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# NEWSLETTER

NATIONAL CENTRE OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY

synapsy

Bringing Together Brain Research and Psychiatry
National Centre of Competence in Research

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## A New Head and Space for Novel Adventures

## Editorial

*by Pierre Magistretti and Alexandre Dayer*

The NCCR Synapsy is undergoing a major life change. Synapsy's management team is moving to the University of Geneva to set up a new home at Campus Biotech. This novel environment offers exciting perspectives for clinical cohort studies that will benefit from state-of-the-art imaging facilities, including EEG, MRI and virtual reality labs. On the Campus site, Synapsy's clinical groups can interact more closely to promote cross-fertilization of ideas and create synergies with the rich and diverse established neuroscientific community. In addition, we are delighted to welcome the new Synapsy manager; Anouchka Junod (-Pickenhagen) as well as Atul Pahwa whose task is to promote new partnerships in the field of mental health. Finally, Alexandre Dayer has been appointed as Synapsy's new Director.

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*Anouchka Junod and Alexandre Dayer*

### Creation of a Women Network

Our arrival in Geneva also generated a new initiative to encourage women in neuroscience, a key issue for long-term successful career achievements for women. Launched by Professor Camilla Bellone and Dr. Meaghan Creed, the Lemanic Women in Neuroscience (LWiN) network aims to promote the scientific careers of female neuroscientist by fostering network interactions and highlighting role models. The first LWiN event will take place in Geneva on the 1st of December.

### Focus on the Early Life Stress Project

Early-life adversity is perhaps the highest, but potentially most preventable risk factor for a broad array of mental disorders. Understanding the mechanisms underlying its impact on the developing brain is key in designing effective preventive strategies. This Newsletter focuses on Synapsy's project 4 through an interview with Dr. Daniel Schechter who explains the goals and findings of this major Synapsy clinical cohort study. In close interplay, rodent models of early-life stress are being used to test specific hypotheses regarding the role of glucocorticoids, serotonin and epigenetic programming on underlying core limbic circuits. As with other Synapsy projects, the integration of both clinical and basic research approaches is providing novel insights into our understanding of the emergence of complex psychiatric phenotypes. **PM/AD**□

## Content



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# Family Consequences of Posttraumatic Stress

**Mothers exposed to traumatic events in early life, including episodes of interpersonal violence, go on to develop violence-related posttraumatic stress disorder (PTSD) that can trigger several disturbances, including increased difficulty in parenting their toddlers (Fig. 1). The mother-child relationship is paramount for the emotional, social and cognitive outcome of the child and traumatized mothers may influence the developmental psychopathology of their child.**

This is the main research area, within the scope of Synapsy's research project 4, in which Daniel Schechter and François Ansermet work (Fig. 2). Daniel Schechter and his team are based at the HUG and their major concern is mothers exposed to interpersonal violence (IPV) during adulthood and how this violence, often following earlier childhood abuse, can lead to the development of PTSD. Francois Ansermet and his team are at the CHUV and are concentrating their efforts on mothers exposed to the stress of having premature babies, particularly those requiring intensive care.


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***Fig. 1*** *PTSD mother having difficulty in parenting her toddler.*

## The Mother-Child Relationship : A Boomerang Effect

Several questions intrigue the Genevois and Vaudois clinicians. One is to know how the mother's PTSD affects her *reading* of her child's emotional communication. Related to this question, they would like to understand how the child's behaviour might in turn affect the mother, "Could an infant's distress, anxiety, anger or helplessness trigger PTSD symptoms in the mother?" Daniel Schechter asks.

The clinicians also want to understand the emotional response and interactive behaviour of the mothers in a situation in which the child is exposed to violent moments. Their hypothesis is that traumatized mothers play a significant role in the increased behavioural disturbances observed in their children following their own exposure to violence. If mothers can be helped to better identify their child's and their own emotions, to attribute mental states to others and themselves that might motivate interactive behaviour, child resilience may be possible. Otherwise an attachment disturbance may become entrenched and lead to subsequent psychiatric problems such as anxiety and mood disorders as well as PTSD.

An important aim is to understand the process of intergenerational transmission of trauma. "We need to identify maternal behavioural signs and endophenotypes that might contribute to knowing whether a child will be at risk to become aggressive, victimized or resilient".

## Behaviour, Physiology and Genetics of PTSD Investigated

The first phase of the team's study concentrated on the child's critical period for the development of social cognition and emotion regulation which occurs between 12 and 42 months, a time when children start to walk and distance themselves from their mother in an attempt to actively explore their environment. This period is characterized by peaks of anger and separation anxiety, topsy-turvy emotion. "It presents an ideal time to observe how mothers are able to deal with the negative emotions of their offspring," says Daniel Schechter.

The clinicians first evaluated the mother's mental representations of her child, her life-event history and her psychopathology. Mothers and children were then welcomed to a laboratory playroom where they were observed by videotaping. They were filmed in their new environment where they could interact with age-appropriate toys (free-play). This was followed by a planned separation in which the mother was given a signal to leave the room and asked to wait outside the door for three minutes. "The reunion that follows is always an important moment.






© Ansermet/Schechter

***Fig. 2***
*Daniel Schechter and François Ansermet research teams*

We look at how the mother handles her child's reaction to the separation and how she reorients the child to playing again" indicates Daniel Schechter. Additional activities are then observed such as tidying-up and structured-play; exercises which lay beyond the child's developmental capacity, needing help from the mother. For the next mother-child separation that follows, only these challenging activities remain in the room, making the separation potentially more distressing for the child. After observing the second reunion, the researchers then investigate how the child and mother interact together when exposed to novel situations such as a clown entering the room with a noisemaker or a roaring mechanical dinosaur robot. "In these moments, we look at how the child copes with excitement, surprise, joy and fear and if and how the mother tries to reassure her child in the new situations". In addition to behavioural studies, the clinicians also look for possible epigenetic and physiological endophenotypes associated with maternal behaviour. For this, cortisol measurements were done every 30 minutes and additional saliva was collected to extract DNA for gene methylation analysis. Furthermore, structural and functional MR imaging were carried out on the mothers while observing videos of free-play and separation with their own child and a non-related child to look for differences in neural activity in PTSD versus non-PTSD mothers, a sort of a *neural footprint*.

## A Mother's Stress Puts Her Child at Risk

The researchers then investigated if the emotional and physiological disturbances observed among PTSD mothers were also mirrored by corticolimbic dysregulation within their brains. In particular, the medial prefrontal cortex is known to be involved in top-down emotion regulation. Mothers with PTSD related to a history of interpersonal violence displayed less neural activity in these regions (Fig. 3) than control mothers in response to seeing film-excerpts of their own and unfamiliar children during separation (stressful condition) versus play (non-stressful condition). "This finding supports the notion that the child itself can trigger the corticolimbic dysregulation as a marker of PTSD symptoms in the maternal brain."

Physiological differences are also seen in PTSD mothers who show a much lower waking salivary cortisol level compared to control mothers. Further, while children of non-PTSD mothers show a typical stress response 30 minutes after the separation-stressor, the children of PTSD mothers show virtually no reactivity. "This discovery reveals that there are physiological differences in the offspring of PTSD mothers already at 12–42 months of age". Epigenetic modifications marked by decreased methylation of the glucocorticoid receptor gene, NR3C1, as well as the serotonin receptor, HTR3A (Fig. 3) were observed in maternal PTSD brains. "The results all point in the same direction: there is a link between genetics, physiology, neural activity and behaviour." >>>

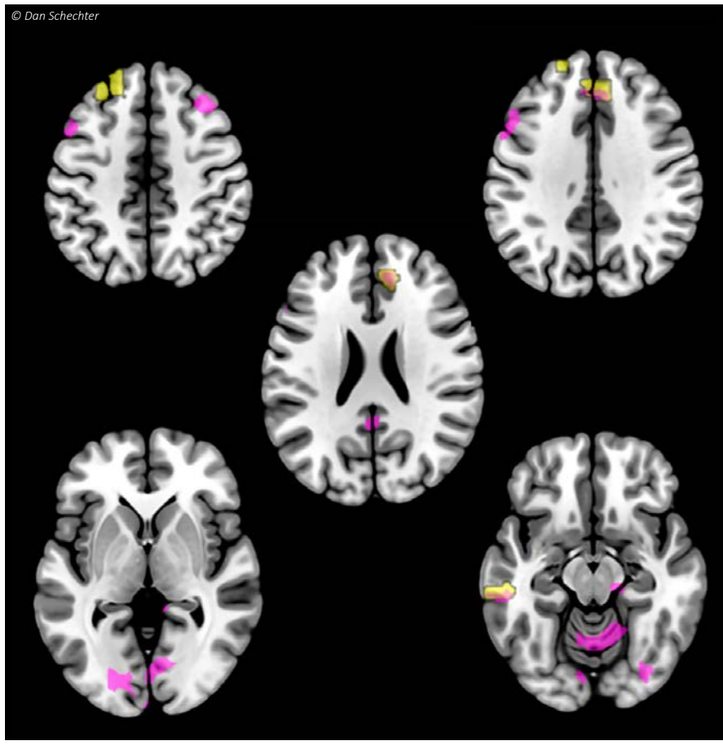
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***Fig. 3***
*Functional Magnetic Resonance images from a mother's brain showing a positive correlation of HTR3A methylation site with neural activity (salmon colour, dorso-medial prefrontal cortex). Yellow and magenta corresponds to negative correlations.*

>>> continued from page 3

## A Follow-up of the Child to Adolescence

The second phase of the project started in February 2016 and involves examining the same children using school-age appropriate measures when they are 5 to 9 years old. Between these ages, typical children have already acquired a firm foundation of social cognition and can begin to mentalize, self-regulate their emotions, arousal, and aggression. Child neuroimaging using high-density electroencephalography (HD-EEG) is now included in a collaboration with Christophe Michel's group, for the longitudinal follow-up of these children. The goal is to understand how the children interpret emotions and to determine whether a long-term biological signature can be defined in children from mothers with IPV-PTSD, who may also have been directly affected by violence and that could be used to predict whether the child will more likely become victim or perpetrator of violence or neither of the two (i.e. resilient).

The peri-pubertal period of development will be the focus of the third Synapsy project phase. This period is again critical in child development as a result of the many hormonal changes involved, as well as the development of the medial prefrontal cortex and related circuits. "We would like to know if puberty acts on PTSD and underlying mentalization and abstract thought capacities within the frame of these developmental events," indicates Daniel Schechter.

## Treatment, the Guide and the Influence

In the end, the most meaningful challenge for the clinical researchers is to generate effective treatments based on the evidence produced from their studies. What kind of interventions can be used to target the emotional/behavioural, physiological and corticolimbic dysregulation that Daniel Schechter has described? "Therapists can stimulate maternal mentalization by working closely with mothers to help them think about what was going on in their own and their child's minds during the filmed interactions (i.e. play, separations, reunions, exposure to novelty). They ask mothers to try to interpret what their child might be thinking and feeling during these moments and indeed, how these processes might inform on their child's (and their own) behaviour."

With this type of intervention that helps mothers "change their minds about their young child," a mother's perceptions of her child can become less negative and more appropriate for the child's age. "The IPV-PTSD mothers tend to have difficulty identifying emotions and in particular confuse anger and fear as well as control and helplessness. We can help to reduce this confusion using this novel technique of clinician-assisted video-feedback exposure." Schechter and colleagues are currently finishing a brief psychotherapy manual based on this technique which will soon be ready for experimental trials. These trials provide a real hope for treatment for these families at high-risk of intergenerational violence and trauma. **YB**□



*by Johannes Gräff*

# How Can We Erase Fearful Memories?

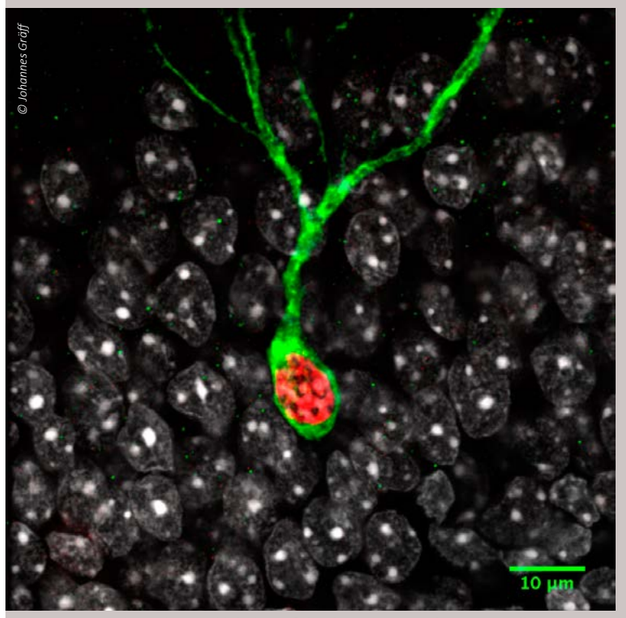



***Fig. 4*** *Immunohistochemical labeling of the dentate gyrus showing a cell concomitantly activated by remote memory recall (green, Beta-gal) and by memory extinction (red, c-Fos). Non activated neurons are shown in grey.*

The main goal of the clinical early-life stress project is to find a way to treat patients. Therefore, a better understanding of fear memory attenuation mechanisms in rodents will undoubtedly lead to ways to help mothers suffering from PTSD to eventually delete traumatic memories from their minds.

To this intent, Johannes Gräff and his laboratory are analyzing the cellular and molecular mechanisms underlying remote fear memory attenuation in rodents. They are using an innovative combination of transgenic mice with *in situ* manipulation of neuronal subpopulations with cell type-specific molecular profiling. Specifically, Johannes Gräff developed a method to persistently tag neurons that were activated by remote memory recall. By following this tag after successful memory attenuation, the neuronal subpopulations that promote remote memory reduction may be identified.

The results obtained so far indicate that effective remote fear memory attenuation is accompanied by significant reactivation of recall-induced neurons during the process of behavioral memory extinction in the two brain areas essential for memory updating; hippocampal area CA1 and the dentate gyrus (Fig. 4).

Simultaneously, using the tag as an anchor for pharmacological manipulations interfering with neuronal activity, a causal implication of the specific neurons in memory attenuation was determined. The results show that recall-induced neurons need to be active throughout the behavioral extinction procedure for effective remote memory attenuation. In turn, these findings suggest that effective remote memory attenuation may be equivalent to a re-writing of the originally traumatic memory into a one of safety. JG□





*by Carmen Sandi*

# How Early Life Stress Exposure Enhances the Risk of Adulthood Psychopathology

Carmen Sandi's laboratory is investigating the mechanisms by which early life stress, becomes a risk factor for the development of psychopathologies in adulthood, using several animal species (rats and mice) as models. The goal is to provide an essential and fundamental basis for the third phase of the clinical early life stress project that aims to determine how puberty affects the pathophysiology of stress (see pages 2 to 4).

Carmen Sandi and her collaborators identified peripuberty as a period of high vulnerability for developing stress-induced alterations in neurodevelopmental trajectories in males, particularly aggression, attention deficit, anxiety and depression. The increased aggression and reduced sociability is also observed in peripubertally stressed females and, interestingly, the offspring of peripubertally stressed males show pathological aggression as well. Stress at the time of puberty modifies the balance between neural excitation and inhibition in several brain regions including distinct amygdala nuclei, the lateral septum, the hippocampus and the medial prefrontal cortex (Fig. 5). These changes are accompanied by modifications in the expression levels of certain cell adhesion molecules, such as neuroligin-2 (top right image in Fig. 5), which is known to be involved in the stabilization of specific synapses and shown to be implicated in stress-induced deficits in sociability and attention. Importantly, stress-induced increase in glucocorticoid levels during peripubertal stress are found to be related to the specific behavioral alterations observed later in life. Sandi's lab is currently addressing the neurobiological mechanisms whereby individual differences in the magnitude of glucocorticoid responses to fearful situations in early life lead to long-term programming of altered behaviors from stress. **CS**□

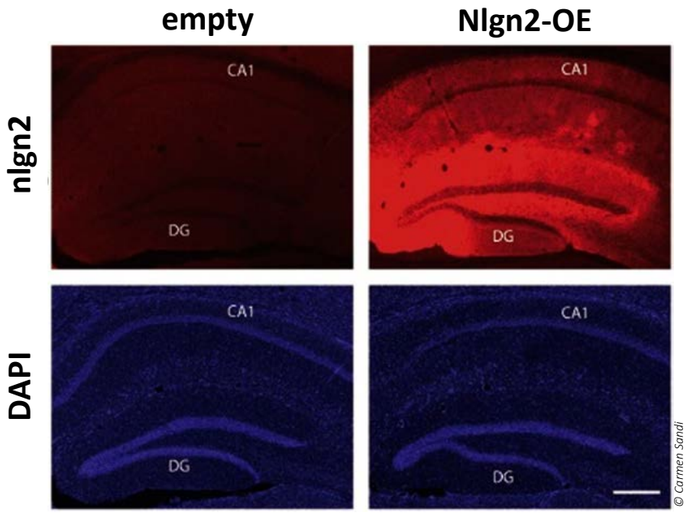



***Fig. 5*** *Hippocampal Nlgn2 overexpression (Nlgn2-OE).*
*Representative immunohistochemical pictures showing increased nlgn2 protein expression in nlgn2-OE animals compared to empty animals.*
*Red: nlgn2, blue:DAPI, scale bar = 200 µm.*

*by Alexandre Dayer and Anthony Holtmaat*

# Investigating the Role of Serotonin in Cortical Microcircuit Development and Function

In humans, early-life stress (ELS) interacts with genes that regulate serotonergic function. Over time this leads to an increased risk for developing stress-related conditions such as mood and anxiety disorders. Furthermore, studies in rodents indicate that early-life serotonin dysregulation during critical perinatal time windows generates stress-related phenotypes in adulthood. Understanding the mechanisms by which early-life programming of serotonin function affects the emergence of stress-related disorders later in life is thus a key question in the field. Alterations in core feedback loops connecting the medial prefrontal cortex (mPFC) and the serotonergic (5HT) raphe nuclei (RN) (Fig. 6) may partially mediate these complex long-term behavioral consequences. However, how 5HT inputs specifically impact local microcircuits in the mPFC and corresponding plasticity remains uncertain.

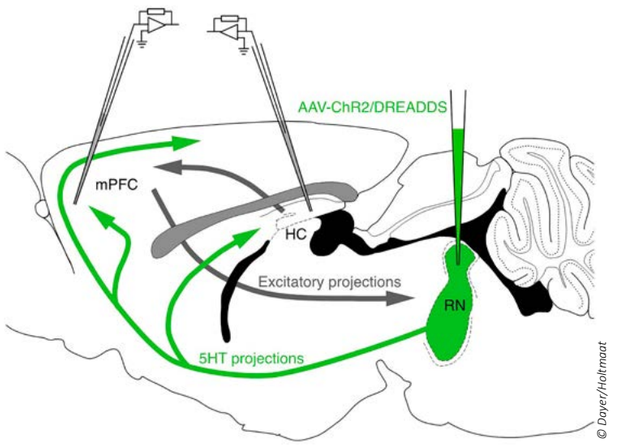
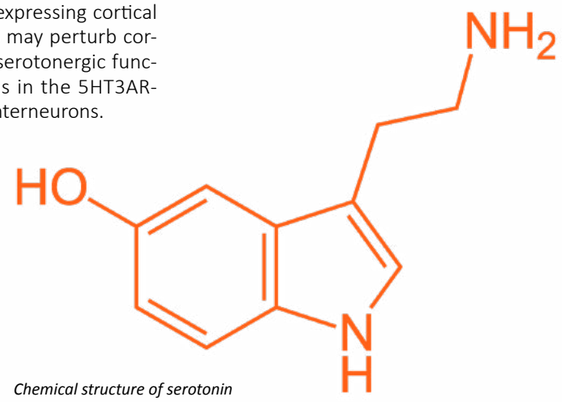



***Fig. 6** Serotonin, prefrontal cortex circuitry*

This Synapsy subproject stems from a joint effort by the groups of Anthony Holtmaat and Alexandre Dayer to dissect the serotonergic interactions with excitatory, inhibitory and disinhibitory synaptic pathways in the superficial layers of the mPFC mouse cortex, with a particular focus on a distinct subclass of interneurons that specifically express the ionotropic serotonin 3A receptor (5HTR3AR). Recent findings from this project have revealed that the 5HTR3AR is strongly expressed in a subclass of cortical interneurons and that this receptor is required for their normal development. Results from NCCR human cohort studies indicate that early-life adversity modifies the methylation status of the 5HT3AR gene promoter region, suggesting that this receptor is a relevant target for the disruptive effects of ELS on the interaction between the serotonergic system and cortical function. Interestingly, we showed that during the early stages of life, serotonin dysregulation affects the migration of 5HTR3AR-expressing cortical interneurons. Thus, ELS may perturb cortical development and serotonergic function through alterations in the 5HT3AR-expressing subclass of interneurons.

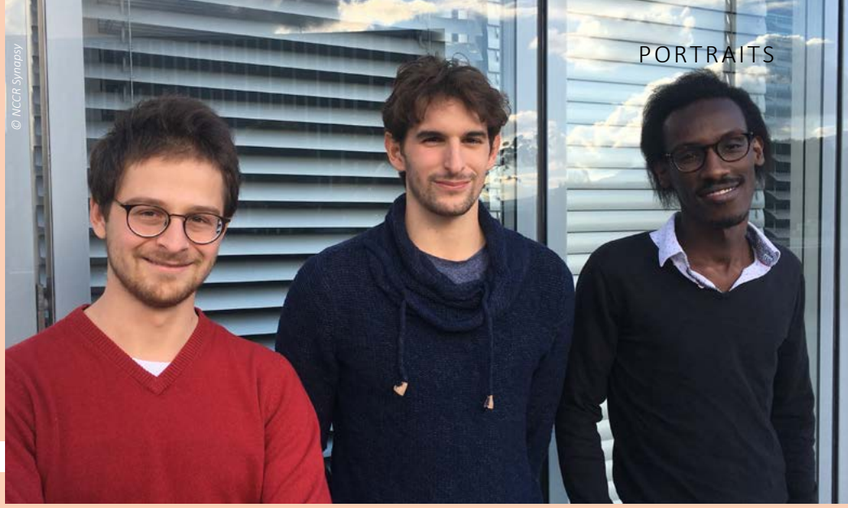
Current collaborative efforts in our labs aim at mapping the molecular and functional diversity of cortical 5HT3AR-expressing interneurons using fate-mapping strategies combined with single-cell RNA sequencing, electrophysiological characterization and optogenetic manipulation (Fig. 6). Targeted patch recordings combined with optogenetic stimulation of RN afferents revealed rapid serotonergic effects on cortical 5HT3AR-expressing interneurons. Using microprisms implanted in the midline fissure we are currently imaging and probing neuronal structure and function in the mPFC following optogenetic stimulation of RN afferents. Finally, using intra-cortical electrophysiological recordings in limbic networks (e.g. mPFC-Hippocampus [HC] interactions) combined with genetic disruption of 5HT3AR receptors and optogenetic stimulation of RN afferents we will test whether the serotonergic system modulates oscillations within these brain circuits. Overall, this combined effort will further our understanding of the role of serotonin in the development and function of mPFC cortical microcircuits and will provide insights into the mechanisms by which stress or serotonergic dysfunction during critical early life developmental time-windows elicit a long-lasting risk of developing mood disorders and anxiety. **AD/AH**□




*Chemical structure of serotonin*








*Michel Godel*
*Gregory Lepeu*
*Martin Ndengera*

# Budding Clinician-Scientists?

**Three medical students tell us about their interest for psychiatry and neuroscience. At a turning point in their careers, they explain why they're hesitating between a career in research or clinics, or both.**

**Gregory Lepeu, Michel Godel** and **Martin Ndengera** are studying medicine at the University of Geneva. For their Master's projects, they all chose subjects in neuroscience and plunged into the peculiar world of clinical or fundamental research for a year. This is a great opportunity for these future doctors to envisage a career in research. The Synapsy team met them last spring at the Neurobiology of Mental Health conference held at Campus Biotech, Geneva.

## The Driving Force of Science

Why choose medicine and in particular brain health? For Gregory Lepeu and Michel Godel their interest in science and human biology pushed them towards the Faculty of Medicine. "Other courses offer some zoology, molecular biology or even engineering, but don't explore the subject of the human being enough," say both students. Martin Ndengera first started technical training in radiology, "which then struck me with a desire to know more". Studying medicine was therefore going to happen for all three students, but in a background of a marked interest for basic science.

The Neuroclub, created by Professor Joseph Kiss at the medical Centre of the University of Geneva has no equal when it comes to awakening the dormant neuroscientist (read the interview of Paul Klauser at http://www.nccr-synapsy.ch/portraits-clinician-scientists). Indeed it's thanks to Professor Kiss's Neuroclub that Gregory Lepeu discovered neuroscience and all three are active club members. The club invites psychiatrists, psychologists and neuroscientists around a table for lively debates about the brain. For Michel Godel, his thirst for neuroscience came in second year after reading, "A chacun son cerveau" (Biology of Freedom) by François Ansermet and Pierre Magistretti. "It was a real eye-opener for me. I was fascinated by the relationship between psychoanalysis and neuroscience expressed in their book". Martin Ndengera's motivation comes from humanism "I want to understand how we can see humanity in the functional brain" he confides.

## The Neurobiology of Mental Health Conference Seen by the Students

It is thanks to the invited speakers of the Neuroclub –some of them well known by Synapsy like Anthony Holtmaat, Alan Carleton, Christian Lüscher, Alexandre Dayer– that the three students heard about the Neurobiology of Mental Health conference held in 2016 at Campus Biotech. Following financial support by Synapsy, they jumped at the chance to go and listen to what really interests them. Visibly captivated by the quality of the speakers and the wealth of seminars, all three said that they were not out of their depth, "we are used to hearing scientific seminars and discussions at the Neuroclub" says Gregory Lepeu. One small disappointment however, "the speakers didn't really address clinical aspects and human behaviour enough" according to Michel Godel. Nevertheless, it definitely provided an insight into the difficulty of effectively relating psychiatry and neuroscience.

So, if following a high level of scientific conference poses no problem, do they think they're well equipped for a career in research? The unanimous reply is: "No, we don't have the necessary tools". According to all three, even though medical studies are thorough, they don't sufficiently cover statistics, molecular biology, computing and experimental techniques in enough detail. Nevertheless, they seem ready to rise to the challenge and add jokingly, "After four years in medicine we're learning machines".

## Clinical Medicine, Research or Both?

Are they ready for a research career and an MD-PhD? Not yet. Despite wanting the best of both worlds they are hesitating. Michel Godel admits that he's constantly changing his mind. Doing both would be optimal: expert in both science and medicine, having two sets of skills could open a large window of opportunities". The research world worries them though because of the lack of options for professional development and the challenge and responsibilities of a research career with a medical background. "Stable positions primarily in research for clinicians are practically unheard of. Many people who hold an MD-PhD end up going back to clinical work only, which does not help the cause".

In this context, it is highly valuable that the Swiss National Science Foundation funds programs like Synapsy, who offers competitive grants to clinician-scientists and graduating schools, helping MD-MSc and MD-PhD students to bridge knowledge gaps and builds their academic careers in clinical specialities such as Psychiatry. **YB**□

LEMANIC WOMEN IN NEUROSCIENCE

# LWiN: a Lemanic Arc Network to Promote Women in Science

Two female neuroscientists are tackling the problem of under-representation of women in academia. Their solution: To establish a Lemanic region network of scientists that will provide mutual support, facilitate exchanges and promote learning from and about each others careers.

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*Meaghan Creed and Camilla Bellone*

The two scientists are at different stages in their private lives and careers. Camilla Bellone is a mother and assistant professor while Meaghan Creed is striving to pursue her career after a post-doc. The first is trying to find the best way to balance family life with running a lab while the second is figuring out how to make a move that will work for both her professional and personal life. Despite these timing differences, both absolutely agree that overall women lack a supportive network, self-assurance and above all mentorship.

In the world of research, most women stop after their Ph.D. According to Camilla Bellone this happens because women lack self-confidence, "Women tend to believe less in their abilities than men. We need to change this attitude, follow men's example and assert ourselves to challenge them". For Meaghan Creed the main problem is the lack of female role models. "I was lucky that I had Camilla as a personal coach, but the scarcity of women in senior positions means that most female students have no one to mentor them in these matters. This 'isolation' makes successful scientific career development all the more difficult".

To attempt to redress the gender balance in academia, the two scientists created the "Lemanic Women in Neuroscience (LWiN)", a network of professional women whose purpose is to connect and share work experiences and ideas to benefit the entire community and help retain women in science. LWiN is set on a single intention to tackle this pressing and contemporary issue.

The two female activists sent out a poll to discover the main obstacles encountered by women in this academic environment. At the top of the poll came: Family responsibilities, lack of opportunities and gender stereotypes. "We are not out to change men but rather to unlock female potential and make women more visible in research", states Meaghan Creed. LWiN's strategy is to hold a first meeting in the form of a conference where both male and female speakers will talk neuroscience, gender equality and career structure outside of an academic context. Specifically there will be a round-table discussion between the speakers and researchers at all levels. **YB**□

*Event supported by NCCR-SYNAPSY, all information can be found at :*
**www.nccr-synapsy.ch/fr/lwin**

## Save The Date

### SOCIETY FOR NEUROSCIENCE ANNUAL MEETING

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

### BRAIN AWARENESS WEEK

March 13-19, 2017
Lausanne, Switzerland
www.lasemaineducerveau.ch
Geneva, Switzerland
www.semaineducerveau.ch

### 19TH INT'L NEUROSCIENCE WINTER CONFERENCE

March 26-30, 2017
Sölden, Austria
www.winterneuroscience.org/2017

### NCCR SYNAPSY ANNUAL MEETING

March 31- April 1, 2017
Villars, Switzerland

### EMBO CONFERENCE

May 7-10, 2017
Cell biology of the neuron : Polarity, plasticity and regeneration
Heraklion, Greece
www.embo-neuro2017.gr

### NEUROFRANCE

May 17-19, 2017
Bordeaux, France
www.neurosciences.asso.fr

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