

## EDITORIAL

by Alexandre Dayer

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# The Harmful Effects of Stress Unraveled

The 12<sup>th</sup> Synapsy newsletter is rich with interviews and portraits of students, clinical scientists and more senior researchers from the developmental stress working group of Synapsy (work package 4, WP#4). Its objective is to evaluate the long-term effect of exposure to stress at different developmental stages. Please take your time to discover their ideas and the exciting progress they are making!

One new focus is anxiety, a key dimension which may act as a common transdiagnostic risk factor for mood and psychotic disorders. In this perspective, the clinical scientists Camille Piguet and Paul Klauser have initiated a promising new project on the effect of mindfulness on the stress response in high-risk anxious adolescents. Zoe Schilliger, a new 2019 clinical scientist, has recently

joined this project and explains how she wishes to study interactions between oxidative stress and neuroinflammation in the context of anxiety. In addition, you will learn more about the projects of Cristina Berchio (Christoph Michel laboratory) and Virginie Perizzolo (Daniel Schechter laboratory), who are using high-density EEG to investigate trait anxiety and high-risk offspring of mothers with violence-related Post Traumatic Stress Disorder. At the basic neuroscience level, you will have the pleasure to discover the projects and career paths of several Synapsy researchers. Silvia Monari, a researcher in the Carmen Sandi laboratory, shares the progress she is making on a translational animal model used to investigate individual difference in stress vulnerability. Bianca Silva, working in

the Johannes Gräff laboratory, explains the strategies she is using to identify new brain areas as targets for therapeutic approaches against traumatic memories. Finally, Foivos Markopoulos explains his work on serotonin and specific subsets of cortical interneurons in the context of a joint project from the Anthony Holtmaat and Alexandre Dayer laboratories.

Last but not the least: we are very excited about the next major Synapsy event! The 3<sup>rd</sup> Conference on the Neurobiology of Mental Health will take place at Campus Biotech on 26–28 February 2020. The speakers are of outstanding quality and we look forward to Synapsy researchers highlighting their excellent research on this special occasion.

Happy reading! ●

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# NEWSLETTER

NATIONAL CENTRE OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY



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## CLINICAL COHORT

## Maternal exposure to violence and child psychopathology

**Synapsy has been following the children of mothers suffering from post-traumatic stress disorder due to interpersonal violence since they were 12 months of age. They are now reaching maturity, just like research projects designed to understand and treat stress-related disorders.**

Domestic violence is all too common in Switzerland, states from the outset Daniel Schechter, medical director for perinatal and young child research in the SUPEA Department of Psychiatry at CHUV and a Synapsy researcher for the work package on developmental stress (WP#4) at the University of Geneva. In 2018, Swiss police logged 18,522 domestic violence offenses, thought to represent barely 38% of the total estimated cases of domestic violence. According to the Swiss Federal Statistical Office (FSO), the main victims of this violence are women, with 109 deaths recorded out of 120 for the period 2009–2018. A 2017 Eurostat analysis found that this is higher than the worldwide average. Furthermore, many of the women who survive will develop stress-related psychiatric illnesses, including post-traumatic

stress disorder (PTSD). Worse still, they can transmit anxiety and stress-related disorders to their offspring, as evidenced in the results of the Synapsy researcher.

### Revaluating the mother-child relationship

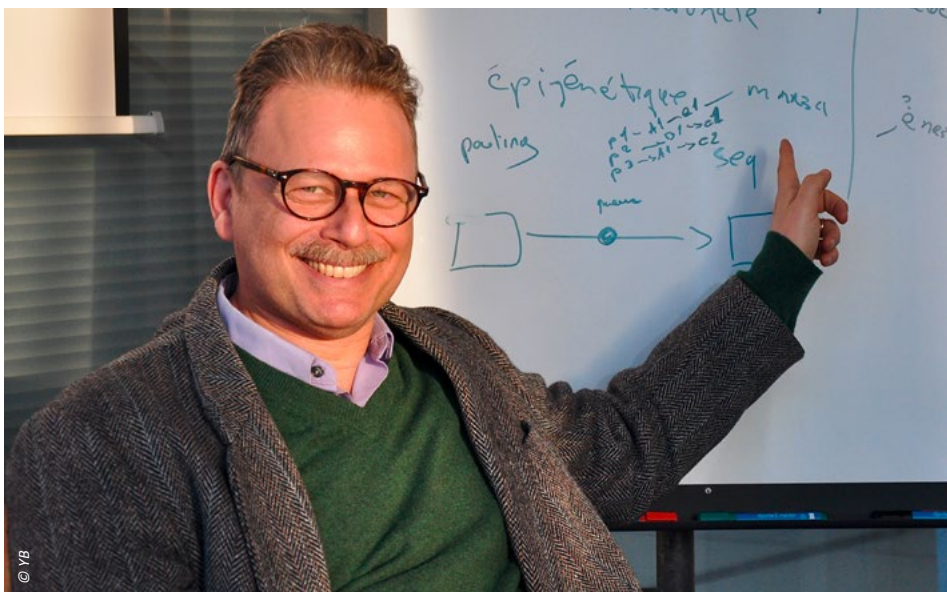
As chance would have it, the publication of this newsletter coincides exactly with the twentieth anniversary of Daniel Schechter's research into the effects of maternal exposure to violence on the mother-child relationship, and child developmental psychopathology. "It all started", begins Daniel, "at Columbia University in New York City with responsibility for a clinical population of families with children ages 0 to 5 years who had experienced or were at risk for maltreatment that I inherited when I was

appointed as Medical Director of the infant mental health ambulatory care program. I realized that we had lots of clinical information about the children, but very little about the mothers apart from the observation they themselves had suffered severe trauma".

In fact, Schechter discovered that 90% of the mothers had clinical symptoms of PTSD and other stress-related disorders, which—in his opinion—must have had an effect on the clinical reality of their young children. As Daniel explains: "The mothers see their children as being uncontrollable, aggressive and authoritarian. And they use inappropriate vocabulary to describe the behavior of a baby: he's manipulative, dangerous or even sexy." Schechter set up an in-depth study into these cases between 2000 and 2008 on American soil with the support of a NIMH Research Career Award, all this before being hired by the University of Geneva and joining Synapsy in 2010. It was then that he decided to replicate and extend his New York studies, creating the WP#4 cohort.

### Mothers, babies and primary schoolchildren all impacted

During the first two four-year phases of Synapsy, Schechter and his team discovered that PTSD mothers had a distorted and negative interpretation of their children's behavior; they were also poor at identifying emotions in themselves and in their children. They and their children displayed both dysregulation of interactive behavior, stress physiology (i.e. salivary cortisol reactivity), and neural activity in response to emotionally evocative stimuli. Maternal patterns of neural activity in response to seeing videos of their children during play and separation



## What is meant by stress, anxiety and fear?

(i.e. medial prefrontal cortical hypoactivity) was predictive of social-emotional difficulties among their children in a longitudinal follow-up. Through their interactive behavior, traumatized mothers may have in many cases inadvertently communicated stress and anxiety to their children during the latter's sensitive early development. Young children, in many cases, provoked maternal intrusiveness and/or avoidant behavior that is disorganizing to the relationship.

The children went on to develop problems noted 4 years after they were first seen in Synapsy as toddlers. These now school-aged children were the subject of research using high-density electroencephalography (EEG) carried out by Virginie Perizzolo at the University of Geneva (read the related highlight "Breaking the transmission of trauma" on page 6). As Schechter briefly explains: "Growing up with unpredictable, at times intrusive, at times emotionally unavailable mothers makes these children much more vigilant about what their mothers do and feel. This means they use more brain energy than the average child when analyzing the emotions given off by a face, especially negative emotions."

### Peripubertal development and stress management

Children of mothers with PTSD are also, as Schechter pointed out earlier, less reactive to stress and have low levels of cortisol when exposed to stress (see boxed text above). "Nevertheless," continues Schechter, "since these children appear to be more vulnerable to anxiety and stress-related disorders, they tend to be much more stressed in their everyday lives." Daniel now wants to try to understand how their development evolves

Anxiety, which is not the same as fear and stress, is generally triggered by situations where there is no apparent immediate danger. Fear, by contrast, is a reaction to a potential, upcoming or imminent threat. "Anxiety is a state of mind in the sense that you can feel anxious, unlike feeling fear, without necessarily knowing why and without being afraid of anything specific," explains Daniel Schechter. Stress, for its part, is a reaction to the environment that demands a change of behavior that can, in its mildest form, range from needing to study harder for an upcoming exam to needing to escape from a violent perpetrator. Chronic stress such as perpetually being vigilant to the whereabouts of a violent perpetrator in the home results in heightened anxiety and can result in fear of the dark or of being trapped.

Anxiety, fear, and extreme stress such as traumatic stress are all associated with a range of physiological reactions such as an increased heart rate, blood pressure, sweating and increased circulating glucocorticoids

(i.e. cortisol in humans). Emotional reactions consisting of readiness to fight or flee appear alongside behavioral reactions such as avoidance and inhibition.

Psychiatrists now distinguish between "anxiety disorders" such as generalized anxiety disorder and panic disorder and "stress disorders" in response to traumatic life events such as post-traumatic stress disorder (PTSD) and acute stress disorder. The fundamental researchers at Synapsy study these disorders by working on animal models, which can then be translated into experimental models involving humans, to understand the synaptic basis both of anxiety and stress-related disorders. The scientists expose the animals to stress that have long-term consequences for the animal's brain and behavior. One of the consequences is that the animal learns to fear the return of the stimulus. The researchers therefore talk about fear conditioning and fear learning, suggesting the importance of the brain's learning and memory mechanisms. ●

during the peri-pubertal period, bearing in mind that puberty is itself especially stressful.

In parallel, Schechter is keen to find out whether an intervention can help these children improve the way they manage their stress. The psychiatry researcher plans to use mindfulness meditation techniques (read the related highlight "Anti-stress meditation" on page 5). Camille Piguet's and Paul Klauser's "Mindfulteen" cohort has been included in the WP#4 cohort for this purpose. Piguet's brain imaging expertise means that it will be possible to carry out magnetic resonance imaging (MRI) measurements under stress conditions—something that has

not been possible until now due to the young age of the subjects—in order to identify the neural areas involved.

### Back to basics

A team of researchers made up of Virginie Perizzolo and Dominik Moser, former doctoral students of Daniel Schechter who have been taken for this project, will also work on the cross-modal analysis of the data from the different techniques collected so far. Finally, concludes Schechter: "We're going to work on Synapsy's legacy, launching a new project where the goal will be to observe what happens during the prenatal period through the first year of life." ●



## INTERVIEW WITH ZOÉ SCHILLIGER

## Halfway between cell biology and patient care

**Zoé Schilliger was one of the three 2019 winners of the Synapsy clinician-researcher grant. She is embarking on a PhD on anxiety that is based on the expertise of two Synapsy work packages. It is a fascinating project that combines Zoé's shared interest in practical psychiatry and fundamental research.**

***What prompted you to push open the door to the world of medical research?***

I was tempted by architecture at first, but it wasn't right for me. The theory and aesthetic side interested me, but I found the frantic pace of the projects a bit meaningless. Then I went into medicine because of my interest in health and human physiology. When I discovered cell biology in the first year, it was a revelation for me in terms of the fundamental side of things! When I did my clinical internships, I discovered a certain pleasure in interacting with patients. So, my interest is now a balance between research and clinical work.

***Why did you choose psychiatry in particular?***

Psychiatry is a specific discipline of medicine where having a well-developed clinical sense is crucial. What's more, the interactions with patients mean you do a lot of soul-searching. Last of all, psychiatry is an evolving field — all of which means you can be sure you'll never be bored, and that's what appealed to me.

***What are you studying for your thesis?***

I'm studying the biological foundations of anxiety and how it could represent a marker of vulnerability for the development of psychiatric disorders in adolescence. My work is supervised by Paul Klauser and Daniella Dwir, and

is directed by Kim Do and Philippe Conus at CHUV's Centre for Psychiatric Neurosciences. The aim is to identify early changes in the brain that indicate a vulnerability to stress in anxious adolescents, as well as blood biomarkers reflecting these changes. My project

is partly based on the clinical data gathered by the Mindfulteen study (read the related highlight "Anti-stress meditation" on the right). The idea is also to make the link with the work of Do and Conus showing that an interaction between oxidative stress and



## Anti-stress meditation

neuroinflammation underlies the alteration of the parvalbumin (PV) interneurons in schizophrenia. We're investigating whether a similar mechanism is involved in the alteration of the PV interneurons observed as a result of stress in adolescents. In practical terms, I take peripheral mononuclear cells from the blood of patients in the Mindfulteen cohort to test the redox and inflammation regulation systems.

### ***Do you also work with Carmen Sandi's group at EPFL?***

Yes, her laboratory has an excellent animal model for studying the inter-individual differences in vulnerability to stress (read Silvia Monari's portrait on page 8): strains of rats selected for their glucocorticoid secretion levels in response to stress. The idea is to investigate whether these strains have differences in PV interneurons in the prefrontal and limbic regions, both of which are involved in regulating emotions and which change a great deal during adolescence.

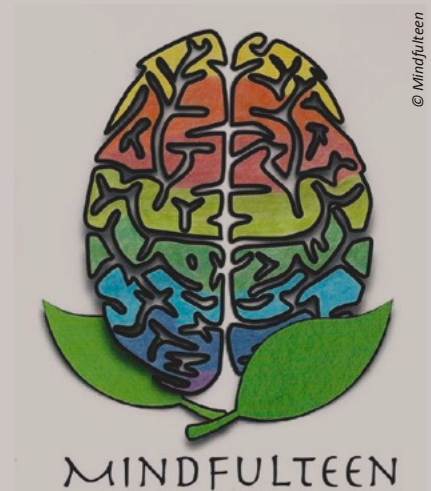
### ***How do you manage the clinical work and research?***

I do part-time clinical work in the CHUV Outpatient Addiction Department. Fortunately, I can rely on the Synapsy grant for my salary as a researcher. It's great to be able to get to the bottom of the basic mechanistic complexity and go back to the patient. What's more, the environment in Lausanne is very open to implementing discoveries from neuroscience. ●

**Is meditation effective as an early intervention to reduce reactivity to stress and anxiety? The Mindfulteen study investigates the question using brain imaging.**

Mindfulness meditation is a technique borrowed from oriental medicine that consists of training oneself to be in the present moment and to accept rather than judge. It was taken up and adapted by Western medicine in the 1970s. Mindfulness was first used for treating chronic pain before demonstrating its benefits in tackling anxiety in adults. Synapsy's researchers are focusing on the approach to enhance stress management in young adolescents. Adolescence is a particularly interesting period for brain development since poor stress management at this stage is regarded as a vulnerability factor for the development of psychiatric disorders. Early intervention targeting young adolescents who express subclinical levels of anxiety could prevent the onset of anxiety, depressive and psychotic disorders.

The aim of the study is to measure the effect of mindfulness meditation on stress reactivity and anxiety while analyzing the neural circuits involved. Backed by Synapsy and the Leenards Foundation, the project is led by Camille Pigué and Arnaud Merglen for the University of Geneva and HUG, together with Paul Klauser for the University of Lausanne and CHUV. The study, which started in February 2019, has successfully included 3 groups of 8–10 participants. The researchers



© Mindfulteen

are targeting 120 13 to 15-year-old children ([www.mindfulteen.ch](http://www.mindfulteen.ch)).

The approach is of great interest to the work package on early psychosis (WP#2), and a collaborative project on stress reactivity is also underway. "Children of PTSD mothers in the Daniel Schechter cohort already have symptoms of stress-related illnesses, so they are the clinical counterpart of the Mindfulteen cohort. Taking identical measurements means the results will be comparable and useful for both studies", explains Pigué. Mindfulteen is also closely linked to fundamental aspects of Synapsy's WP#2. "The interactions between inflammation and oxidative stress are important in the development of psychiatric disorders. We're investigating whether the meditation approach could influence these interactions," adds Paul Klauser (read Zoé Shilliger's interview on the left). ●

## CLINICAL FOCUS

# Breaking the transmission of trauma

**Children of mothers with post-traumatic stress disorder have difficulty processing their emotions. Defining the neural bases of this dysfunction will help develop future treatments.**

Transmitting information, you do not have is by its very nature a tricky, even impossible, exercise. This is the situation faced by mothers suffering from post-traumatic stress disorder (PTSD) that develops after experiencing interpersonal violence. These mothers suffer from dysregulation—poor modulation of their reactions and emotions—and are unable to transmit them to their offspring, with the result that the latter develop disorders. In an attempt to understand, the group led by Daniel Schechter (read the article “Maternal exposure to violence and child psychopathology” on page 2), which includes Virginie Perizzolo, is trying to define the major developmental stages in emotional processing.

## Fear or anger?

While working on her thesis, Virginie asked 47 children and their PTSD mothers to match specific emotions to different faces. “Three pictures depicting faces expressing fear, anger and happiness were presented to subjects and they had to match the two of them sharing the same emotion.” Virginie’s data shows that children of mothers suffering from PTSD due to interpersonal violence (IPV-PTSD), make an increased number of mistakes in identifying negative emotions, with greater confusion of fear and anger. “IPV-PTSD mothers also mixed up in the same emotions and errors correlated with the severity of PTSD symptoms,” adds the researcher.

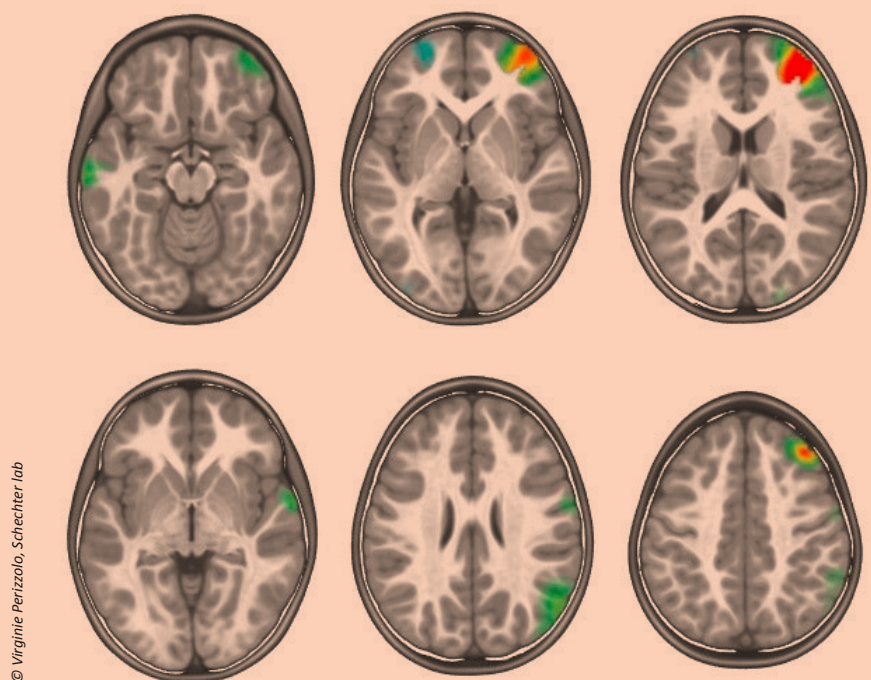
In parallel, Perizzolo recorded brain

activity in the 47 children using high-density electroencephalography (EEG) when they were undertaking the behavioral task. Reduced activation of the right dorsolateral prefrontal cortex was highlighted in response to anger and fear in these children. This is the first demonstration that maternal PTSD significantly affects a child’s neural activity.

## Future interventions

Virginie was taken on as a post-doctoral fellow after obtaining her PhD in 2018. She is currently working on several inter-Synapsy and international collaborations. “For example, we investigated data regarding child level

in emotional comprehension using the Test of Emotion Comprehension (TEC) as well as maternal prediction regarding their own child’s skills in emotional comprehension and its link between with PTSD. We’re also studying trust and threat-related avatars processing using high density EEG recordings in IPV-PTSD mothers and non-PTSD controls, that we had the opportunity to investigate in collaboration with Princeton University”, adds Virginie. This work is crucial for the future implementation of interventional treatments aimed at interrupting the intergenerational transmission cycles of violence and associated trauma. ●



EEG signals showing a decreased activation in the prefrontal cortex in response to angry and fearful faces.



## INTERVIEW WITH VIRGINIE PERIZZOLO

## Making a living on two wheels and electroencephalography

**Virginie Perizzolo tells us how cycling and speech therapy helped her recently graduate from the Lemanic Neuroscience Doctoral School.**

***What training did you do to become a doctor in neuroscience?***

First, I got a bachelor's degree in speech therapy & psychology from the University of Neuchâtel. I was more taken by the neuroscientific side of psychology and came to the University of Geneva to start a master's in neuroscience. I joined David Sander's research group during the master in Neuroscience at the University of Geneva and could learn about the EEG. Then I joined Daniel Schechter's group and started my PhD at the end of the first Synapsy phase. I could take part in the last interviews of Phase 1 WP#4 cohort and then take an active part in setting up the second clinical phase of the cohort. During my PhD, I could increase my knowledge regarding clinical aspects of trauma and anxiety disorders as well as in neuroimaging.

***Now that your doctorate is in the bag, what are your career plans?***

I'm working as a part-time post-doctoral fellow with Daniel. We collected a significant amount of data during phases 1 & 2 and now need to analyze and publish them. I'm very grateful to have been able to stay in the same environment after finishing my PhD. A part-time postdoc fellow also allows me to share my time with my passion for sport and cycling, and to join an helvetico-russian woman professional cycling team. In 2019, I was able to ride



World Cups in the USA among other international races, as well as la Vuelta Espana, which is a very famous stage race for men.

***Is it possible to combine professional sport and clinical research?***

I started cycling very young and always shared my time between studies, work, and cycling. I feel good in both environments, and always appreciate this balance. For example, long endurance rides often allow me to get some distance from the lab, to see things differently and get some links between scientific findings, and then I can move forward in my work.

***Does sport feed into your research and vice versa?***

Yes, kind of. At an organization level, planning my research work is closed to planning a race season and daily training, with short, middle and long-time goals on both sides. There is also a team spirit in both of them in recognizing everyone's skills, work together with efficiency and make the team move forward toward a goal. Finally, we could find self-reliant aspects of being autonomous in some situations, for example in decision-making to find the best solution, especially when time is running. All that makes you very disciplined, both in your private life and your work as a scientist. ●

## PORTRAIT OF SILVIA MONARI

## No clinical work without understanding the basics

**Silvia Monari explains the difficult choice she had to make between medicine and life sciences when deciding on what direction her studies would take. Silvia tells us how she intends to detect biomarkers of disease and possible therapeutic intervention for post-traumatic stress disorder during the course of her thesis.**

Silvia Monari is a doctoral student in Carmen Sandi's laboratory at EPFL. She chose medicine to start her university career. Medical studies in Modena, Italy, are very much geared towards the fundamental sciences, meaning Silvia could immerse herself enthusiastically in life sciences. After an Erasmus program in Münster (Germany), she was selected for a summer research program at the institute of molecular pathology (IMP) in Vienna (Austria), where she was introduced to the world of neuroscience. There, she studied the role of the insular cortex in fear and the reward system. "I learned a great deal of biology there I discovered neuroscience and was fascinated by the scientific community," says Silvia of her first steps in academic research.

### Research rather than a residency

After Silvia returned to Italy for her last—fifth and sixth—years as a medical student, she was rather disappointed. In her opinion, the training was not sufficiently practice-oriented and, unfortunately, was lacking opportunities to combine academic training with research experiences. For example, it lacked an MD-PhD track. However, the opportunity to carry out clinical work towards the end of the medical graduation represented again another important milestone in her trajectory; she was greatly stimulated by this experience. "I enjoy clinical work! As every patient is different, I have to carefully think about the best solution for him or her, considering their psychological, social and physical state." However,

Silvia's desire to become a scientist was still there, since she considered that having a good fundamental knowledge is essential for improving clinical practice. "I'm really attracted to psychiatry, but before prescribing psychotropic drugs, I'd like to understand how the brain works, and contribute to developing basic knowledge that can inspire the development of novel treatments". It was for this reason that Silvia decided to do a PhD rather than embark on a medical residency.

### Synapsy: a revelation

It was a tricky decision to take, continues Silvia, given that research is not the classical path for a medical doctor. Above all, my strong desire to carry out translational research was not easy to satisfy. "Most of the time, the clinicians are on one side, the fundamental researchers on the other, and there's no one to make the connection." The young researcher was amazed, therefore, to find out that Synapsy existed. She applied to two affiliated laboratories and was accepted by Carmen Sandi in 2016 to start a project on stress.

Stress is a subject that particularly speaks to Silvia since it concerns all of society, she says. "We're all stressed and that affects our physiology. It's a system that's been thoroughly preserved throughout the evolution of our species, but which has not evolved as quickly as society. In addition, stress has huge consequences for the development of psychopathologies. And that's why it's important to study it properly." It is also an area in which Silvia would like to stay when it comes to her future career.





## Mapping the emotional management of trauma

### Glucocorticoids to counter the effects of stress

Silvia's thesis focuses on the intra-individual variability of the stress response. In humans, low blood cortisol levels are seen in people with post-traumatic stress disorder (PTSD), but the cause and effect link has not been explained.

To shed light on this link, Silvia is working on an animal model of vulnerability to PTSD. She uses strains of rats divided into three groups based on their different corticosteroid levels—the equivalent of human cortisol—in response to stress. She observed that rats with low glucocorticoid responsiveness remain frightened for longer than others during fear learning and extinction, an observation that was linked to a small hippocampus. Given that these two aspects are combined in people with PTSD, Silvia is using this animal model to ascertain whether a small hippocampus size can provide vulnerability to develop trauma-related disorders. At the same time, she is trying to validate a causative link between low corticosterone and impaired fear extinction and assessing whether administering glucocorticoids could be efficient to treat PTSD. Moreover, she is also using this animal model to get further insights on the link between sleep disturbances—particularly in REM sleep—and PTSD pathophysiology. As this type of sleep is important in the formation of emotional memories, and is largely modulated by glucocorticoid, Silvia is trying to determine whether an external supply of corticosteroids can restore normal sleep and thus ameliorating PTSD symptomatology. ●

**Trauma can induce fear pathologies, which are treated using psychotherapeutic approaches whose brain pathways have recently been identified.**

Fear leaves traces in the brain, and remembering it causes a feeling of discomfort. During extreme trauma—such as the shock of war, interpersonal violence or road accidents—a condition called post-traumatic stress disorder (PTSD) may occur. Although most people manage to live satisfactorily with the memory of their trauma, individuals who develop PTSD are terrified of everyday reminders. For instance, an innocuous red car that has been parked properly in the street may cause anxiety attacks in a person who has experienced a road accident.

Although patients do not manage to get rid of these anxieties themselves, there are effective therapeutic approaches known as exposure-based therapies. The very act of repeatedly reliving past events and describing the associated fears

in a psychotherapy session succeeds in greatly reducing the symptoms. This process has long intrigued neuroscientists seeking to understand the neurobiological mechanisms involved, and it is the question that interests Bianca Silva, a postdoctoral fellow in the laboratory headed by Johannes Gräff at EPFL.

### A new route

The first observation the young researcher made whilst reviewing the literature was that “the work undertaken on the subject doesn't address the question properly. The vast majority of the experimental paradigms used to induce trauma and then directly start exposure therapy. But, in reality, PTSD only shows itself months, if not years later.” As a result, the team led by Gräff embarked on a

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new experimental paradigm to start the investigations anew from the beginning, namely identifying the brain circuits to reduce long-lasting traumatic memories in mice.

To address this question, Bianca uses a technique based on c-Fos expression—a transcription factor where the level of expression increases sharply with neuronal activity—that means it is easy to quantify activity. “It’s a bit like doing magnetic resonance brain imaging but statically,” explains Bianca. Mice are conditioned to fear by being exposed to electric foot shocks in an environment designed for this purpose. After a month during which they return to the peaceful life of laboratory mice, they are re-exposed to the same environment—but without the electric shock—in order to evoke the memory of fear (known as fear recall). They are subsequently repeatedly re-exposed to this environment until they realise that it is not hostile and their fear disappears (known as fear extinction). The level of c-Fos expression is then measured.

### The false memory track

“Our first observation was that the brain structures involved in recent memory are not engaged.” It is the thalamus, and more particularly the nucleus reuniens, that demonstrates the greatest c-Fos expression. This nucleus receives connections from many brain structures, mainly limbic. And it sends projections to the medial prefrontal cortex, the hippocampus, the entorhinal cortex and many other associated structures.

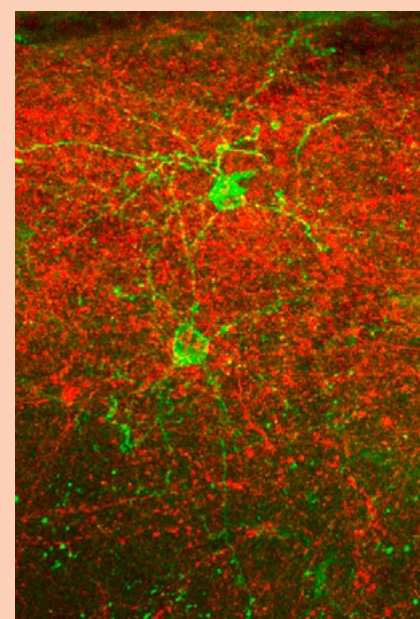
### A structure for unlearning

Interestingly, the nucleus reuniens was not only active at the end of the extinction procedure (when fear levels are back to normal), but also during the very initial stages of extinction, when fear levels are still high. To directly investigate the role of the reuniens in extinction Silva applied an inhibition strategy using chemogenetic approaches. This is a combination of techniques borrowed from genetics and pharmacology used to activate and deactivate neuronal activity, DREADD respectively. Inhibition of the nucleus reuniens specifically impaired the fear extinction process, while its activation ameliorated it.

“This suggests that the nucleus reuniens is only involved in the extinction phase and that activating it could help the mice calm their fear without having to go through a long re-exposure procedure.” This is the system that Silva has implemented using optogenetics tools — a combination of techniques from genetics and optics to activate and deactivate neuronal activity. She discovered that the high-level fear mice are able to quench their fear much more easily when their nucleus is artificially activated. “A simple reminder in the conditioning environment was enough to make them unlearn and return to reasonable fear levels. The activation of the nucleus is therefore sufficient in itself!” Bianca and the group led by Gräff are now in the process of identifying what types of neurons are involved in these extinction mechanisms and are refining the discovery of the mechanistic paths involved in PTSD psychiatric theories. ●

**Studying neurogliaform-type interneurons involves the five key elements of stress-related pathologies: brain development, the prefrontal cortex, serotonergic pathway, interneurons and plasticity. Here’s how.**

Experience constantly alters the activity of the brain and the structure of the neural networks. Known as activity-dependent plasticity, it is an essential process for memory and learning. Although it is especially pronounced during development, it continues throughout life. The underlying mechanisms of plasticity are particularly interesting for Synapsy since they play a role in most psychiatric illnesses (see



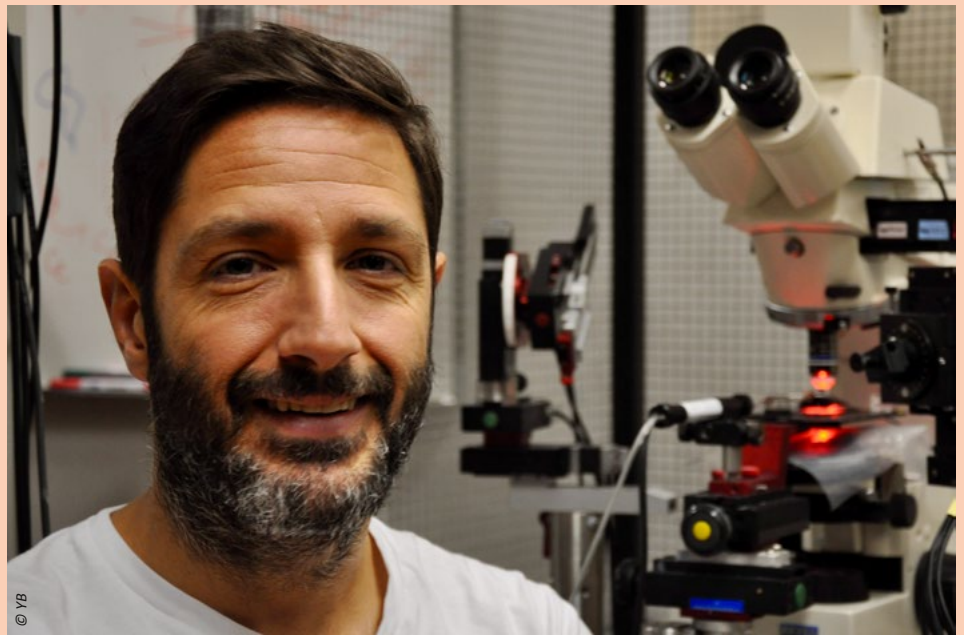
Neurogliaform cells (NGCs, green) and axons from the posteromedial thalamus (red), expressing different light-activated ion channels, in barrel cortex layer 1. This combination allows for selective optogenetic activation of the one or the other element in order to study the inputs and outputs of NGCs. © Foivos Markopoulos, Holtmaat lab

## Tracking neurogliaform cells and their role in the cortical microcircuit

boxed text on page 3). The group led by Anthony Holtmaat at the University of Geneva is studying the functional and structural aspects of this form of neural plasticity. Alexandre Dayer's group, on the other hand, is trying to ascertain how neuronal activity and genetics can alter the developmental trajectories of neural cells during development and thus modify the connectivity of the neural networks. These are complementary approaches that lie at the heart of a collaborative project between the two laboratories involving Foivos Markopoulos, research fellow (maître-assistant) at the University of Geneva. The project aims to understand how a type of cortical interneuron called the neurogliaform cell regulates plasticity processes.

### Serotonergic pathway singled out

But why study neurogliaform cells in particular? The answer comes from research carried out by Dayer's laboratory on serotonin — a neurotransmitter involved in physiological functions such as sleep and mood. This research indicates that a dysfunction in the serotonergic pathway during brain development affects the development of cortical interneurons, such as the neurogliaform cell. In addition, Geneva-based researchers have identified that a serotonin receptor —HTR3A— influences the development of neurogliaform cells in the cerebral cortex. Interestingly, variation in the HTR3A gene has been associated to post-traumatic stress disorder (PTSD), which is studied in the cohort of Synapsy researcher Daniel Schechter (read the related article "Maternal exposure to violence and child psychopathology" on page 2). In addition, animal models that do not



express the HTR3A receptor gene are unable to erase their fear, which is a typical PTSD trait.

### Focusing on the mechanistic

Neurogliaform cells intrigue Foivos since they have been identified as the source of long-lasting inhibition "but to investigate their role in activity-dependent plasticity, we needed to be able to manipulate these cells with specificity". For this reason, Markopoulos collaborated with Mathieu Niquille and Greta Limoni from the Dayer lab, who used genetic tools to trace the origins of 5-HT3AR-expressing interneurons. The scientists found that a specific pool of these interneurons comes from a different region than other types of interneurons, located outside the cerebral cortex in the preoptic zone. Furthermore, they travel long distances to reach the cortex a few days after birth and take several weeks to reach maturity. By investigating their electrophysiological and morphological profile,

Markopoulos was able to identify these interneurons as the cortical neurogliaform cells.

With this information and the tools that have been developed, Markopoulos intends to investigate the specific role of neurogliaform cells in circuit mechanisms underlying activity-dependent plasticity. The aim is to have a full understanding of the role that these cells play in learning and behavior, and what the consequences are of a dysfunction of these mechanisms in the context of stress-related disorders. "We're focusing on the circuit mechanisms that involve these cells. Since the activity of neurogliaform cells is likely to undergo negative regulation in the event of early exposure to stress, we hypothesize that this unbalances the modulation of synaptic activity mediated by these interneurons, with an impact on activity-dependent plasticity", concludes Markopoulos. ●



## CLINICAL FOCUS

# Neural signature of trait anxiety

## The neurological basis of trait anxiety, a risk factor for the development of neuropsychiatric diseases, revealed by Synapsy researchers.

Trait anxiety is a personality dimension related to the extent to which events are perceived as potentially threatening. The identification of the underlying neurobiological mechanisms may advance the understanding of stress-induced neuropsychiatric disorders, particularly anxiety disorders and depression. Since little is known about the influence of trait anxiety on motivated behavior or physical effort, Synapsy researchers joined their expertise in order to investigate this.

Dr. Cristina Berchio, senior researcher in the laboratory of Jean-Michel Aubry and Christoph Michel at the University of Geneva, who performed this research in collaboration with Joao Rodrigues from the Carmen Sandi laboratory at EPFL, explains their approach: “we applied a dimensional approach that integrates behavioral aspects of anxiety and high-resolution EEG to interrogate the brain

fine-grained temporal dynamics during a specific task”.

## Anterior Cingulate Cortex as a Biomarker

Synapsy researchers used a modified version of the so-called Monetary incentive delay paradigm where individuals could earn different monetary incentives by squeezing a handgrip. They used EEG to assess brain responses to different incentive levels, and focused on the investigation of reward anticipation.

“High anxious individuals showed an increased sensitivity to monetary incentives, and their brain responses to low incentives markedly differed from those of non-anxious individuals,” explains Cristina. Specifically, highly anxious individuals showed heightened activation of the anterior cingulate cortex when presented with the lowest incentive levels. The study reveals a role for the anterior cingulate cortex in trait anxiety-related differences in incentive processing when rewards are dependent on effortful performance.



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## CONTENT

### Editorial

The Harmful Effects of Stress Unraveled 1

### Content

Maternal exposure to violence and child psychopathology	2-3
Halfway between cell biology and patient care	4-5
Anti-stress meditation	5
Breaking the transmission of trauma	6
Making a living on two wheels and electroencephalography	7
No clinical work without understanding the basics	8-9
Mapping the emotional management of trauma	9-10
Tracking neurogliaform cells and their role in the cortical microcircuit	10-11
Neural signature of trait anxiety	12

## Home Institutions



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