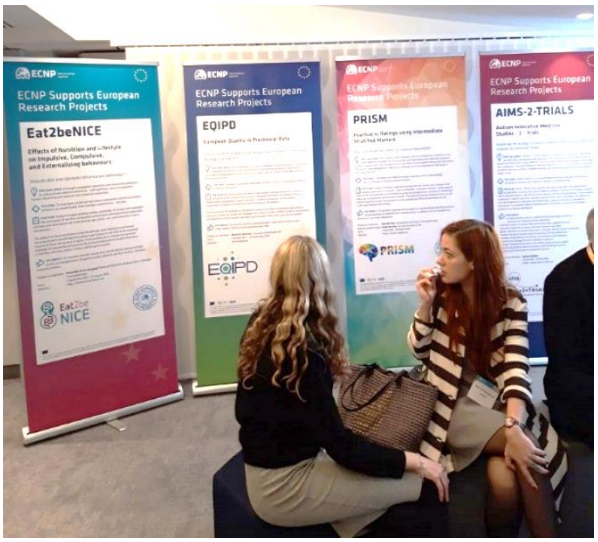
Diary of the 2019 ECNP Workshop for Early Career Scientists in Europe

The **2019 ECNP Workshop** in Nice, France (7-10 March 2019) provided a unique opportunity for 100 early career scientists in Europe to gather together and discuss the latest advances and perspectives on applied neuroscience with research leaders in the field.

During the three days in Nice, France, the participants followed a series of exciting talks from top experts about novel insights and the latest advances in preclinical and clinical neuroscience. This year, focus was on the prevention of psychiatric and neurological disorders. A career development session was also in the programme.

The participants also had the opportunity to present their own research and discuss it with colleagues and experts. Twenty of them presented their data to the audience in the main room, and two sessions were dedicated to the presentation of the posters. The best poster presenters will have the opportunity to show their findings at the next ECNP Congress in Copenhagen, Denmark (7-10 September 2019). Other participants have been also chosen to receive travel awards and attend the Congress. Finally, the abstracts of their research have been published in a supplement of the ECNP journal *European Neuropsychopharmacology.*

The ECNP Workshop also provided an opportunity for the presentation to participants of five research EU projects – PRISM, EQIPD, Eat2BeNice, AIMS-2-TRIALS and conect4children – through a dedicated space with infographics and information terminal.



ECNP recognises the importance of networking for early career scientists: breakfasts, a welcome dinner and lunch gave time for informal discussion with colleagues, friends and senior scientists. The participants also had a free afternoon to visit together the beautiful city of Nice.

The **first day**, **Martien Kas** (University of Groningen, the Netherlands), chair of the ECNP Workshop Committee, welcomed the participants and introduced the Workshop programme and speakers.

Right after, **John F. Cryan** (University College Cork, Ireland), neuropharmacologist and microbiome expert, opened the scene with his intriguing **keynote lecture** about the connection between brain development and gut microbiome.

A fascinating aspect of the field starts from the consideration that microbes were here a long before our brain. Cryan explained that the microbiome influences the health of our nervous system and this occurs from development through maturation, in aging and in disease. A germ-free world is not ideal for our nervous system. When Cryan and colleagues looked to animal models in which the gut microbiome has been completely removed, they observed an abnormal development of the brain and an effect in their social behaviour.
The microbiome is therefore crucial since the first phases of neurodevelopment. But the data presented show that our brain can also age better with a "good" microbiome. It is indeed not simple to give a definition of "good microbiome", but the data are suggesting that the more diverse the microbiome is, the better it is for our health. Now Cryan and others are working on the characterisation of the microbes, the molecules that they release, and how these can influence the development and homeostasis of the nervous system. Moreover, an important line of research is to understand how stress, diet, medications and other factors can change the microbiome, and with what consequences. Data from animal models and patients suggest that the status of our microbiome across the lifespan might increase or reduce the risk to develop psychiatric disease in children and adolescents or dementia in elders. The link between the microbiome and brain is now established and opening a new research field with possible translational possibilities. Cryan concluded his keynote lecture with a captivating take-home message: "*A state of gut will mark your state of mind*".

The discussion continued during the **welcome dinner**.

The **second day** started with a morning session about new findings in *molecular and cellular mechanisms* related to the causes, characteristics and control of psychiatric and neurological disorders.

Can we study autism spectrum disorders (ASD) in animal models? The research presented by **Gaia Novarino** (Institute of Science and Technology, Austria) starts from the observation that ASD have a strong genetic component. Several genes implicated with these disorders have been identified and most of them converge on a much smaller number of biological pathways. Novarino explained that the generation and analysis of mouse models for ASD-associated mutations can help us to better understand the pathological mechanisms underlying these disorders. Starting from patient data, her group identified a gene – *BCKDK* – associated with ASD and other comorbidities that encodes for a kinase involved in the metabolisms of the branched-chain amino acid (BCAA). Next, they identified mutations in the gene *SLC7A5*, encoding for a branched chain amino acid transporter. *SLC7A5* mutant mice showed low brain levels of BCAAs, abnormal protein translation, reduced synaptic transmission, sociability impairment, seizures and motor abnormalities. Interestingly, she also explained how it is possible to rescue some of these features by providing the BCAAs to the animal. Other genes involved in transcriptional regulation and epigenetic changes – such as *SETD5* – are associated with ASD and data suggest that these different mechanisms may converge to affect specific neuronal circuits and lead to the same phenotype. The study of these models can provide insights about the pathology, but also this might point to the possibility to treat some symptoms of ASD even after their onset.

Brigitte L. Kieffer (McGill University, Canada) has isolated the first gene encoding for an opioid receptor, opening an entire research field aimed at understanding the molecular basis of opioid-controlled behaviours. She started her talk by reflecting on the history of opioids and their use for over 4,000 years for their pain-relieving and euphoria-producing properties. Kieffer explained that nowadays the abuse of prescription opioids has escalated, and we face a worldwide health and societal burden represented by addiction to heroin and other synthetic opioids.

An opioid used in pain therapy should efficiently relieve the pain without producing side-effects, sustain efficacy in chronic treatments, and, very importantly, not be addictive. Where are we in identifying such "ideal opioid"? Kieffer remarked that there is indeed a better understanding of the opioid system and its role in the brain: the opioid receptors *mu*, *delta* and *kappa* have been identified**,** and we know more about their endogenous ligands, the enkephalins. These findings helped in developing new molecules to target these receptors. But the research for the ideal opioid is still ongoing, she remarked. The opioid system has several roles including the modulation of reward processes, the control of the pain, and in the regulation of autonomous peripheral functions. The three classes of receptors contribute to all the several facets related to the opioid system and its ligands, including both the positive aspects – the pain-relief, the euphoria and the anxiolytic action – and the negative ones – addiction. The receptors play different roles depending on how much they are stimulated and their localisation in specific brain regions. The pharmacological research is now looking for modulating the effects of the opioid receptors by using the concept of the biased signalling, as Kieffer explained. A distinct ligand that binds a certain receptor can modulate the conformation of the receptor in a certain way. Specific sets of signalling components are then activated, and this can trigger diverse responses. Hence, the idea of biased signalling is based on developing new molecules – designed also with the help of computer modelling – that are capable to target specific opioid receptors that would activate only those signalling pathways that are relevant to the therapy, but not those that might produce unwanted effects.

Novel insights into *behaviour* and the neurobiological mechanisms and neural circuits underlying its induction, control and co-ordination were presented during the session in the afternoon.

Christian Lüscher (University of Geneva, Switzerland) showed how optogenetic tools can be used to investigate the mechanisms of addiction *in vivo*. Optogenetics – a biological technique that is extensively used in neurobiology – makes use of light to modulate the activity of neurons that have been genetically changed to express light-sensitive ion channels. This technique is nowadays also used in animal models to study and modulate certain behaviours and further understand brain disorders. With the use of optogenetics and neuroimaging, Lüscher showed how it is possible to characterise the various stages of addiction in the animals, which circuits are involved, and how these circuits change in terms of activity over time.
Lüscher also highlighted how is crucial it is to understand the mechanisms underlying the transition from a controlled consumption to a compulsive use. Once the neural circuits have been identified and characterised, optogenetics allows to even modify the addiction-associated behaviour of the transgenic animal for example by stimulating or inhibiting certain neural circuits. Lüscher proposed to use optogenetics to delineate the circuits, which could be targets of deep brain stimulation, a recognised therapy for Parkinson's disease. This successful approach – called optogenetically inspired deep brain stimulation – demonstrated the translational potential of the technology and might be used in the future to develop treatments also for addiction.

The group of **Claudia Buss** (University of California, Irvine, USA) studies foetal programming of brain development and how conditions during pregnancy can alter the developmental trajectory of the foetal brain, which ultimately may increase the risk of developing a psychiatric disease in adulthood. Buss explained that maternal stress mediators (e.g., glucocorticoids, pro-inflammatory cytokines) play a fundamental role in neurodevelopment and that there is a link between maternal stress, the levels of these mediators during pregnancy and increased risk of mental disorders in her offspring. The exposure of the foetal brain to these stress-related mediators has an impact on the development of the foetal brain in terms of structural and functional neural connectivity. Buss remarked that this can affect the future neurocognitive functions of the brain and there is a potential risk of developing psychiatric problems. However, it is still not completely elucidated whether and how a specific type of stress in the mother can "mark" the foetal brain to develop a certain disease. Moreover, further investigations are needed to understand how to prevent and to reverse an acquired defect.

The day concluded with the first **poster session**.

Recent findings in the field of *clinical neuroscience* were presented in the morning session of the **third day.**

Damiaan Denys (University of Amsterdam, the Netherlands) psychiatrist and philosopher, gave a talk about the application of deep brain stimulation (DBS) in the treatment of psychiatric disorders. With this technique – which makes use of electrodes surgically implanted in the brain of the patients – one can electrically stimulate specific brain areas to treat disorders (although DBS is also used to study pathophysiology and investigate research hypothesis). In psychiatry, DBS has been used to treat different diseases, including obsessive-compulsive disorder (OCD), Tourette's, depression and anxiety, but the total number of treated patients is still quite limited. Denys explained that the patient must be selected and prepared carefully for DBS: he or she should be severely ill and refractory to any other treatment. No comorbidities should be present and there should be a potential for improvement. The surgery to implant the electrodes is relatively quick, but the optimisation of the treatment and follow-up require much more time. Next, Denys showed some cases of patients successfully treated with DBS, including examples of severe anxiety, Parkinson's and OCD. An intriguing example analysed during the talk was about an OCD patient obsessed by compulsively cleaning his house all day. This behaviour stopped with the DBS treatment, Denys explained. After that, this person was looking for a job and is now working as a cleaner for few hours a day. Denys highlighted that this is an interesting case because DBS changed the experience of the behaviour from compulsive to voluntary. The future of DBS now looks to set to switch from an open loop stimulation – that requires the continuous intervention of the doctor to set up the stimulation parameters – to a close loop stimulation – in which the DBS device is capable of monitoring and changing the electric stimulus *ad hoc* without the doctor intervention.

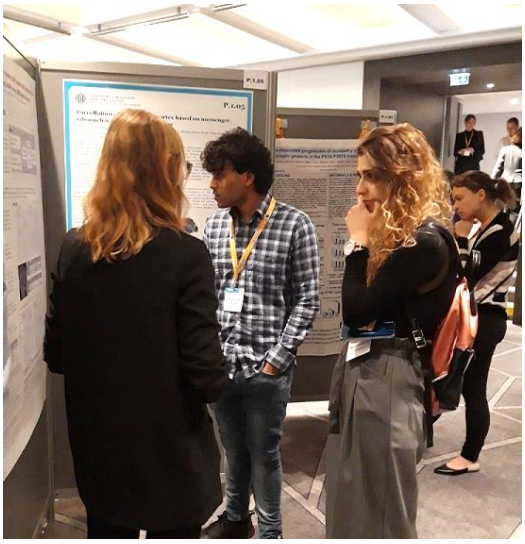
Kim Q. Do (Lausanne University Hospital, Switzerland) highlighted how the interaction of genes and environmental risk factors during neurodevelopment leads to cognitive, affective, social and behavioural impairments in schizophrenia (SZ). These risk factors converge on a critical hub made of NMDAR hypofunction, neuroinflammation, dopamine dysregulation and redox imbalance/oxidative stress, affecting parvalbumin interneurons (PVI) circuits, thus leading to structural and functional dysconnectivity. Based on peripheral and central oxidative stress markers in SZ patients, this hypothesis received support from genetic experimental models (*gclm*-KO mice) with glutathione synthesis deficiency, thus preventing an adequate redox balance regulation. Do showed that these mice reproduce numerous phenotypes described above. Many other SZ models also present a convergence on microcircuit impairments induced by oxidative stress. Additional insults in juvenile and peripubertal ages – but not in adult *gclm*-KO mice – lead to permanent PVI-microcircuit impairments, highlighting damaging consequences of childhood trauma in patients. Oxidative stress during peripuberty increases neuroinflammation, a process involving the MMP9-RAGE pathway. This reciprocal interaction of oxidative stress with neuroinflammation and glutamate/NMDAR hypofunction leads to long-lasting deleterious positive feed forward processes. N-acetyl-cysteine (NAC), an antioxidant GSH precursor prevents these alterations. In chronic SZ patients, supplementation with NAC improved their negative symptoms as well as the mismatched negativity and local synchronisation. In first episode patients, it also improves cognition (processing speed) and structural connectivity. This translational approach paves the way for early prevention, aiming at modifying the disease course by redox modulators.

In the afternoon, the participants followed the *career development* session.

Niall Boyce (UK) is the editor of *The Lancet Psychiatry* and during his talk shared ideas and suggestions on how to publish high-quality papers. He explained that the most important thing is to ask yourself two fundamental questions: “Is my scientific question a relevant one?” and “Is the method that I have chosen the proper one to answer to the question?” The method should fit the question, and not the other way around. Moreover, the authors must explain the context of their work concisely and set out clear future directions for research. Many aspects should be considered when one wants to publish scientific data. For example, the decision about which journal to choose for publication should not be dictated by its impact factor, but by the interest and relevance of the work for the journal and its audience. Boyce also remarked that if reviewers ask for revision, it is good news because peer-review

is a constructive process that will improve the work. Finally, he reminded the audience that authors should consider their engagement strategy in disseminating their work: nowadays it is not only about publishing the paper, but how one can communicate its message to a variety of stakeholders using both old and new media.

Freya Robb (UK) of the *Science Media Centre* in London explained that scientist engagement in public debate is vital nowadays. This is especially important in mental health, as it is extensively covered by news media. Robb highlighted that the public understanding of science is critical, if we look at some famous examples, such as autism and vaccination. Science and health issues regularly make the news, and the general public trusts the scientists and still gets information about science through the national news. Knowing this, scientists must consider that if they do not join the public debate, the discussion will be covered by other people with not enough expertise or with conflicts of interests. Finally, she described how organisations, such as the Science Media Centre, work together with scientists, news media and other stakeholders to assure that accurate and evidence-based information about science is provided to the public and to the policy makers. "Media do better science, when science do better media" – she concluded.



The **second poster session** closed the day.

The **last day** gave space to a session about the *preventative intervention* in brain disorders.
During neurodevelopment, neurons establish contacts each other via synapses and neuronal apoptosis may occur as part of the normal maturation process of the nervous system. Importantly, the onset of several psychiatric disorders overlaps or immediately follows the period of brain development and an increasing amount of evidence show that the development of the neuronal circuitries is affected in psychiatric diseases. Cellular and animal models can be used to better understand the mechanisms, to test hypothesis and develop preventive intervention.

Following this line of research, **Oscar Marín** (King's College London, UK) and collaborators are investigating the neural circuitry established over time between the glutamatergic pyramidal neurons with GABAergic interneurons in the cerebral cortex of mice *in vivo*. Marín and colleagues used DREADD (designer receptors exclusively activated by designer drugs) expression to control the activity and survival of these groups of neurons. As an example, he showed how modifying the activity of pyramidal cells alters the survival of interneurons.
He remarked that an important factor in the experiment is the time: they observe in fact that neuronal survival or synaptogenesis are influenced by the time point during which the DREADD-modification (activation or inhibition) occurs. Those neurons – that enter in the apoptotic pathway if inactive during a certain window of time – do not do the same at another later time point. Starting from this model, Marín identified two main pathways – PTEN and AKT – which are involved in neuronal apoptosis. Therefore, this model provides an interesting platform to understand the basic pathological

mechanisms of brain diseases, and raise new intriguing questions concerning, for example, the effect of the environment and genes on these mechanisms. It is however already clear that neurodevelopment is crucial for brain health and represents a window of therapeutical intervention.

Celso Arango (Hospital General Universitario Gregorio Marañón, Spain) started his talk highlighting how the prevention of mental diseases plays a critical role in the future of applied neuroscience. Prevention in psychiatry – differently from other fields such as oncology and cardiology – has been a neglected topic for a long time, because considered not possible or too expensive. Arango showed that this is not true: recent data reveal that prevention of mental diseases is possible and preventing mental disease does have a huge pay-off in terms of costs in the long term. Several mental disorders have a neurodevelopmental background and there is a widespread consensus that the earlier is the intervention, the better is the outcome. Different factors – including genetics and environment – concur to shape our brain. The level of mother's and father's stress during the conception, the use of abuse substances during pregnancy, birth and perinatal complications (such as pre-term birth), bullying and abuse in childhood: all together these factors may increase the risk for an abnormal neurodevelopment and lead to the onset of psychiatric diseases. The future of psychiatry lies in developing *ad hoc* preventive strategies based on the knowledge of these causative factors: a great example of successful prevention is represented by the programmes to prevent bullying in schools. Paraphrasing Frederick Douglass, Arango concluded his talk with the reminder that, "it is easier to build strong children than to repair broken men": this applies also for psychiatry and can pave the way to the promotion better mental health and to prevent brain diseases.

Finally, **Martien Kas** closed the 2019 Workshop with congratulations to all the early career scientists for their work and for their participation to the Workshop and inviting all of them to join the next ECNP Congress in Copenhagen.

We are looking forward for the next 2020 ECNP Workshop!
Visit the ECNP website for more information, or send an email to: nice2020@ecnp.eu

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Link to the abstracts of the ECNP Workshop for Early Career Scientists in Europe, 7 - 10 March 2019, Nice, France in *European Neuropsychopharmacology*.