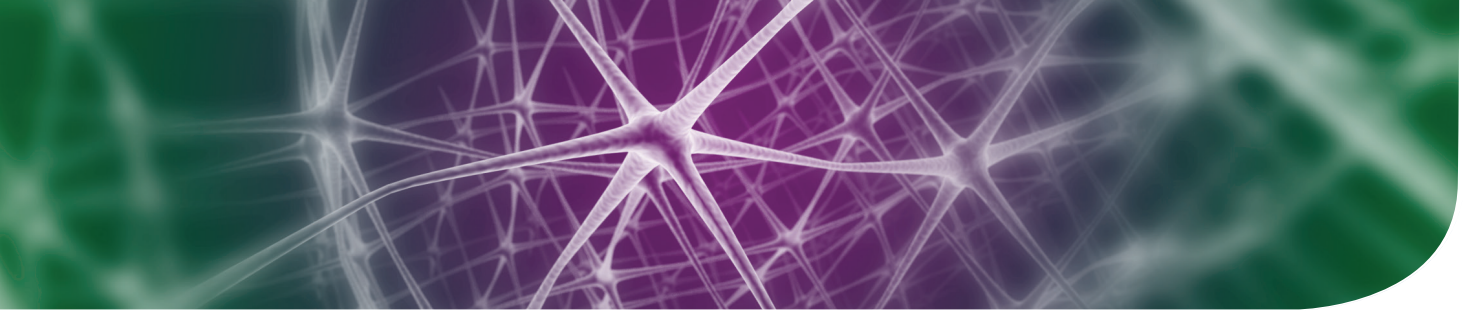
Marlies Dorlöchter

The world as we had known it has tremendously changed worldwide in the last few months. The COVID-19 pandemic has affected everyone and every aspect of our lives, including scientific research and researchers, patients with neurological diseases and their families, as well as other features NEURON is involved in. However, we continued working, collaborating transnationally from home offices around the globe to keep our joint funding schemes running, our actions in motion and with plans for the future.

One of our accomplishments for this time period is the publication of ERA-NET NEURON's updated Strategic Research Agenda 2020 (SRA2020) 'Taking on the Challenges of Nervous System Disorders 2021 – 2025'. The SRA was developed by a group of renowned international researchers and it includes hot topics, future perspectives, and bottlenecks in the field of fundamental neuroscience, neurology, psychiatry, and sensory organs. Three main areas are addressed: (i) understanding disease mechanisms, (ii) understanding disease progression, and (iii) interventions. The SRA is a scientific document and NEURON invites the scientific community to comment on it. This document will guide the funding agencies on the topics of interest for the joint calls for proposals and enabling activities in the upcoming years.

Recently, ERA-NET NEURON had the honor to partake in the FENS2020 Forum (July 11-15th), the largest neuroscience event in Europe, which has gone virtual due to the worldwide COVID-19 pandemic. Our participation began with a NEURON plenary lecture by Sonia Garel from the Institut de Biologie de l'Ecole Normale Superieure, who spoke about Microglia regulation of cortical wiring and neuroimmune interactions throughout development. Followed by a special lecture by Alberto Parras Rodriguez, winner of the 2019 EPNA Award, who spoke about Autism-like phenotype and risk gene mRNA deadenylation by CPEB4 mis-splicing.

This summer issue of the NEURON newsletter covers the latest foresight scientific symposium on neurodevelopmental disorders, which was held virtually on May 12th. The symposium was chaired by Etienne Hirsch and Bernard Poulain. Seven renowned speakers from various fields of research on neurodevelopmental disorders presented overviews

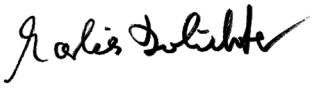


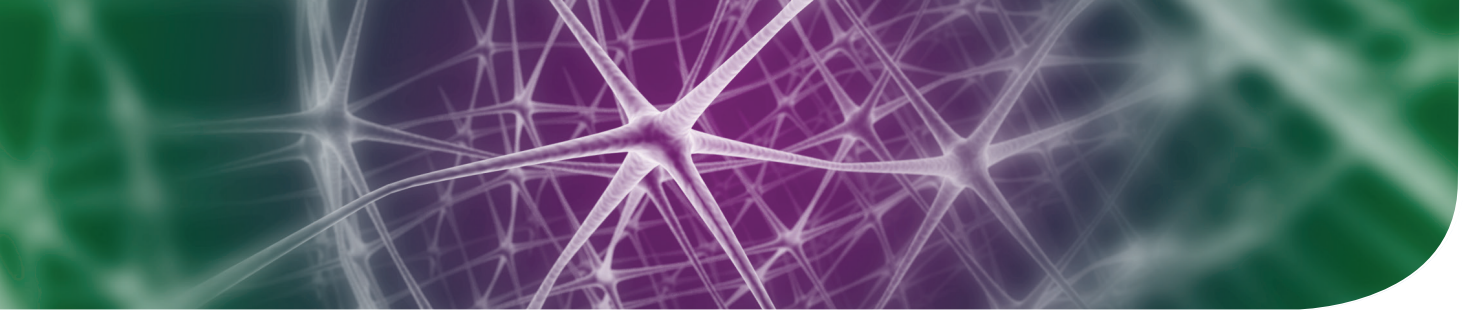
about the state-of-the-art in the respective research areas. Two patient representatives, Tony Lloyd (ADHD foundation, also speaker) and Harald Neerland (Autism Europe) gave a talk and a brief statement, respectively, and participated in the subsequent panel discussion.

This issue also includes an interview with one of the NEURON-subsidized participants in the Cajal-course on 'Advanced Techniques for Synapse Biology' that took place in October 13th to November 1st, 2019, at the Neurocampus in Bordeaux (see pg. 13). Within the partnership with the Cajal Advanced Neuroscience Training Programme, NEURON offers stipends for the registration fee for early career researchers that have been selected among applicants and are partners in a NEURON-funded project.

Wishing you health and safety for both body and mind during this erratic time.

Sincerely,





Foresight symposia on Neurodevelopmental Disorders – May 12th

Thirty representatives from 20 NEURON partner organisations, 7 speakers, 5 members of NEURON's scientific advisory board and two guests participated in the virtual foresight symposium on 'Neurodevelopmental Disorders', which was organized by Etienne Hirsch, Bernard Poulain, Alexis Mareschi, and Christine Tuffereau. The symposium served as a consultation step for the NEURON funding organizations to receive a scientific update on the topic.

The field of neurodevelopmental disorders is highlighted in the new NEURON Strategic Research Agenda (SRA) as a prioritized issue. In the updated SRA it is acknowledged that many mental disorders root in events in the developing brain and that understanding the role of endogenous and environmental alterations during brain development of children, adolescents or young adult is crucial. It is emphasized that the early part of life has strong implications for the individual's brain health. It is thus particularly important to encourage research on the role of alterations in the brain development occurring before and after birth and in childhood. Hereafter, you will find short summaries of some of the presentations given at the symposium.

Wieland B. Huttner

NERVOUS SYSTEM DEVELOPMENT

Prof. Wieland B. Huttner

Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

The expansion of the neocortex is one of the major features of nervous system development in humans, as increased brain size and folding are hallmarks of hominid evolution. This neocortex expansion relies heavily on the embryonic neural progenitors in the developing brain. Apical progenitors, found in the primary proliferative or ventricular zone, generate the basal progenitors found in the secondary subventricular zone. The basal progenitors, which later generate neurons, can undergo mitosis in the larger subventricular zone, hence maximizing neuron production and making these cells the key for brain expansion.

Investigations on the genomic basis for neocortex expansion in the human brain revealed the importance of human-specific genes, emphasising the need for relevant models. For example, studies on the ARHGAP11B gene proved the usefulness of transgenic mice, ferrets and marmoset monkeys as models, allowing to highlight the role of this human-specific gene in the increase in basal progenitor proliferation, lengthening of the neurogenesis period, increase in the number of upper-layer neurons and folding of the brain. At a cellular level, this protein has been shown to promote glutaminolysis in the mitochondria, a metabolic pathway characteristic of rapidly developing cells, pinpointing the importance of understanding the metabolism of neural progenitors to understand brain development.

Some studies however require models more closely related to humans. One such model are three-dimensional cerebral organoids, for example of chimpanzee, which have been used to investigate the differences caused by human genes, such as the increased duration of metaphase in human apical progenitors. Lastly, the molecular mechanisms of folding were more closely studied in ex vivo cultures of foetal human neocortical tissue, pinpointing the role of hyaluronic acid in the extracellular matrix in neocortex folding.

Fiona Francis

GENERAL OVERVIEW OF NEURODEVELOPMENTAL DISORDERS

Dr. Fiona Francis

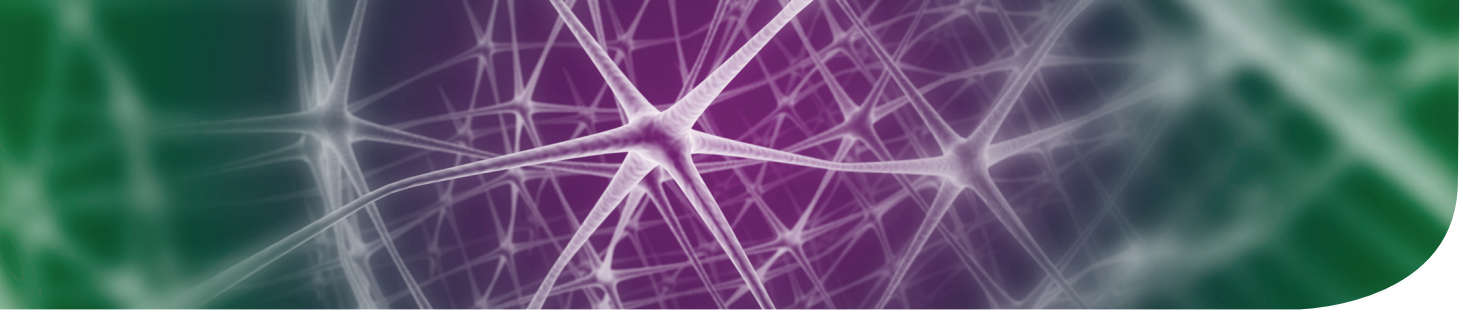
INSERM UMR-S 1270, Fer à Moulin Institute, Pierre et Marie Curie University, Paris, France

Cortical disorder research is a rich topic that illustrates how much knowledge still needs to be acquired in the field of neurodevelopment. The required investigations rely heavily on genetic findings and unravelling the associated cellular mechanisms in animal and in vitro human models. However, the large number of disease genes continuously identified in patients make investigating all the hypotheses a challenging and time-consuming process, pinpointing the need for efficient validation methods for mutant genes.

For cortical malformations alone, associated with epilepsy and intellectual disability, the range of disorders and associated genes to investigate is very broad. On one side of the spectrum, microcephaly is characterized by an insufficient number of cortical neurons due to either cell death or deficiencies in the division of neural progenitor cells. In the latter case, a number of identified disease-genes have pinpointed a role at the centrosome, a key organelle in cell division, yet these genes are still likely to have other roles during cortical development, a subject of ongoing investigation.

Further cortical malformations are due to abnormal neuron migration and subsequent cortical layering abnormalities, causing impairments of neuron function that are still being explored. In the lissencephaly ('smooth brain') spectrum, genetics has pinpointed an important role of the microtubule cytoskeleton in migrating neurons, but also in radial glial cells. In periventricular heterotopia (abnormal clusters of neurons close to the ventricles), the commonly identified genes hint for disease-associated mechanisms at the actin cytoskeleton, which regulates adhesion components in progenitor cells and migrating neurons, or in some cases, affecting the extracellular matrix. Lastly, cobblestone lissencephaly research has revealed defects of radial glial cells, with abnormal glycosylation of a basal membrane glycoprotein components, impairing the normal interactions with the extracellular matrix. Some similarities of this disorder with polymicrogyria also suggest that other yet unknown mechanisms may be involved.

All these examples show how large a gap currently exists between understanding the patho-mechanisms of cortical development disorders and identifying adapted therapies for these disorders.



GENETICS OF NEURODEVELOPMENTAL DISORDERS, PRENATAL DIAGNOSIS

Prof. Anita Rauch

Institute of Medical Genetic, University of Zurich, Switzerland

With over 2,500 established recessive disease genes identified and even more genes unrecognized, it is undeniable how important a role genetics play in neurodevelopmental disorders. Genetic testing, before and during pregnancy, is thus key for early diagnosis solutions.

Modern sequencing methods, for example, allow for high-throughput sequencing pre-conceptional carrier screening for autosomal recessive disorders, with interesting results on investigation risk couples frequency. Yet, this approach is strongly impaired by the considerable number of genes involved: considering only 400 of the many recessive disease genes identified, a 2011 study shows that every individual is a carrier of an average of 3 autosomal recessive diseases. This is even without considering the issue of correct variants classification, as we can only use information of obvious pathogenic variants in prenatal diagnostic, nor the numerous genes with undefined disease association and mutational mechanisms.

Furthermore, about 60% of the severe neurodevelopmental disorders are caused by de novo variants that can only be investigated during pregnancy through conventional carrier typing and chromosomal microarray, which methods are not as efficient for all fetal phenotype. To achieve proper diagnosis during pregnancy, there is yet to tackle the major hurdle of variant interpretation and to build knowledge on genotype-phenotype correlation for many diseases genes causing different phenotypes that are still not easily predicted. In addition to these monogenic pathogenic variant, it is important to consider and investigate common variants in terms of polygenic risk factors and protective variants that may further modify the disease risk and severity.

Pierre Gressens

FOCUS ON AUTISM SPECTRUM DISORDERS

Prof. Pierre Gressens

Université de Paris, NeuroDiderot, Inserm, Paris, France

Centre for the Developing Brain, Saint Thomas' Hospital, King's College, of London, UK

Observations in different neurodevelopmental disorders suggest that common determinants and mechanisms could be shared over many disorders, even though we do not truly understand these relations yet. In autism spectrum disorders (ASD), for example, genetic determinants have a strong influence, with over 1,000 described genes potentially involved, but environmental factors and epigenetics also seem to play an important role.

In fact, the increasing incidence of autism over the last decade could hypothetically be linked to exposure to more environmental factors toxic for the developing brain. One of such factors is prematurity, with pre-term infants having 7 times higher risk to develop ASD compared to term infants, a risk that could be even further increased when combined with other factors such as inflammation.

The case of systemic inflammation highlights the importance of non-neuron cells in ASD and neurodevelopmental disorders in general. Indeed, inflammatory cytokines in the blood leads to the activation of microglia, which then disrupts the normal brain development. This links back to genetic factors, as inflammatory microglia impairs the normal modulation of specific gene expression at timepoints of the brain development. Microglia itself could also be directly affected, as it express several synaptic genes that are known genetic factors for autism. Evidence has also been collected that interneurons transcriptome and density are affected in ASD patients, potentially impairing the interneuron-dependent plasticity.

The genetics factors in neurons, microglia, astrocytes and interneurons are of the upmost importance for ASD, as well as how they are affected by environmental factors such as prematurity, inflammation, microbiota and gut dysfunction. Lastly, changes in the clinical phenotypes have been observed during adolescence that may hide new pathological and resilience mechanisms not yet understood.

Julia Jacobs

CHILDHOOD EPILEPSY

Prof. Julia Jacobs

Departments of Pediatrics and Clinical Neurosciences, Alberta Children's Research Institute & Hotchkiss Brain Institute, Alberta Children Hospital, University of Calgary, Canada

Department of Pediatric Neurology, University of Freiburg Medical Centre, Freiburg, Germany

Epilepsy is a mostly paediatric disease affecting 1 million children and adolescent in Europe, with an increasing incidence in children. Yet, prognosis solutions are still lacking, as the disease evolve through a process, epileptogenisis, that is not well understood, making it difficult to predict when could occur the first seizure and whether or not it could evolve toward chronic epilepsy. In this regard, new biomarkers should be investigated, using improvements in clinical neurophysiology, neuroimaging and genetics.

Other issues revolve about treatments, as one third of the patients are still beyond current solutions, which mostly focus on suppressing the seizures.

Research efforts are being made for disease-modifying treatments, with either drugs or gene therapies that rather target specific mechanisms of epilepsy or epileptogenesis than suppress seizures. Other therapeutic approaches focus on the role of neuroinflammation and immunomodulation, beyond commonly associated etiologies, and on more precisely targeted therapies. Yet, all these solutions meet a severe hurdle in that they are generally not tailored for the developing brain, and efforts are needed to improve clinical trial designs and to investigate the mechanisms and long-term effects of these treatments.

Lastly, it is important to consider how much of a burden epilepsy can represent for families, especially facing the lack of understanding on the comorbidities in paediatric and adult epilepsy. Dialogue must be fostered with families and caretakers in order to develop educational and seizure-detection tools, for example, that really answer their needs.

Tony Lloyd

PATIENTS CARE, EPIDEMIOLOGICAL STUDIES, SOCIO ECONOMICS

Dr. Tony Lloyd

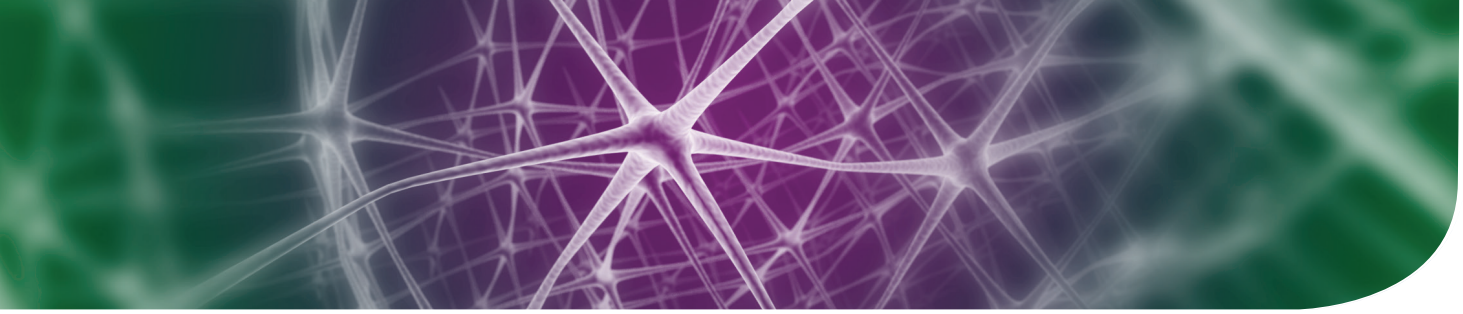
CEO of ADHD Foundation, Liverpool, UK

As a whole, neurodevelopmental disorders have a very high prevalence, with potentially 1 in 5 people in the general population affected by one or more of these disorders. Yet, those are still heavily underdiagnosed or suffer diagnosis biases.

As an example, half of the new ADHD diagnoses in the UK are adults, many of whom only learned about their disorder by having their child diagnosed, possibly explaining the prevalence difference between children and adults by the lack of access to proper information and diagnosis. This bias is especially serious considering the cost of undiagnosed and unmanaged disorders. Studies in Denmark showed ADHD diagnosed in adulthood induces around 8,600€ additional private costs per person per year and around 9,000€ public costs, mostly resulting from lower income.

Another very detrimental bias resides in how those individuals, especially children, are often viewed through the lens of only one particular diagnostic, rather than through a broader spectrum of neurodevelopmental conditions. The frequency of comorbidities is very high both between neurodevelopmental disorders and with other conditions such as obesity, diabetes and mental, sleeping or eating disorders, and these co-occurring conditions needs to be addressed together.

In terms of patient care, observations pinpointed how neurodevelopmental disorders affect the quality of life of patients, especially regarding mental health and socioeconomic outcomes. Considering the importance of an early diagnosis of these conditions, it appears critical to strongly involve parents, school workers and family practitioners by efforts in information dissemination and training. For ADHD, as an example, it is suggested to transition from psychiatry alone into primary care settings that would foster an integrated multidisciplinary approach.



INTERVENTION ON NEURODEVELOPMENTAL DISORDERS

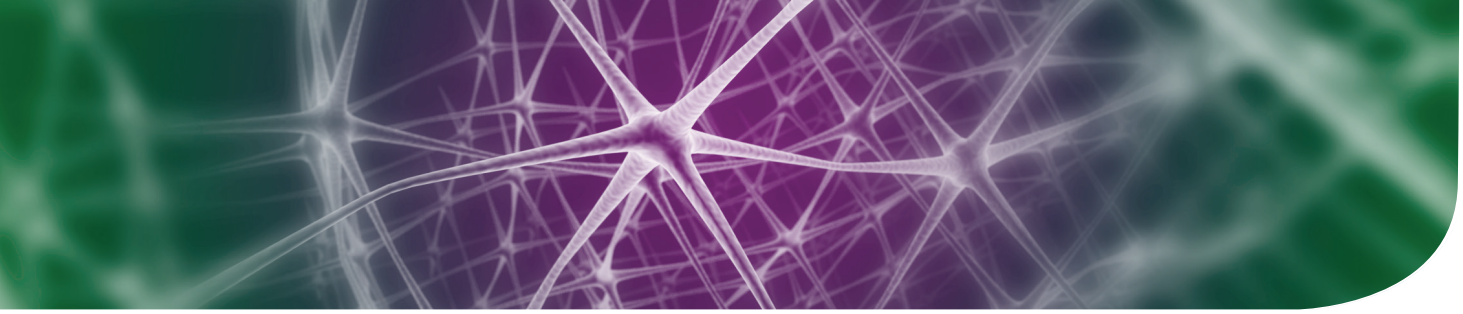
Prof. Renzo Guerrini

Neuroscience Department, Anna Meyer Children's Hospital, University of Florence, Italy
DESIRE European project

Beginning intervention as early as possible is among the key principles regarding interventions on neurodevelopmental disorders, thus pinpointing the importance of sensitivity and specificity of diagnostic approaches for earlier identification. A second principle is the need for intensive interventions, preferably even transferred to the daily life to amplify its time range, involving families and caretakers. Lastly, in an effort to develop more tailored interventions, more and more attention has been drawn on interventions based on natural history of the disease, epigenetics, influence of environmental factors, and identification of gene abnormalities, which pushed toward initiatives in precision medicine. In this perspective, setting up disease registries is particularly important.

Progresses are made relying on these principles, yet several burdens remain that slow these progresses. In epilepsy for example, identification of a large number of disease-associated genes has not led to a parallel increase in the number of medications, while on the other hand, identification of specific biological pathways should in theory prompt new etiology oriented clinical trials. In addition, looking at the example of autism spectrum disorder, interventions using medication, if they can help, are overall considered non-sufficiently specific. On a different level of intervention, behavioural and communication approaches are being deeply investigated with trials exploiting device-assistive technology, biofeedback, diagnostic telemedicine and parent-mediated intervention.

In addition, interesting US studies have been characterizing the structure of the brain in autism based on brain banks. In Europe, an epilepsy brain bank has been running for several years and has proven itself very informative. As challenging as it may be, brain bank initiatives in Europe for specific neurodevelopmental disorders could be very efficient to develop improved interventions on these diseases.



PANEL DISCUSSION WITH REPRESENTATIVES OF EUROPEAN PATIENT'S ORGANIZATIONS

Harald Neerland

President of Autism Europe, Norway

Dr. Tony Lloyd

CEO of ADHD Foundation, Liverpool, UK

The concluding panel discussion provided insights from the patient community to put forward their priorities on research and care for neurodevelopmental disorders.
Research efforts focusing on earlier diagnosis appear to be key for the patient community, as it would allow to begin the intervention at an earlier age, strongly improving the outcomes in neurodevelopmental disorders. In this regard, it is essential to work on improving both the diagnosis and the knowledge on causes and risks factors of these disorders, by building understanding on the genetic background of the conditions and particularly investigating the multifactorial environmental factors and their epigenetic impact on health, education and well-being at all ages.
Furthermore, a very important priority focus on providing support for patients, which involve a broad spectrum of professionals. Indeed, while the diagnosis of neurodevelopmental disorders is medical, the help for the patients is predominantly educational, and proper support can only be achieved by providing information and resources to families, caretakers and school systems. So far, dissemination of knowledge on these disorders to the general population is lacking and information does not seems to find correctly its way from the scientific community to families, school workers and health practitioners.
This communication problem also raise the issue of stigma surrounding these disorders. An over reliance on genetics alone in medicine and scientific research tends to reinforce the "disease" model of neurodevelopmental conditions, Yet, with a prevalence so high that around 1 in 5 people in the population could have some form of neurodevelopmental disorder, a point was made that these individuals may not be considered "disordered" from an evolutionary point of view. In this regard, it would be beneficial to use our understanding of these disorders to improve life chances, education, mental health and employability, rather than seeking to really "cure".

Interview with NEURON-subsidized participant in the Cajal Course on 'Advanced Techniques for Synapse Biology'

Andrea Santuy

Andrea Santuy

1. Please tell us about yourself.

I did my PhD in the Cajal Laboratory of Cortical Circuits, directed by Javier DeFelipe in Madrid (Spain). My research focused on the characterization of the cerebral cortex using 3D electron microscopy. Last year I was awarded an Alexander von Humboldt fellowship to pursuit postdoctoral research in the Hertie Institute for Clinical Brain Research, located in Tübingen (Germany). The project focuses on the study of the regulation of synapses in the human brain by combining electrophysiological recordings with electron microscopy imaging to analyze how synaptic transmission is altered when we silence the network or alter postsynaptic proteins.

2. What ERA-Net NEURON project is your lab involved in and what is your role in it?

The Cajal Laboratory of Cortical Circuits lab is involved in the translational collaborative project called "Multi-scale investigation of synaptic dysfunction after stroke" (MISST). Stroke is the leading cause of long-term disability in Europe, and while there are effective treatments for acute stroke, the mechanisms responsible for chronic disorders that appear afterwards (like depression, progressive cognitive dysfunction, or dementia) are unknown, and therefore, there are no treatments. The project tries to characterize and understand the structural and molecular basis of chronic remote changes occurring after stroke on the synaptic level. In our lab we investigate possible microanatomical changes of pyramidal cells in the contralesional hemisphere after stroke and determine possible alterations in the density and spatial distribution of excitatory and inhibitory synapses. The goal is to combine this knowledge with other techniques such as in vivo neuronal labelling with viral vectors, in vivo brain imaging by super-resolution microscopy (STED), high field MRI, behavioral tests, electrophysiology, and zymography to develop novel therapeutic strategies which may protect the brain from chronic synaptic dysfunction and functional decline.

3. Can you briefly describe the Cajal Training Course on "Advanced Techniques for Synapse Biology" that you participated in?

Hard at work in the Cajal Training Course on "Advanced Techniques for Synapse Biology"

The Cajal Training Course on "Advanced Techniques for Synapse Biology" took place over three weeks in October 2019 in Bordeaux, France. It was a very dense packed program composed of talks in the mornings, lab rotations in the afternoons and discussions some evenings during dinner. The focus of the course was the synapse, studied from every perspective, from the electrophysiology, the biochemistry, or the anatomy, to the network implications of their malfunction. The talks in the morning were given by outstanding researchers in their field, many of whom also tutored the research projects we developed in the afternoon. Every student participated in two 10-day long projects, together with one or two more students and in close contact with the researcher. During those three weeks we had a lot of science and a lot fun.

What made this course so great (besides the organization) is where it took place, the Bordeaux School of Neuroscience has been specifically designed for such courses, with labs devoted to every technique in molecular and cellular neurobiology and with access to state-of-the-art microscopes belonging to the Bordeaux Imaging Center, allowing the students to develop high level projects.

4. How did the course contribute to your research work? What was the most significant outcome from this course for you?

When I took the course, I was transitioning from the lab where I did my PhD to the lab where I am now conducting postdoctoral research. My focus until that moment had been on electron microscopy, but this course taught me a broad spectrum of techniques, it broadened my horizons and stirred my curiosity. It gave me confidence in using lab equipment in a friendly environment, and it put me in contact with people from very different fields, people that now are friends I can contact whenever I need help.

5. Do you think it is important to support participation of early career researchers in such training courses? Why?

I think these courses are especially of great interest for early career scientists. From the morning lectures to the hands-on sessions, I cannot think of a better way to learn neuroscience in such depth. The fact that organizations, such as ERA-NET NEURON, support us economically is a great help, since not all laboratories can cover the expenses and without grants, many would miss this great opportunity.