



Editorial by Alexandre Dayer

New frontiers for Synapsy's mood cohort

The Geneva-Lausanne Synapsy mood cohort is at the center stage of our 6th newsletter. In Geneva, Camille Piguet, a promising clinician scientist,



L-M Cantonas, A. Dayer, G. Fossati

is using functional multimodal imaging in order to assess stress vulnerability in high-risk offsprings of individuals suffering from bipolar disorders. In Lausanne,

and with the aim of identifying early biomarkers of the disease, Pierre Marquet has established a new collaboration with Laval University (Quebec) and is applying high-resolution digital holography microscopy to explore disease-related phenotypes on iPSC-derived neurons from patients. At a more basic level, Pierre Magistretti is providing fundamental new insights on the key role of lactate in depressive-like behaviors and is translating these findings into the start-up GliaPharm, newly established at Campus Biotech. Finally, Andrea Volterra's lab is studying the role of neuroinflammation on astrocyte signaling and cognitive dysfunctions in stress-related phenotypes.

Villars 2017 was a great success with our highest attendance yet. The poster session was of high quality, congratulations to our poster prize winners! To our delight, our invited speakers—WHO Director of Mental Health Shekhar Saxena, as well as the advisory boards members Elisabeth Binder, René Hen, Kathleen Merikangas and Trevor Robbins—gave exceptional talks.

In the coming weeks, Synapsy has to plan its transition into the third phase. This will require substantial work from all members in order to finalize the proposal by June 2017. Thus, I would like to already acknowledge all members for their efforts spent towards the success of the future phase III. □

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NEWSLETTER

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by Yann Bernardinelli

Disturbed Moods

Bipolar disorder comes under the cognitive neuroscience spotlight with Camille Piguet

The physiopathological mechanisms that lie behind mood disorders are poorly understood. Although psychiatrists and researchers recognise that genetic and environmental factors play a part, they know very little about how these aspects influence the onset of such disorders. The members of Synapsy's WP#5, including Camille Piguet, are focusing their work on identifying endophenotypes and vulnerability markers linked to mood disorders. Dr. Piguet is investigating the problem from a new angle: cognitive neuroscience. The former winner of the Synapsy clinician-scientists scholarship is endeavouring to spotlight the neuronal circuits involved in certain impairments in cognitive functioning.

GENETIC AND ENVIRONMENTAL HEREDITY

In the context of this research, at-risk populations need to be pinpointed. Martin Preisig in Lausanne and Kathleen Merikangas at the NIH (a member of Synapsy advisory board) have been genuine pioneers in this field: they were the first to tackle population issues relating to mood disorders. Over the past two decades, they have drawn on epidemiological data that demonstrates there is

a trend among offspring of individuals with severe mood disorders —such as major depressive disorder (MDD) and bipolar disorder (BP)— to develop the same illnesses as their parents. With Dr. Preisig and Prof. Merikangas focusing their research on this population at risk of suffering psychological problems, it makes sense that the same group was chosen by Dr. Piguet and Synapsy.

The various known biomarkers and endophenotypes include genetic factors. Family studies clearly reveal that heritability exists. Although some of the genes at play have been identified, we are still ignorant about the causes. Bipolar disorder is complex and doubtless multi-systemic, meaning that there are numerous genes, including (inter alia) circadian and serotonergic and genes linked to the cortisol system. Under these conditions, it is difficult to link a specific gene to the symptomatic of the illness and to determine which system influences the disorder. Nevertheless, a recurring system is the response to stress: for example, a high incidence of childhood trauma promotes the early onset of illness. Furthermore, epidemiological and genetic studies show that negative life experiences have an impact on the occurrence of mood disorders, although less clearly than childhood trauma.

COGNITIVE NEUROSCIENCE'S PERSPECTIVE

From a cognitive neuroscience standpoint, bipolar disorder and depression are disorders linked to dysregulated emotional responses. In MRI, it is partly in the same neuronal circuits that effects are observed in each type of patient. However, certain differences are also noted, and the overall dynamic seems different, with emotional dysregulation being a periodic phenomenon in bipolar patients who have similar emotional responses to normal subjects in between episodes (if they do not have personality disorders associated with their bipolarity).

By combining emotional and cognitive investigations, Dr. Piguet aims to establish (i) whether a form of

vulnerability to stress is a precursor of the disorder; and (ii) whether it is also present in stabilised bipolar patients, since poor stress management is a type of emotional dysregulation. She plans to use brain imaging to ascertain whether bipolar patients have less control over their responses to stress and whether this correlates with less activity in the prefrontal region, especially the dorso-lateral cortex, and limbic hyperactivity. In other words, Dr. Piguet is attempting to prove that bipolar patients and their offspring have high emotional reactivity by focusing on the cerebral circuits involved in stress reactivity and emotional control.

Camille Piguet
Villars, April 2017
watch her interview



CUSTOMISED PROTOCOL

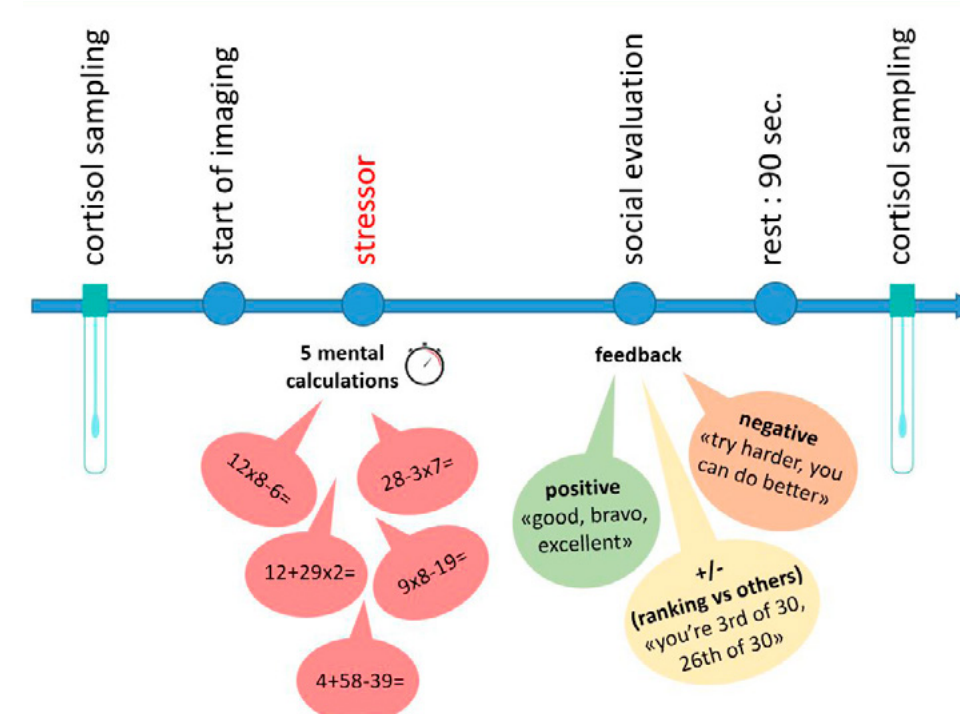
Dr. Piguet and her colleagues have devised a powerful multi-modal protocol that includes a mechanism for measuring stress reactivity. Epigenetic and biological parameters (cortisol, pupillometry, physiological constant, auto-immunity test) are calculated concurrently with tasks that combine cognitive control and emotional response while undertaking functional and structural neuro-imaging measurements and a clinical diagnosis. For stress reactivity, patients and their offspring have to perform mental calculations in a set time. They then receive either positive ("Well done") or negative ("You are not good; you can do better") feedback while being compared to the rest of the imaginary group. There is a rest period of 90 seconds after the calculation task. It is these periods of rest and "social" feedback that are

analysed. The assumption is that patients and their offspring do not differ in their ability to perform mental calculations in a given time compared to healthy subjects (since they do not have known cognitive disorders in this area). By contrast, patients with mood disorders should be more socially sensitive and take longer to recover (regain their balance) after stress.

POOR MANAGEMENT OF POSITIVE EMOTIONS

Encouraging results —though not definitive— are beginning to emerge. A specific difference is observed between patients and their offspring compared to the control groups during the recovery period. They activate the brain regions linked to processing emotions and the reward system to a lesser degree after experiencing stress with a positive connotation than stress with a negative

Fig. 1 Experimental paradigm



connotation. Bipolar patients, therefore, respond normally to negative stress but seem to have an attenuated response to positive emotions. Interestingly, this also appears to be the case for their offspring, even if they do not show any symptoms. This may represent a vulnerability trait; other studies have shown that the quest for positive sensations may be more intense in bipolar patients, even when they are not in their “high” phases, and could lead to behaviour that is more impulsive.

Patients also activate the amygdala region to a greater extent; this is involved in the “salience” of an emotion, proving once more that such patients have a more sensitive emotional recognition system. The more specific differences in the dynamics of recovery after stress still need to be analysed so that the connectivity aspects between these networks can be highlighted.

It has taken a long time to collect data from the project because it is difficult to find subjects for this type of study, which is relatively complex. Nevertheless, the research team is coming towards the end of the recruitment phase and the data is very rich. It will provide answers to several questions about this cognitive vulnerability to bipolar disorder. □

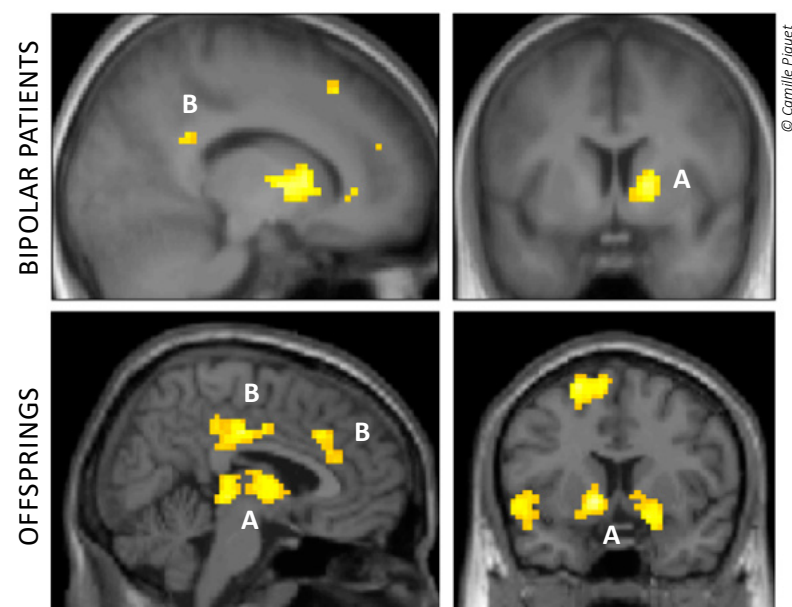


Fig. 2 Decreased activity in ventral striatum (A) and posterior and anterior cingulate cortex (B) during recovery after a positive social feedback in both patients (top) and offspring (bottom).

HIGHLIGHTS



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by Pierre Marquet

Clinical cohort

International joint research unit between the Universities of Lausanne (UNIL) and Laval (ULaval) to promote the identification of novel endophenotypes of mood disorders

The identification of high-risk biomarkers and endophenotypes, associated with the neurodevelopmental component of major psychiatric disorders (MPDs) including bipolar and major depression disorders is a foremost challenge to define at-risk syndromes during childhood. This is a prerequisite for the successful development of optimal treatments and primary prevention strategies and will be likely to provide new insight into the pathogenesis of these disorders.

The strategy to identify such biomarkers, ranging from cognitive impairment to cellular phenotypes,

resulting in particular from the study of neural differentiation of patient-induced pluripotent stem cells, is built on longitudinal studies of cohorts of patients suffering from MPDs and their high-risk offspring. Thanks in particular to the support of Synapsy and the Department of Psychiatry of the CHUV, ULaval and UNIL have created an International Joint Research Unit (IJRU) in neurodevelopmental and child psychiatry directed by Prof. P. Marquet. For several decades already, unique high-risk cohorts (HRCs) have been recruited under the leadership of Prof. M. Preisig in Lausanne, Prof. J.-M. Aubry in Geneva and Prof. M. Maziade in Quebec City,

respectively, and the IJRU has allowed for the launch of collaborative studies aimed at simultaneously identifying biomarkers in these HRCs.

This collaboration has already started and, thanks to these rich and diverse cohorts, the identification of varying symptom patterns has shown that cognitive impairment is a strong biomarker of psychosis. As psychosis is present in different MPDs, the identification of such biomarkers represents a very attractive strategy to define, within the wide clinical spectrum of each MPD, specific subtypes for which the core pathogenic mechanisms could be less heterogeneous. □

HIGHLIGHTS

by Claudia Laperchia and Andrea Volterra

Glia and mood disorders

Studying the link between neuroinflammation and cognitive impairment in mood disorders

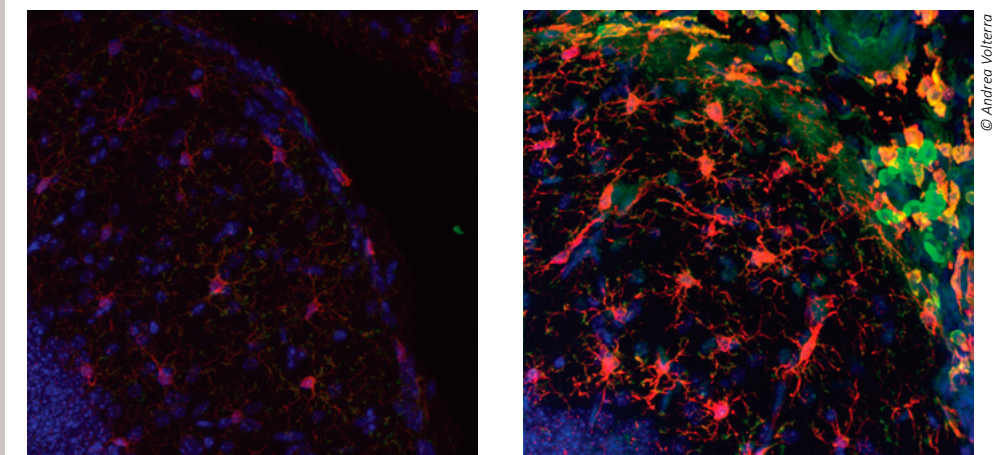
Andrea Volterra's lab is studying the possible link between neuroinflammation, alteration of astrocyte signaling, and cognitive dysfunctions in mood disorders. The study aims at identifying the mechanisms leading to the onset of a cognitive endophenotype in a mouse model of anxiety and depression. In the brain, a physio-logical concentration of the cytokine TNF α is crucial for cognitive functions including learning and memory. TNF α acts through the specific receptor TNFR1 on astrocytes modulating the astrocytic release of glutamate and, therefore, contributing to the control of synaptic activity.

Dr. Volterra's lab has recently demonstrated in a mouse model of multiple sclerosis that increased levels of TNF α in the dorsal hippocampus — a region critically involved in contextual memory — causes altered glutamate release from astrocytes, resulting in a persistent alteration of excitatory transmission and impaired contextual memory.

Interestingly, a recent study indicates that mice exposed to chronic psychosocial stress in a chronic social defeat protocol show increased hippocampal levels of TNF α and cognitive alterations together with an anxious-depressive behavior. Moreover, high levels of TNF α would transform astrocytes into noxious neuronal partners in several pathologies combining neuroinflammation and cognitive impairments.

On this basis, the lab wants to use the chronic social defeat paradigm in different transgenic mouse lines in which astrocyte signaling is selectively manipulated. Thereby, they aim at understanding whether elevated levels of TNF α influences astrocyte-neuronal signaling through TNF α /TNFR1, and whether this alteration contributes to cognitive impairment and might, therefore, be considered a target for future therapeutic approaches in mood disorders. □

Fig. 3 & 4 Inflammatory changes in dorsal hippocampus in a multiple sclerosis model (red: activated microglia; green: infiltrating leukocytes): overproduction of pro-inflammatory TNF α modifies synaptic transmission in memory circuits causing cognitive impairment (modified from Habbas et al., Cell, 2015).



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TECHNOLOGY
TRANSFER

GliaPharm was created in 2016 as a spinoff company from Prof. Magistretti's laboratory at EPFL. GliaPharm has expertise in brain drug discovery and development and is specialized in the development of therapeutic strategies targeting brain energy metabolism. GliaPharm has identified several drugs from its screening platform that promote neuroprotection through the regulation of brain energy metabolism.

Neurodegenerative and neuropsychiatric diseases represent some of the diseases with the highest unmet need. Neurodegenerative diseases are expected to become the first cause of death by 2050. Finding treatments for these diseases has been a challenge for the pharmaceutical industry for the past decades with limited progress so far. Although challenging, this represents an opportunity for novel and innovative solutions. Research in Prof. Magistretti's laboratory for the past 30 years has unveiled important and innovative ways to protect neurons from degenerating and supporting proper neuronal function by focusing on primary interventions on glial cells. These scientific evidences led to the creation of GliaPharm SA to pursue the development of treatment against neurodegenerative and neuropsychiatric diseases.

Its innovative approach is to target astrocyte to prevent neurodegeneration and hence treat neurodegenerative and neuropsychiatric diseases. This method can be applied to amyotrophic lateral

sclerosis (ALS), Alzheimer's disease, mild cognitive impairments and depression, which all share similar deficits.

Co-founders of GliaPharm include Prof. Pierre Magistretti as scientific advisor, Dr. Sylvain Lengacher as CEO, Dr. Charles Finsterwald as CSO and Mr. Ambroise Magistretti as CFO.

The main objectives of the company are to create value through efficient drug development and finding the right partners to bring molecules to market. Furthermore, it wishes to establish a patent portfolio and a drug discovery platform using astrocytes as the main target to treat brain diseases.□

Charles Finsterwald, Ambroise Magistretti, Pierre Magistretti, Sylvain Lengacher



INTERVIEW

Interview by Yann Bernardinelli
Dr. Shekar Saxena

Dr. Saxena, current Director of the WHO's Department of Mental Health was our guest during our annual meeting in Villars where he gave a well received talk about KTT. We took the opportunity to interview him further.



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Synapsy—What is the current global mental health situation?

Dr. Shekar Saxena—The current situation requires a lot of improvement. The burden of mental disorders is very high and the number of people with mental disorders or other mental health problems is extremely high and is continuously increasing. Moreover, the available resources to look after people's needs are extremely scarce. On average, governments spend 3% of their total health budget on mental health and this percentage is much smaller in low and middle-income countries. A serious increase of financial and human resources is needed, not solely for people suffering from mental disorders but also for their families, which also require a lot of support.

S.—What could be done in order to improve global mental health?

Dr. Saxena—A number of steps are required. First, the socio-economic reality needs to be changed to make this world more equity based. That would certainly help but even then, people with mental disorders would still be there. Thus, health and social services need to be strengthened to look after their needs. In most countries, the primary health care system —the general doctors and nurses or even the community health

workers— is not able to identify or treat even common mental disorders. This is a pity because it's the logical place to identify depression, anxiety or other mental health problems and provide treatment. This isn't happening because the initial training of workers is not good enough on mental disorders. Moreover, in many countries, the treatment of mental disorders is still institutionally based in large and old-fashioned mental hospitals that serve more custodial purposes rather than the treatments purposes. WHO's advice is to provide treatments in a community-based setting, e.g. in primary health care centers, in general hospitals as well as in mental health centers. That's a very urgent requirement because most of mental hospitals are neither good for treatments nor for respecting human rights.

S.—Synapsy's aim is to bring together psychiatry, psychology and neuroscience in order to better treat mental disorders. What is your opinion regarding our approach?

Dr. Saxena—There is definitely a need to develop and use knowledge together. Neurologists, neuroscientists and even basic neuroscientists need to work much more closely with psychiatrists and other mental health

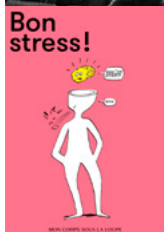
professionals to understand the needs of people and work to find solutions. They have to find answers that can be applied to every health care setting and for all classes, rich and poor. When the manpower is small and the facilities are primitive, interventions that can reach everybody in this world are needed. Those interventions can be diagnostics. For example, finding out a quick economic way to diagnose common and severe mental disorders in a short time with a high amount of reliability. Today, most psychiatrist's diagnoses are based on symptoms and signs through an expert interview, a check list. We are looking forward to identify some biomarkers, electromarkers or other mechanisms which can be used to diagnose on a wide population base with a high reliability. Thus, moving forward in neurosciences or electrophysiology can be extremely beneficial for this purpose. Unfortunately, we keep thinking that it would be next year, but it doesn't come! Projects like Synapsy, which are putting together professionals from different areas to think together, can be useful.

S.—What are the ways in which we could encourage biopharmaceutical companies to re-invest in research programs?

Dr. Saxena—There is a need for more research. The question is who should do it and where the resources should come from. This certainly will be a joint exercise between private companies, governments and philanthropic organizations. We cannot expect companies to invest if the risk-reward ratio does not improve. In such situations, other financial resources can join hands and work toward a system which can be sustainable, have enough rewards for investors but also for public health. I believe that new models need to be sampled in order to situate that there are enough resources for global and sustainable solutions.□

CONFERENCE

Brains under stress: should we be worried?



Download the brochure made by Bioscope, UNIGE (FR)

Many Synapsy researchers and clinicians are studying and measuring stress in their project. They analyze the influence of stress on behavior, clinical trajectories and neural networks. Adolescence is a sensitive developmental period characterized by increased emotional lability and risk for mood episodes. Prevention strategies are needed and the opportunities for stress specialists to speak to an audience of teenagers are extremely sparse.

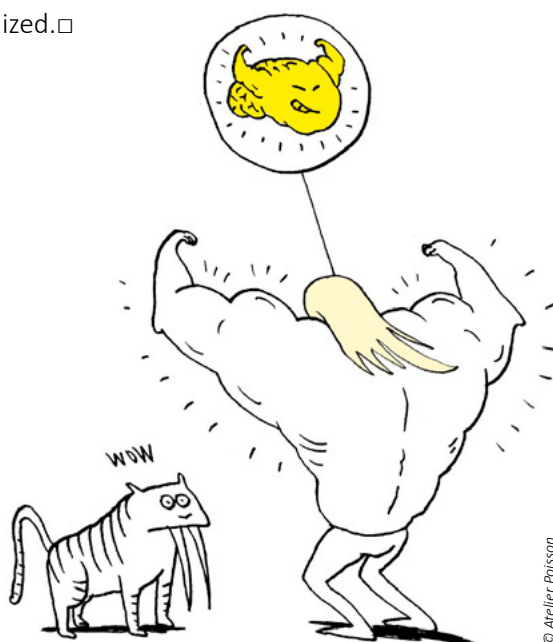
Thanks to a conference organized by the Société Académique du Valais (SAV) on Friday 28th of April in Monthey, four Synapsy clinicians had the great possibility to talk about stress and its impact on mental health, in front of 450 students aged from 15 to 17 years old.

The following presentations were addressed:

- Stress and the brain: the who, what and where?
- Early life stress & emotional regulation learning
- Stress during adolescence: a high-risk period
- The consequences of stress: burnout and mood disorders

The attentive students from the high schools and ECGG-Valais, accompanied by their teachers, learned from the rich expertise of Alexandre Dayer, Daniel Schechter, Camille Piguet and Jean-Michel Aubry.

The exercise was quite successful and speakers were pleased to have been able to benefit from such contact. According to Synapsy, other meetings of this type do deserve to be organized. □



Positive stress

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