N°4 – MARCH 2016

NEWSLETTER

NATIONAL CENTRE OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY

synapsy
bringing together brain research and psychiatry
National Centre of Competence in Research

Research Project

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UNIVERSITÉ DE GENÈVE
UNIL Université de Lausanne

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CHUV Centre hospitalier universitaire vaudois
HUG Hôpitaux Universitaires Genève
FNSNF Fonds national suisse Schweizerischer Nationalfonds Fondo nazionale svizzero Swiss National Science Foundation
UNI BASEL
FMI Friedrich Miescher Institute for Biomedical Research

Scientists and Clinicians Unite Against Autism

Great interdisciplinary collaboration makes modern biomedical research happen! After six years of activity, the NCCR SYNAPSY program is carrying out groundbreaking results.

This year we reached the midterm of SYNAPSY's Phase II. To our delight, we see that dialogue between clinicians and researchers has matured, increasing the interaction and exchange of ideas between members. This has led to an engagement in solid translational approaches. Evidence is in the rich debates we observed in recent steering committees and scientific meetings. Clearly the NCCR is succeeding in its primary task to bring scientists and clinicians together.

Editorial
by Prof. Pierre J. Magistretti
NCCR-SYNAPSY Director

In addition, SYNAPSY provides a framework for building large cohorts of patients. They are essential for conducting and carrying out clinical trials, for the particularly complex brain diseases SYNAPSY is exploring. The cohorts also serve to inspire researchers on where to guide their investigations. This issue of the SYNAPSY Newsletter focuses on autism, the third project of axis I, supervised by Dr. Marie Schaer. She describes the establishment of the Autism Spectrum Disorders (ASD) cohort, a major achievement of the NCCR. Other co-leaders of the autism program present their aims and recent successes, inspired and driven by the patients.

Another important objective of the NCCR SYNAPSY is to encourage women's careers. The NCCR autism project definitely constitutes a very good example of their promotion to the highest academic positions. Indeed, out of the six group leaders contributing to the project, four are females. Together with Marie Schaer, professors Nadia Chabane, Camilla Bellone, and more recently Claudia Bagni, have joined the autism team. To emphasize women's excellence in biomedical research, the present newsletter publishes an interview with Camilla Bellone, who manages to combine a harmonious life-work balance.

The capability to raise funds represents a critical step in launching financially steady projects. Among the investigations driven by the NCCR, clinical studies are especially costly. Despite the significant support of the Swiss National Science Foundation, our ability to solicit other funds in parallel could be mandatory for the trial's outcome and implementation.

With the help of Professor Stephan Eliez, SYNAPSY received external financial support from the Fondation Pôle Autisme for the autism cohort. Hopefully, the future projects initiated by SYNAPSY will obtain this type of private income.

We hope to see you all at the Neurobiology of Mental Health Conference, organized by SYNAPSY and housed at the Geneva Campus Biotech this coming April 7th to 9th.□

A Translational Approach to Better Understand Autism Spectrum Disorders

By Prof. Marie Schaer

Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental disorders characterized by social and communication deficits, as well as repetitive behaviors or restricted interests. At a time when ASD is estimated to affect nearly 1 in 68 children (Baio, 2014), there is a critical need for the development of therapeutics that can lower the burden of the disease on affected individuals, helping them towards better scholar and professional achievements and social integration. Currently, the main factors that impair the development of targeted treatments are the relative lack of a detailed understanding of the pathophysiology of this disease, combined with the broad heterogeneity of the autism spectrum.

ASD develops during the first years of life, and hundreds of putative genes have been implicated. Despite considerable variations in the degree of severity of autistic symptoms and cognitive impairments, extant clinical studies to date point to the fact that social deficits are the core symptoms of ASD. Indeed, deficits in communication skills and interpersonal interactions are the most unifying characteristics presented by individuals on the spectrum (McPartland et al., 2011). Further, recent clinical trials have taught us that we can improve the outcome of ASD with early interventions that target the development of social skills. These interventions, such as the Early Start Denver Model (ESDM, Dawson et al., 2010), however, have to be started during the first 3 years of life, considered as a "window of opportunity" for the most optimal long-term outcome. As specialized centers for early intervention become available in Switzerland and worldwide, clinicians are increasingly facing the challenging task of identifying children with ASD as young as possible. Diagnosing autism at an early age remains indeed challenging, and novel techniques such as eye-tracking represent promising candidates to aid clinicians identify risk factors earlier on. Also, an important difficulty in autism research is to understand the mechanisms by which these early and intensive interventions help restore developmental trajectories of affected children, and whether some individuals will respond better than others.

The NCCR project aims at contributing to some of these key questions in ASD research. Over the years, the autism pole of the NCCR SYNAPSY has evolved, with the goal to propose a translational approach to help understanding the pathophysiology of autism, and develop mechanism-informed tools to aid early diagnosis and improve therapeutic strategies (see Fig. 1).

Since the start of the NCCR SYNAPSY, P. Scheiffele's and R. Schneggenburger's laboratories have worked on mouse models of autism. With his colleagues, Peter Scheiffele has made the hypothesis that the highly heterogeneous genetic lesions impact a much smaller group of molecular core pathways. Pathways that have emerged include mGluR-signaling, regulators of protein translation and the PI3K-mTOR pathway (Baudoin et al., 2012). The circuit-based information is currently used to prioritize and validate intervention strategies at the circuit and synaptic plasticity level; potential treatment approaches are evaluated in rodent models for their efficacy of normalizing social behavior, with promising results so far (see Highlight No. 1). In parallel, Ralf Schneggenburger and his group have examined the GABA-mediated synaptic transmission, focusing on the role of inhibitory synapses in social and aggressive behaviors. Again, attempts to restore the impaired pathways and measure the impact on the social behavior of the mouse models are under way (see Highlight No. 2).

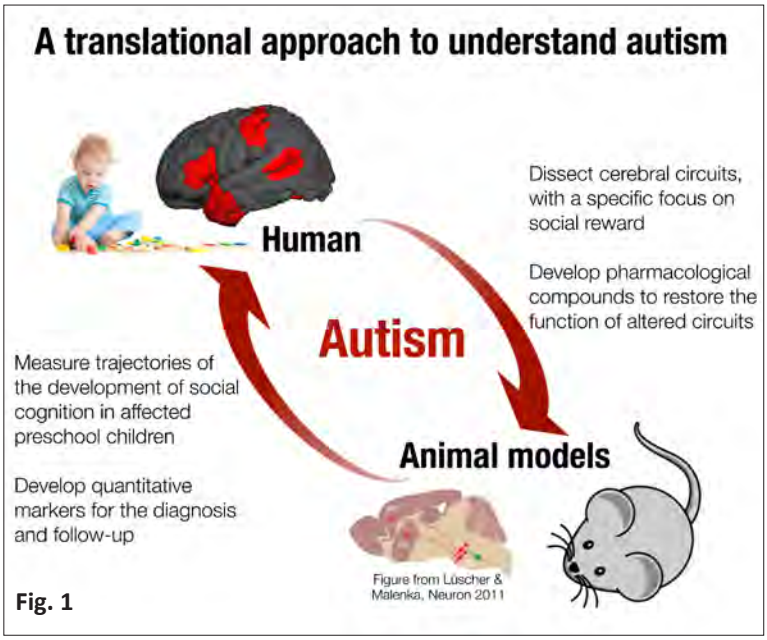

Fig. 1

In 2012, a human counterpart was added to the NCCR autism pole, with the constitution of a longitudinal cohort of young children with ASD. This cohort includes toddlers who received a recent

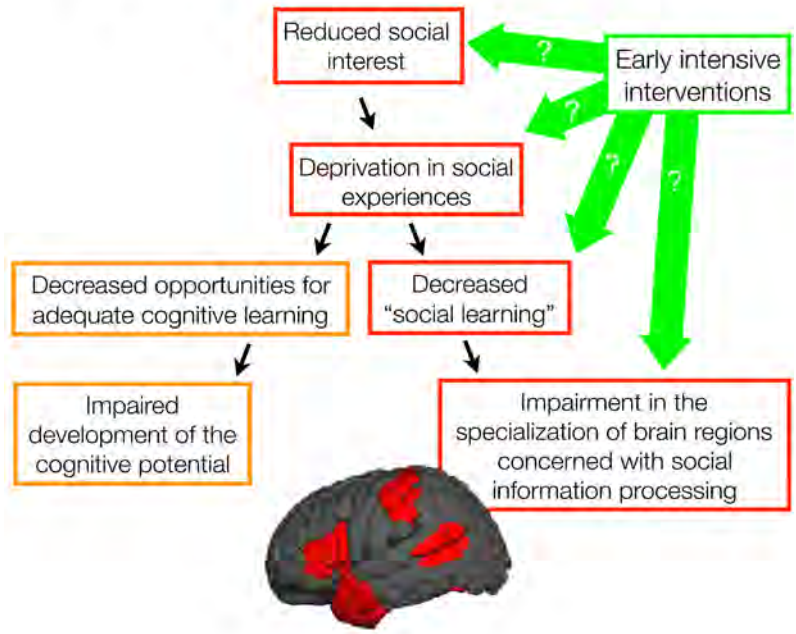

Fig. 2

diagnosis of ASD (~2 years old), as well as their typically developing peers, who are repeatedly assessed over time to measure the development of their social cognition. A variety of standardized eye-tracking and EEG experiments have been designed to address the assumption that the primary deficit is a lack of social orienting. The so-called "social motivation hypothesis" (reviewed in C. Chevallier et al., 2012) suggests that a deficit in motivational aspect in orienting to people, and maintaining interactions with them, explains how ASD symptoms and cognitive difficulties develop progressively during early childhood (see Fig. 2).

The social motivation hypothesis provides a conceptual framework that can at the same time account for the diverse range of autistic symptoms, help understand the pathogenesis of the disorder and inform the development of targeted therapeutic interventions (see Schaer et al., 2014 for a review). So far, data from eye-tracking paradigms support the theory that a lack of social orienting has cascading effects on the development of communication skills (see Highlight No. 3). Already at the time of diagnosis, preliminary EEG results in the brain of young children viewing biological motion, point to a reduced activation of the salience system in the brain of young children while they are viewing biological motion, thereby providing a neurobiological substrate for the reduced interest in people. In addition to contribute to the understanding of the neurodevelopmental alterations associated with autism, this well-characterized longitudinal cohort of preschoolers serves to develop quantitative biomarkers that provide objective measures to probe how outcome can be modified with therapeutic intervention. Currently, the effect of behavioral interventions on these biomarkers is being assessed. In the longer-term, the cohort and establishment of rigorous biological markers will provide a platform for targeted clinical studies with pharmacological treatments identified in preclinical rodent trials.

More recently, Camilla Bellone and her team joined this NCCR effort to further our understanding of autism, bringing unique skills to examine the neural circuits involved in social reward in mouse models of ASD. Her work has demonstrated that selective reduction of SHANK3 in the ventral tegmental area alter dopaminergic transmission and is associated with social deficits. Within the NCCR, Camilla Bellone and her group are further examining the cellular mechanisms by which SHANK3-VTA results in a lack of motivation for social interactions. They also assess more broadly the neurobiological mechanisms of social rewards in mouse models (see Highlight No. 4), maximizing opportunities for efficient translation with the human clinical project focused on the social motivation hypothesis.

Year after year, the autism NCCR research pole is growing and delighted to welcome new Principal Investigators who are bringing additional skills and forces, constituting a fruitful environment for the continuous refinement of our research goals as a team. Coming from Paris, Nadia Chabane was appointed as a Full Professor to lead the cantonal center for autism in Lausanne. She wishes to contribute to the NCCR by recruiting and assessing young children with autism, following the model set in Geneva (see Highlight No. 5). Finally, Claudia Bagni is the newest addition to the team bringing her research expertise to contribute the NCCR autism projects, following her appointment as a Full Professor in the Department of Fundamental Neuroscience in Lausanne. In Leuven-BE, and in many renowned international universities before that, Claudia Bagni has been studying mouse and fly models to examine how molecular mechanisms are altered at the synaptic level in Fragile X or ASD, leading to learning deficits or behavioral issues.

As a result of these increased opportunities for collaborations between clinical and fundamental scientists, the synergy between autism subprojects is gaining a unique momentum, with the goal to lead to significant advances in autism research in the coming years.□

Highlights no 1 to 5 ☞

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1/ Targeted Pharmacological Interventions in ASD

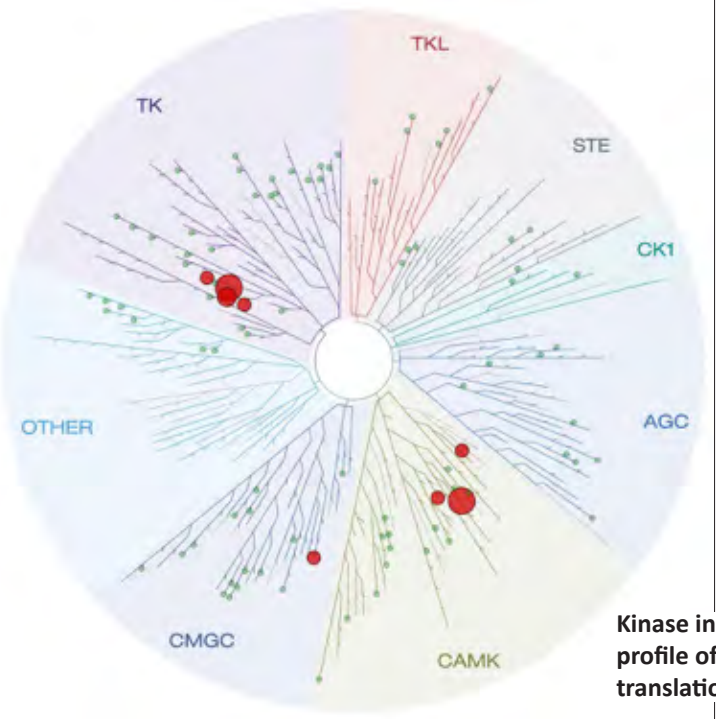
by Prof. Peter Scheiffele

The genetic and phenotypic heterogeneity of autism represents a major challenge for designing therapeutic strategies. A significant fraction of autism cases are thought to arise from high-impact mutations in individual genes or copy number variations. To date, more than 100 such mutations, which modify multiple cellular functions, have been identified.

However, there is an apparent convergence of signaling alterations related to synaptic plasticity, which shape neuronal circuit during development. This indicates that –despite the genetic complexity of the syndrome– a more limited number of cellular core processes might underlie the etiology of the disorder.

In recent studies, we demonstrated that mice carrying a mutation in neuroligin-3 –one of the high impact risk genes for autism– exhibits a defect in metabotropic glutamate receptor-dependent long-term plasticity in the cerebellum. Surprisingly, we discovered that loss of this synaptic adhesion molecule also results in a severe disruption of mRNA translation, a process that is perturbed in a number of ASD models carrying seemingly unrelated mutations. Thus, interventions that restore translation homeostasis may represent a promising entry point to improve neuronal circuit function and behavior in autism.

There are several cancer drugs targeting mRNA translation initiation that can be examined for their potential to treat it. In our recent studies we identified such pharmacological interventions that bring back normal levels of cap-dependent translation in neuroligin-3 mutant mice. The same interventions rescue ASD-related behavioral phenotypes in these animals. To advance the development of preclinical candidates for autism we are now examining novel chemical derivatives of these inhibitors with optimized brain-penetration and increased target-specificity.□



Kinase inhibition profile of novel mRNA translation modulators

2/ Role of Medial Amygdala Synapses in Autism-related Social Deficits

by Prof. Ralf Schneggenburger

In our project, we use mouse models to address the synaptic and circuit mechanisms which might underlie the pathophysiology of ASD. We are especially interested in the hypothesis that social behavior deficits represent a central behavioral symptom of autism (see articles by Marie Schaer), and that ASD might be caused by dysregulation of GABA-mediated inhibitory synaptic transmission. Although this hypothesis has been around for some time, deficits in inhibitory synaptic transmission in mouse models of ASD have not been directly linked with circuits involved in social behavior.

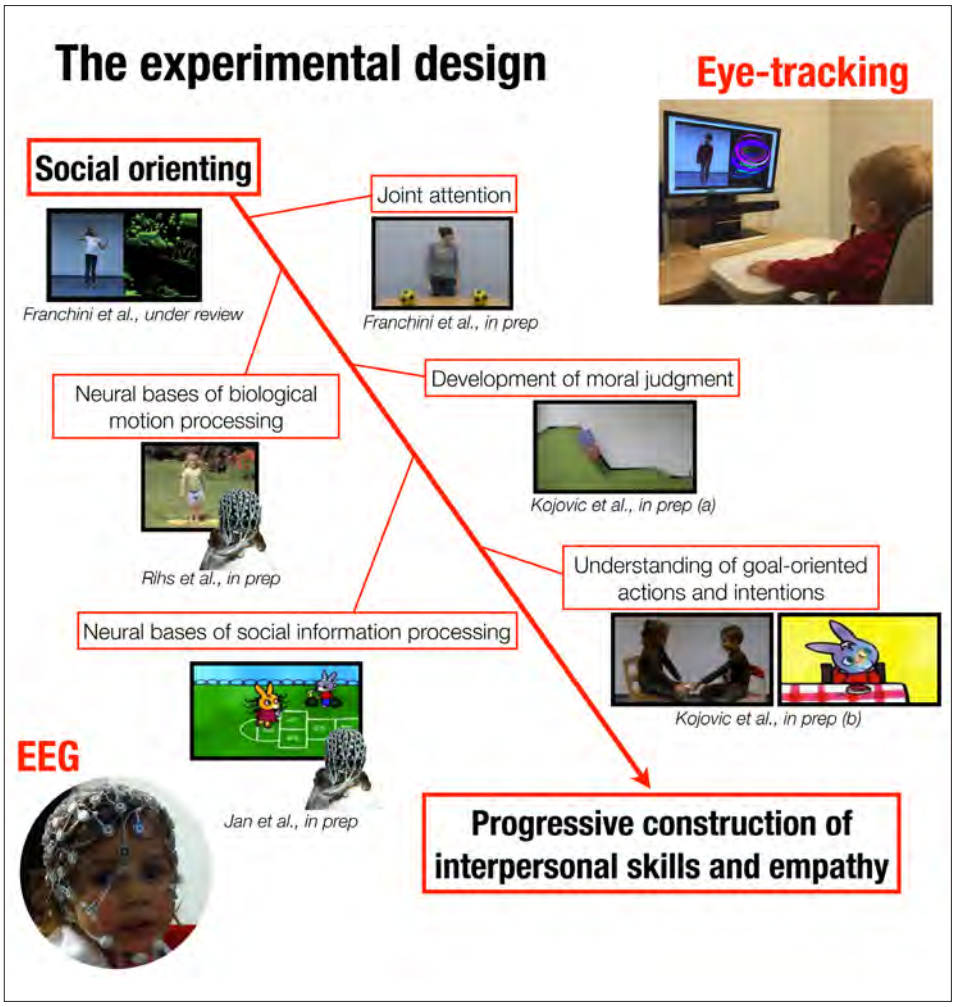
We investigate the medial amygdala, an area which is intricately involved in social behavior, and which contains several types of GABA releasing neurons. Interestingly, we find that at least two distinct, genetically defined GABA neuron populations of the medial amygdala make long-range projections to other areas highly relevant for aggressive behavior.

We are currently performing in-vivo optogenetic experiments to establish the role of these neurons in social behaviors, focusing on aggression and social preference. If we can consolidate these findings, we will next ask whether GABAergic synapses made by genetically identified medial amygdala neurons are abnormal in mouse models of ASD. We will also investigate whether optogenetic manipulation of these neurons can ameliorate the social deficits of these mice. This research thus attempts to clarify possible GABAergic synapse dysfunctions in autism, studied in brain areas relevant for social behavior.□

3/ Autism Cohort

by Prof. Marie Schaer

The aim of a longitudinal cohort is to contribute to critical challenges in autism research, such as: 1) allowing earlier age of autism diagnosis, by providing biomarkers that could ultimately be used by clinicians, 2) deepening our understanding of the trajectories of brain development and of social cognition in the years following diagnosis, in a manner that can serve to improve existing therapeutic strategies, 3) helping to identify biomarkers of prognosis or response to treatment, by defining subgroups of individuals with shared characteristics within the wide heterogeneity of the spectrum.



To tackle these questions, we started constituting a longitudinal cohort of young children with ASD and typically developing controls, who are repeatedly examined over the 2 to 6 years age range, a period of dramatic development of interpersonal skills. In this growing cohort, we use an extensive protocol that combines standardized behavioral and neurodevelopmental assessments, high-density EEG and original eye-tracking paradigms to dissect the "social motivation hypothesis".□

4/ The Reward System in ASD

by Prof. Camilla Bellone

In my laboratory we are interested in studying how neuronal circuits, and in particular the reward network, contribute to social behaviors and how dysfunctions in this circuit participate in the social deficits observed in Autism Spectrum Disorders. Mice are an ideal model to identify disease-relevant networks that are vulnerable to genetic insults. Indeed, it is possible to genetically modify specific areas of the brain and investigate links between genes, circuits and behaviors.

Loss or mutations in the SHANK3 gene contained in the q13 portion of chromosome 22 are associated with the neurological and psychiatric phenotypes intertwined with Phelan-McDermid Syndrome, one of the most common single gene causes of ASDs.

Impairments in social behaviors in ASDs are defined by a lack of interest in orienting toward social stimuli, in seeking and taking pleasure by reciprocal interaction and in working to initiate and maintain relationships. It has been therefore hypothesized that social deficits are the consequences of reduced motivation (C. Chevallier et al., 2012). The reward circuit is an ideal substrate for this assumption. Indeed this circuit is a key detector of reward stimuli and plays a major role in controlling motivation and reinforcement learning. Combining molecular approaches (viral-mediated removal of candidate genes, protein-protein interaction, translatome profiling) with ex- and in- vivo electrophysiology, optogenetic and pharmacogenetic methods and behavioral paradigms, we investigate the synaptic basis of reward circuit dysfunction in a SHANK3 mouse model. Our research thus attempts to uncover the biological processes that are affected by SHANK3 deletion in neuronal networks relevant for social behaviors.□

5/ Multimodal Approach for Early Intervention in ASD

by Prof. Nadia Chabane

Thanks to increased cerebral plasticity during the developmental process, early diagnosis and intensive intervention in ASD are possible, allowing therapists to modify spontaneous trajectories in very young children and thereby limiting the severity of the disorder. Current early intervention programs are proposed by either 25 hours of education per week with the child, or a program involving partnership with the family, more adapted to everyday life. Albeit very promising, these models are, to date, insufficiently investigated.

Our research goal is to detect ASD in 18-month-old children located in our geographical area using the M-CHAT-R/F marker and to determine the developmental trajectory of positively diagnosed children. Related children with a high risk of ASD (brothers and sisters) will also be evaluated in a longitudinal perspective. The main and stable clinical sign in ASD is a lack of eye contact, which reflects anomalies in social perception and motivation. Studies using eye-tracking methods have allowed clinicians to highlight abnormalities in ASD patients. This method determines fixation points and the direction of sight that precisely informs us on the way subjects react to a visual stimulus in a specific situation. Besides other possible behavioral measures, at present only Dr. Marie Schaer in Geneva is implementing the Eye Tracking method as a possible marker of clinical improvement. With her help and expertise, we are currently testing her protocols in Lausanne and aim to investigate the clinical patterns of very young children and their behavioral responses to early intervention programs. This will be combined into a multimodal approach including genetic, neuroimaging and cell biology measurements.

This novel approach should improve our understanding of the wide variability of developmental outcomes and will provide new clues to ameliorate the developmental trajectory of very young children with ASD. We believe that a multimodal approach in the very first period following the expression of early symptoms will limit the handicap linked to this neurodevelopmental disorder and thereby enhance communication, socialization and integration abilities.□

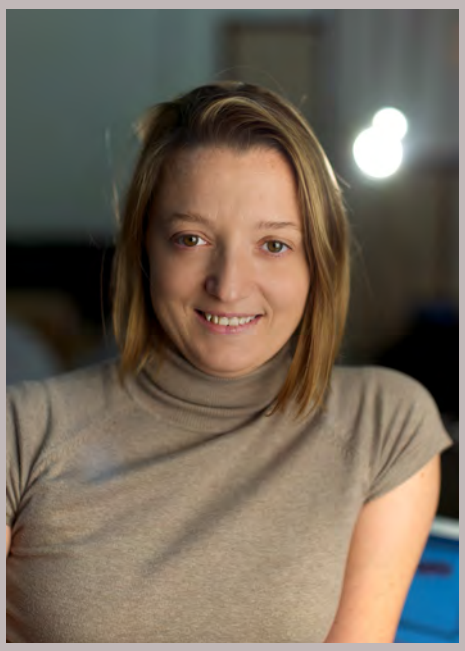
Camilla Bellone has recently joined the NCCR-SYNAPSY's autism project as a new group leader. In 2014 she was awarded a Professeur Boursier (Scholarship Professorship) from the Swiss National Science Foundation and celebrated this accomplishment by having her first child, a baby boy. She is tackling the challenges of being a mother on top of building her own research lab. We asked her how her career and projects are progressing.

SYNAPSY: You were very busy over the last two years. Can you give us an update?

Camilla Bellone: I was awarded a Professor Boursier scholarship from the Swiss National Science Foundation in May 2014. A week after, I found out I was pregnant. So I had to build my laboratory at the University of Lausanne at the same time as my baby was being born. Giovanni, my son, has been very understanding.

S: Having children is often seen as an obstacle to a woman's career. You prove that women can combine family-life and science. How do you manage it?

CB: It is somehow hard to carry out, but clearly feasible, even though I have three major handicaps. Firstly, my husband



PORTRAIT

"Newly Professor, Newly Mom."

An interview with Prof. Camilla Bellone

travels a lot for the World Health Organization. Secondly, the grandparents live in Italy. Lastly, daycares are problematic in Switzerland: they're usually full and not very practical. I only manage because of my husband's solidarity. In fact, we had to arrange a tripartite with a nanny. So it's really a question of organizational skills.

S: Concerning women's careers in science: What were the main barriers you faced? What advice would you give to the next generation?

CB: Girls are generally afraid of scientific careers because of all these gender stereotypes, but I personally never experienced any sexist problems! Girls need to believe in themselves, they can do it, it is feasible. And for this, having a great example, a mentor, helps. This was the case for me: Monica Di Luca was "The woman to be". Also, girls have to learn how to say no, really.

S: How did you get into neurosciences?

CB: I studied pharmacy at the University of Milano where I did a Master's degree with Monica Di Luca. She was very inspiring. Following her courses was instrumental in my choosing neurosciences. Her lectures made me realize how brain sciences are an open field of research with millions of possibilities. I, then, started a PhD in her lab and had the opportunity to move abroad, thanks to the Italian PhD program, and joined Christian Lüscher's group at the University of Geneva where I learned synapse physiology. Then I did my postdoctoral research with Roger Nicoll at the University of California studying NMDA receptors. I was so fortunate to have Monica, Christian and Roger, as such excellent mentors all through my career. I came back to Geneva and got an "Ambizione" grant from the Swiss National Science Foundation. I'd like to say that this grant is a unique opportunity to start asking your own unique questions and learn how to manage people before building your own lab.

S: NCCR-SYNAPSY aims to connect neuroscience and psychiatry. Is SYNAPSY doing it well?

CB: SYNAPSY is launching an entire new world! It gives the possibility to speak to and hang out with clinicians. This is mandatory because it brings different points of view to fundamental scientists, offering other perspectives. The NCCR really serves to fill this gap. More than interacting with doctors, I would love to meet patients. I'm convinced it would help to formulate new questions. Moreover, I enjoy the SYNAPSY environment a lot, it gives an opportunity to young researchers like me to be integrated into a wider network and to learn from it.

S: Could you tell us more about your current interests?

CB: I am pursuing what I initiated with my Ambizione grant. I am looking at the postnatal development of the reward circuit. More particularly, I am questioning the critical period that is sensitive to reward. Developmental defaults of this system are implicated in several brain pathologies, including autism spectrum disorders and schizophrenia. This is a very promising field, especially because the VTA is seen more and more as being concerned with additional brain functions other than addiction.

S: Being a Professeur Boursier is only a step in an academic career. What are your own career plans?

CB: My dream would be to stay in Switzerland with a Full Professorship. Switzerland is the best place for science, with great funding opportunities, selection criteria mainly based on performance and a competitive, but relaxed, atmosphere.□

Journal Club

PAPERS ON AUTISM

- Prof. Camilla Bellone recommends
  Mice with Shank3 Mutations Associated with ASD and Schizophrenia Display Both Shared and Distinct Defects Yang Zhou et al. Neuron 2015. DOI: 10.1016/j.neuron.2015.11.023.
- Prof. Peter Scheiffele recommends
  Oxytocin-dependent consolation behavior in rodents J. P. Burkett et al., Science 2016. DOI: 10.1126/science.aac4785.
- Prof. Marie Schaer recommends
  Different Functional Neural Substrates for Good and Poor Language Outcome in Autism Michael V. et al., Neuron 2015. DOI: 10.1016/j.neuron.2015.03.023.

NEWS

Alexandre Dayer

Has been appointed as Co-Director of NCCR-SYNAPSY.

Camilla Bellone

Has joined NCCR-SYNAPSY's Steering Committee, and has been awarded the position of Assistant Professor from the Swiss National Science Foundation.

Philipp Baumann

Has received a "Bourse de relève clinique Leenards" 2016, allowing him to spend 50% of his time for research.

Marie Schaer

Has been awarded the position of Assistant Professor from the Swiss National Science Foundation.

Katya Rubia

Elisabeth Binder

Prof. Rubia and Prof. Binder are replacing Prof. Helen Mayberg as NCCR-SYNAPSY Advisory Board Members.

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NCCR SYNAPSY MANAGEMENT TEAM

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Save The Date

BRAIN AWARENESS WEEK

March 10-17, 2016
Lausanne and Switzerland
http://www.lasemaineducerveau.ch

NCCR SYNAPSY ANNUAL MEETING

March 16-17, 2016
Villars, Switzerland

THE NEUROBIOLOGY OF MENTAL HEALTH CONFERENCE

April 7-9, 2016
Campus Biotech, Geneva,Switzerland
www.nccr-synapsy.ch/conference

INTERNATIONAL NEUROSCIENCE WINTER CONFERENCE

April 2-6, 2016
Sölden, Austria
http://www.winterneuroscience.org/2016/

EMBO WORKSHOP

Neural control of metabolism and eating behaviour
May 5-7, 2016
Cascais, Portugal
http://events.embo.org/16-neural-circuit/

OPTICAL IMAGING OF BRAIN CONNECTIVITY

June 13, 2016
Roscoff, France
https://www.neurosciences.asso.fr/

FENS FORUM

July 2-6, 2016
Copenhagen, Danemark
http://forum2016.fens.org

SOCIETY FOR NEUROSCIENCE ANNUAL MEETING

12-16 Nov, 2016
San Diego, California
www.sfn.org