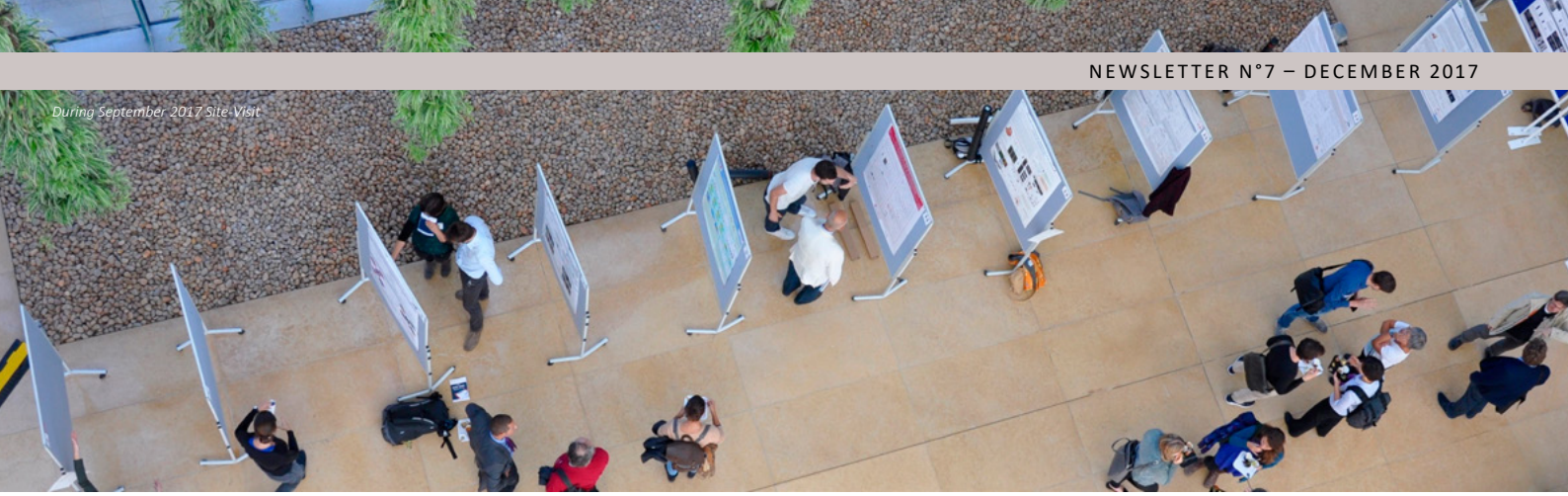


During September 2017 Site Visit

22q11DS cohort reaches maturity

As Synapsy is addressing 22q11 deletion syndrome and schizophrenia in its seventh Newsletter, the 22q11 cohort is reaching maturity, poised to deliver the fruits of a successful synergy between clinical work and fundamental research. Synapsy looks back at the origins of the cohort and discusses its promising future with Stephan Eliez.

like a Swiss watch

Stephan Eliez returned from Stanford, California in 2001 to start work as an independent researcher in Geneva. Armed with the experience of setting up a first cohort of 30 patients with 22q11 deletion syndrome in the United States, Eliez repeated the experiment as soon as he arrived. His aim was to use genetics and imaging to quantify the symptoms of schizophrenia clinically. The future Synapsy research was in line with Eliez's vision, namely to find a correlation between human clinical data and the fundamental mechanisms detected in animal models at the molecular and cellular levels as well as at the level of neuronal networks. It made perfect sense for Eliez to take part in developing the Synapsy project with Pierre Magistretti, Dominique Muller and others in 2010, as Eliez himself explains: "Synapsy was the unique opportunity to understand the physiological and patho-physiological mechanisms related to 22q11DS; it was the missing link between genetics and the neurodevelopmental phenotype of the disease." Today, there is nowhere else in the world which brings everything together around the same cohort: genetics, EEG, brain imaging, cognitive neuroscience and clinical work. "It is the logic of the Swiss watch, where every part is machined and nested with extreme precision. It is a way of differentiating our cohorts from other cohorts with larger funding support," adds the professor.

Stephan Eliez

Huge potential within reach

In the first two phases of the Synapsy project, Work Package 1 (WP#1) succeeded in establishing a resonance between the human cohort and the mouse lineages. This link, explains Eliez, "means we can now set up cross-validation protocols between observations made on mice and human observations." In the third phase of Synapsy, pre-symptomatic patients will be treated during the right neurodevelopmental time-window to avoid loss of hippocampal differentiation with the same drug approaches identified by the fundamental neuroscientists. Conversely, the resilience factors observed in humans will be studied in mice. Three axes will be looked at in detail: (i) stress and its impact on key neural circuits; (ii) cannabis and the link between consumption and the development of schizophrenia; and (iii) medication designed to protect the mechanisms of parvalbumin neuron functioning in connection with the studies of the Carleton and Caroni groups.

Synapsy and its 22q11DS cohort are entering a key phase where the use of the animal model will be geared towards clinical work. "We are going to test the differences with an undeniable advantage: the rapid brain development of the mouse model," concludes Eliez.□

N°7 – DECEMBER 2017

NEWSLETTER

NATIONAL CENTRE OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY

synapsy

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

Editor
NCCR SYNAPSY
MANAGEMENT TEAM

Texts & Photos
YANN BERNARDINELLI (YB)

Print
REPROGRAPHIE UNIMAIL

Contact
NCCR SYNAPSY
CAMPUS BIOTECH
CH. DES MINES 9
1202 GENEVA
SWITZERLAND

+41 21 379 11 21
SYNAPSY@UNIGE.CH

nccr-synapsy.ch

HIGHLIGHT PSYCHIATRY :
CLINICAL COHORT

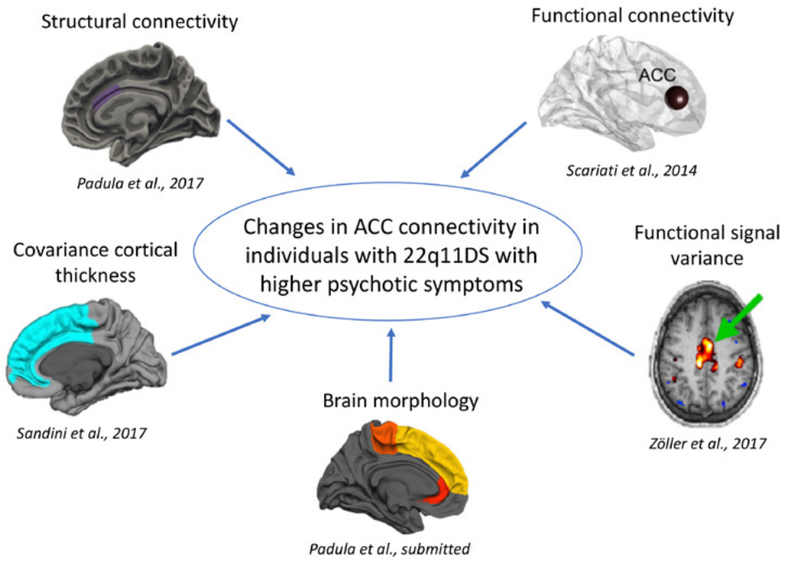
Perceiving schizophrenia

One in every 100 children develops schizophrenia in adulthood. But how can we know which children? Brain-imaging studies performed on the 22q11ds at-risk population provide some preliminary answers.

In Switzerland, as elsewhere, one per cent of the general population develops schizophrenia around the age of 20. The ability to predict which children are likely to develop the illness on the basis of neurobiological, genetic, psychological and cognitive phenotypes would help further our understanding of the pathological mechanisms and ensure early patient care. It would also make it possible to assess the effectiveness of new treatments before the illness occurs. In this context, brain imaging and other quantitative neuro-functional assessment tools (EEG, Eye tracking, etc.) is the preferred investigative technique for identifying biomarkers of the illness.

A tailor-made cohort

The prevalence of 1%, although significant in epidemiological terms, is not high enough to make it easy to follow the intellectual and cerebral development of future schizophrenics. Stephan Eliez points out that even the cohort supplied by Dunedin (the famous New Zealand study) –1,037 individuals followed from the ages of 7 to 30– only gave rise to twenty schizophrenics. "Obviously, it's not viable statistically," says Eliez. The solution lies in analyzing an at-risk population to increase the probabilities. 30% of people carrying the 22q11 microdeletion chromosome abnormality (22q11DS) become schizophrenic between 14 and 23 years of age, and it is on this basis that Eliez made the logical decision to choose this at-risk population when setting up in Geneva in 2001. Today, thanks to his colossal recruitment work via Swiss, Belgian, French, English and Irish patient associations, Eliez's 22q11DS cohort is highly conducive to studying schizophrenia.



When the cohort was being established, the diagnostic tools consisted of IQ tests and a clinical interview. "We needed tools to characterize the illness as close as possible to the neurodevelopmental phenotype," explains Eliez. It follows that, over the last 15 years, the cohort has benefited from the implementation of new technologies by his research group. Eliez, supported by Marie Schaer (his student at the time), introduced (inter alia) eye-tracking and a new approach to neuro-imaging – the gyrification index – to assess the thickness, volume, area and cerebral folding in an integrated manner. Eliez explains that these tools are a real asset for the cohort. In addition, the longitudinal nature of the study makes it unique in the world since brain-imaging measurements have been conducted up to five times on some patients, from the age of 4 to 30 years.

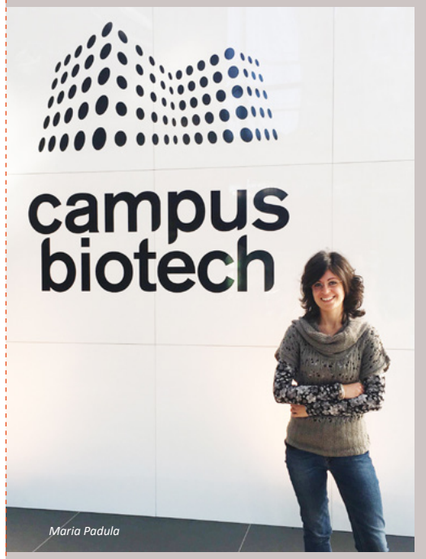
The heterogeneity of 22q11

As such were the conditions in which the young biologist Maria Padula began her thesis under the direction of Eliez and Schaer in 2013. Padula's initial goal was to use structural and functional magnetic resonance imaging (fMRI) together with diffusion tensor imaging (DTI) to determine whether predictors of schizophrenia exist during development. Four years later –and following Padula's successful PhD thesis last September– the young doctor in neuroscience has ten publications to her name (two of which are forthcoming), and has largely succeeded in identifying cognitive and structural biomarkers for schizophrenia. Despite this impressive record, Padula has retained an exemplary modesty, declaring that she "benefited from the cohort and techniques that were already in place as well as my skilled and talented colleagues".

5 QUESTIONS FOR

Maria Padula

Maria Padula studied biology at the University of Salento Lecce in Italy before obtaining a master's degree in neurobiology at the University of Pisa. Maria joined Stephan Eliez's group in 2013 for her PhD thesis in Neurosciences, which she obtained with great distinction in September 2017.



As a biologist, why did you choose to work on a clinical topic?

Before starting my thesis, I worked with murine models but wanted to move closer to clinical work and people. The group run by Stephan Eliez was a real opportunity for doing just that, and it was really lucky for a neuroscientist to be able to access clinical work.

What did you gain from interacting with patients?

I felt that I could contribute to helping these people. Contact with patients makes things more concrete compared to basic research.

What role has fundamental neuroscience played in setting up clinical trials?

I had lots of interactions with neuroscientists during my PhD. We collaborated a great deal with the group led by Francesco Papaleo, in Italy and with Pico Caroni's lab. What's more, a translational study is in progress in collaboration with Pico's lab where we use the same behavioral paradigms in humans as in mice, involving tasks on memory and mental flexibility. In addition, the results obtained in the murine model contributed to the development of an ongoing clinical trial in patients with 22q11.2 deletion syndrome.

What are your future career plans?

After four years of clinical research, I would like to switch to the fundamental neurosciences so that I can maintain a profile that is highly translational and become an expert in both aspects. Therefore, I will soon start a postdoc in Pico Caroni's lab, while continuing the collaboration with Stephan Eliez and the work on brain imaging. In the long term, I would love to carry on with mouse-patient models. In my opinion, the ideal situation for this type of research would be to have a single person who masters the clinical and fundamental sides rather than having a specialist in each setting. I'm trying to ensure that I have the profile to be the person wearing these two hats but, since I'm neither a psychologist nor a psychiatrist, it will not be easy to manage the clinical aspects. It would be ideal if neuroscientists could have access to clinical work, with the necessary training. Today, in my opinion, the only possibility is to obtain an additional degree in medicine or psychology.

What do you think of Synapsy?

The "Synapsy" approach is highly pertinent because it is clearly the future of clinical work and neuroscience. In my opinion, you can't understand mental diseases without understanding the basic mechanisms. As the collaboration that we developed within Synapsy shows, this kind of research is really promising in promoting the development of treatments. The two disciplines are becoming increasingly linked, so much so that you can't do one without the other. At the same time, a mouse will never be a human being, therefore it remains challenging to interpret the translational findings!□

Despite appearances, not everything was easy for this young researcher at the outset. Her initial plan was to compare 22q11DS patients with different symptomatic profiles. Indeed, the 22q11 patient population is highly heterogeneous. In addition, when comparing 22q11DS patients with controls, several confounds need to be taken under consideration, in particular their intellectual capacities. However, these analyses could not be conducted during the first phase of her project, as the sample size was not big enough for such intra-group comparisons. Therefore, the initial comparisons were conducted between 22q11DS patients and healthy controls. "As soon as we had the adequate sample, we quickly turned to a comparison between 22q11DS patient sub-groups," says Padula. The 22q11 population was divided into two categories: patients with low symptoms and patients with high symptoms, that have a greater risk of developing schizophrenia. It is this categorization that has enabled her project to progress so rapidly.

Altered structures and connectivity

At the structural level, Padula and Eliez's team have been able to demonstrate that 22q11 patients with positive psychotic symptoms –hallucinations and delusions– have an intensified reduction in cortical thickness. For patients with negative psychotic symptoms –less motivation and social engagement– the situation is not so clear, but a defect in the cerebral fold may be detectable during the child's development.

Furthermore, connectivity defects expressed by hyperactivity in the anterior cingulate cortex in 22q11DS patients with positive psychotic symptoms were also identified. The functional imaging results correlate with the EEG data collected by the team led by Christoph Michel, which were carried out on the same cohort. Finally, and remarkably, the fundamental work performed by Alan Carleton's and Pico Caroni's groups has demonstrated a dysfunction in the inhibitory neurons in 22q11 mice, which corroborates the hyper connectivity observed in humans by Padula's research. It is clear, therefore, that they constitute the cellular mechanistic basis of schizophrenia.

The anterior cingulate cortex is a strong candidate marker of schizophrenia. But Synapsy's researchers and the Eliez group do not intend to stop there: their aim is to take advantage of this discovery to devise new treatments. The idea is to inhibit this region through intracranial stimulation, work that will be carried out during NCCR Synapsy's third phase.□

Re-orchestrating neural networks to counter schizophrenia

A three-level study of the synaptic structure, neural network and behavior is particularly helpful for understanding neuropsychiatric diseases, including schizophrenia and patients with 22q11 microdeletion.

The structural properties of neurons at the synaptic scale influence their effective and functional connectivity. Knowing how this link affects the dynamics of neural networks and how it is reflected in behavior is the hobby horse of Thomas Marissal and the group led by Alan Carleton at the University of Geneva. The Geneva researchers are tackling the issue by working on an animal model: the LgDel mouse line that carries 22q11 microdeletion. These mice have known defects in their synaptic structure, and Marissal soon observed in an in vitro experimental model (an organotypic hippocampal culture) that the network activity was decorrelated. "The neurons," explains Marissal, "tend to be out of sync in 22q11 mice. They don't 'sing along' together although individually they function normally".

A cellular conductor

To understand the basis of this observation, Marissal immediately thought that there must be a conductor directing the global neural activity. Parvalbumin (PV) neurons, which represent 1% of the neuronal population of the hippocampus, are inhibitory neurons known to govern the activity of the excitatory neurons. They were quickly identified by the neuroscientist as ideal candidates: "They are switchboard operators for the neural network," says Marissal.

On studying these neurons, Marissal discovered alterations in their physiological properties. Specifically, the PV neurons of the 22q11 mice are hyper excitable thus generating fewer action potentials. Since the exogenous modulation of neuronal excitability is technically easy, whether pharmacologically or genetically, Marissal and his colleagues were able to play with the excitability of PV neurons. They succeeded in reversing the hyperactivity and demonstrating that it was possible to reverse the synchronization problem of the excitatory neurons. They then established the causal link between neuronal desynchronization and behavioral disorders by managing to drastically reduce the behavioral symptoms associated with 22q11 deletion until a return to normal. Marissal was a very happy man, declaring: "Our results are fantastic! The 22q11 mice are indivisible from the control mice after treatment".

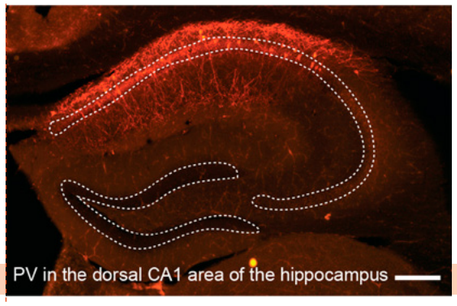


Fig. 1 *Virally-labelled Parvalbumin interneurons (red) in the CA1 area of the hippocampus from a mouse model of 22q11DS.*

Fig. 2 *Locomotor tracks of a wild-type mouse (black), a mouse model of 22q11DS untreated (red) or after treatment (blue). Note the hyper-locomotor behavior of the mouse model of 22q11DS, which is reduced after treatment.*

The strength of the Synapsy's network

These behavioral disorders concern learning, anxiety and somatosensory integration problems which can be directly transposed to humans. In addition, some of the behavioral tests carried out on mice may be applied to humans without being modified, suggesting that there is significant translational potential. Although Alan Carleton's group is keeping silent about the name of the pharmacological treatment given to the mice, it is a known molecule that acts specifically on PV neurons. It works in adults and not during a developmental phase, as is the case for treatments assessed by Pico Caroni and Stephan Eliez on sub-populations of PV neurons. There is a clear correlation between the two research groups, with shared treatment pathways and exciting research synergies. The fact that the molecule is already known implies that the possibilities of technology transfer and filing a patent are, unfortunately, very limited. On the other hand, a collaboration with the group led by Eliez and the 22q11ds clinical cohort could lead to future –and already promising– treatment trials on humans.□

5 QUESTIONS FOR

Thomas Marissal

Thomas Marissal was born in Carpentras, France. He holds a bachelor's degree in biology and a master's in neurobiology from the University of Aix-Marseille. Thomas subsequently completed a doctoral thesis under the supervision of professors Yehezkel Ben-Ari and Rosa Cossart before moving to Switzerland and the laboratory of the late Dominique Muller and Alan Carleton.

What did you demonstrate during your thesis?

I identified a sub-population of pyramidal neurons in the hippocampus with distinct morpho-physiological properties and different embryonic origins. This population is in the majority since it equates to nearly 80% of the neurons in the hippocampus. At the time, knowing that there were discrete sub-populations in a population that appeared to be highly uniform was a real step forward. Knowing that neurons had different roles in the functional tasks of the hippocampus was important, especially in the pathological context of epilepsy.

What are your career plans?

Academic research is clearly my career goal: it gives you creative freedom and means you can make a small contribution to the sum of knowledge and do something new. And, on a selfish level, it's really exhilarating! As well as the exploratory side, it's true that a researcher's work is useful, and I like it. I realized over the years that some patients were combing the scientific literature to find out about their pathology, which means we are all the more responsible to them and makes us feel useful.

Do you want to go in the direction of clinical work?

Nowadays, I don't see myself working with anything other than a subject that has clinical potential, no matter how small. Of course, I can't go towards clinical because I am not a clinician, but I would like to move as far as possible to the preclinical level and keep as many interactions as I can with hospitals.


Thomas Marissal

Did this desire come to you thanks to Synapsy?

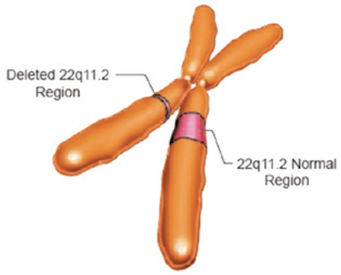
Yes, exactly, it did. And it's something I've realized increasingly since working in a more pathological context with the 22q11 project. The interactions that Alan Carleton's group has with the 22q11 cohort and Stephan Eliez are fantastic. In the future, I would do anything to have that kind of interaction.

What do you think of Synapsy's approach to bringing psychiatrists into neuroscience?

This is important but the two areas shouldn't be confused. Basic biology is at the service of the people working in the field: caregivers and doctors. There is a clear and natural directionality towards medicine. It's obvious that, if we can cure a disease, knowing the basic mechanism is useless. On the other hand, if there is no treatment, knowing a mechanism to find a drug is absolutely essential. Maybe we need to build bridges so that "fundamentalists" are more in touch with patients or patient associations, without turning into medical doctors.□

SCIENTIFIC
PUBLICATIONS

Synapsy phase-2 22q11 selected publications



Sandini C, Scariati E, Padula MC, Schneider M, Schaer M, van de Ville D, Eliez S;
Cortical dysconnectivity measured by structural covariance is associated with the presence of psychotic symptoms in 22q11.2 deletion syndrome.
Biological Psychiatry (in press)

Scariati E, Schaer M, Karahanoglu FI, Schneider M, Richiardi J, Debbané M, van de Ville D, Eliez S;
Large-scale functional network reorganization in 22q11.2 deletion syndrome revealed by modularity analysis.
Cortex 82:86- 99 (2016)

Karunakaran S, Chowdhury A, Carvalho F, Donato F, Quairiaux C, Michel CM, Caroni P;
PV plasticity sustained through D1/5 dopamine signaling required for long-term memory consolidation.
Nature Neuroscience 19:454-464 (2016)

Donato F, Chowdhury A, Lahr M, Caroni P;
Early and late-born parvalbumin basket cell subpopulations exhibiting distinct regulation and roles in learning.
Neuron 85:770-786 (2015)

Gschwend O, Abraham N, Lagier S, Begnaud F, Rodriguez I, Carleton A;
Neuronal pattern separation in the olfactory bulb improves odor discrimination learning.
Nature Neuroscience 10:1474-1482 (2015)

...and many more on our Synapsy website :
http://nccr-synapsy.ch/research/scientific-publications

CAREER

Pierre J. Magistretti

A life-long passion for neuroscience

Professor Magistretti has devoted his career to studying the interactions between neurons and glial cells, psychiatry and developing neuroscience at home and abroad – and he looks set to continue to do so!

A one-day symposium was held in honor of Pierre Magistretti on October 23, 2017 to mark his retirement from EPFL. The professor's impressive career and legacy –both scientific and institutional– was reviewed during the event, with former members of his laboratory in attendance alongside leading scientists in the fields of neuron-glia interaction, cerebral energy metabolism and synaptic plasticity. Attendees took turns to highlight the importance of Pierre's thirty-five years of research on the metabolic coupling between neurons and astrocytes. The event was further enlivened by a series of heartfelt testimonials and stories about life in and around the lab, painting a portrait of a man full of humor, humanity, passion... and future projects.

Taking a look in the rear-view mirror

Pierre Magistretti later told us that he had been afraid that this special day would mark the end of an era and would be tinged with too much nostalgia. "There was definitely a feeling of sadness and a bit of nostalgia but there were also so many pleasing stories and testimonials of friendship that it ended up being an excellent day, full of positive emotions." A string of first-rate lectures was given by individuals who had collaborated with and taken part in Magistretti's research or been inspired by his work. In addition, the symposium gave Pierre the chance to look back over these thirty or so years of research from a different angle: "What strikes me and makes me proud is seeing that a real "story" has been built up year after year and result after result. It was not about a particular phase or a discovery but all these years of research rolled into one day." Magistretti admits that he took special delight in discovering previously unknown mechanisms: "That's the thrill of research: recognizing that thirty years ago, the concepts we have described were still unknown." Pierre is a true research pioneer in interactions between neurons and glial cells. His work has shown not just that astrocytes (a type of glial cell) are crucial elements for maintaining neuronal integrity but that their function also includes participating in plasticity mechanisms.

Pre-thought mechanisms

However, Pierre Magistretti's career has encompassed much more than his fundamental work on neuron-glia interactions. He started off studying Latin, Greek and philosophy before being drawn towards science. Pierre's fascination with the human mind and thought subsequently led him to biology: "I said to myself that biology must lie behind the thinking that produced all those poetic and philosophical masterpieces already 2500 years ago, because only biology could ensure this continuity and journey across cultures and time". This was the genesis for Magistretti's desire to understand the human brain: psychiatry was the logical choice, never losing sight of the fact that knowing how the brain functions is crucial to the discipline. In fact, it was to meet this need for fundamental knowledge that Magistretti embarked on a neuroscience doctorate at the University California at San Diego: here he tackled the issue of energy metabolism linked to glia for the first time by studying glycogenolysis –a topic he pursued throughout his career as a researcher. At the same time, Pierre kept up his interest in psychiatry and the human mind, publishing psychoanalytical works with François Ansermet and creating the NCCR-SYNAPSY. "I'm really happy that I had a background in human science, psychology, psychiatry and psychoanalysis but what satisfies me most is the fundamental and scientific part," explains the professor.


Pierre J. Magistretti

Promoting neuroscience

After fifteen years focusing heavily on research, Magistretti became increasingly involved in neuroscience initiatives in Switzerland and on the international stage. He played a leading and unifying role in building the EPFL Brain and Mind Institute (BMI), the Federation of European Neuroscience Societies (FENS), the Centre for Psychiatric Neuroscience (CNP) at the University of Lausanne, the Biomedical Imaging Centre (CIBM), the Lémanique Doctoral School of Neuroscience, and more recently the Faculty of Biology and Environmental Sciences at KAUST University in Saudi Arabia.

Brimming with projects and plans

Although Pierre is retiring from EPFL (where he will now serve as an emeritus professor), he will carry on with his research work at CNP and will be active at KAUST as a researcher and dean. He will also continue his involvement in developing the start-up GliaPharm and his projects on the role of lactate in mood disorders at Synapsy. In short, Pierre is still involved in a wide range of research projects, and his enthusiasm for neuroscience is intact. A fourth decade of research on his favorite topic – the role of astrocyte lactate – is under way: "Now we're going to explore in detail the molecular mechanisms by which lactate modulates gene expression in neurons, which results in neuroprotection and takes part in neuronal plasticity".□

Equal gender opportunities

New Synapsy perspectives

During the first and second phases of NCCR-Synapsy, several practical actions for the advancement of women were realized, inter alia, via a fruitful collaboration with EPFL's Equal Opportunities Office. Synapsy's management has now been transferred to the University of Geneva, and this novel environment is offering exciting innovative perspectives for equal gender opportunities. On top of supporting the blooming of LWiN, Synapsy is starting a new collaboration with the Equal Opportunities Office of UNIGE.□

Gender equality

A publication by Claudia Bagni

Claudia Bagni

Despite women slowly reaching leading positions in academic institutions, a marked gender bias is still occurring. Claudia Bagni and her colleague Patricia C. Salinas from the University College London have published a study on the topic of gender equality (Nov 15, 2017 issue of the Journal Neuron).

In this publication, Bagni and Salinas review progress and deficiencies made in European institutions during the past 50 years and highlight worldwide promising new initiatives. They urge all stakeholders of academic research to implement an equality plan to ameliorate the gender balance, not solely for the benefit of science, but also for the benefit of society and economy. A research community built by women and men for women and men, where "[…] diversity really matters by making a workplace creative and successful".□

https://doi.org/10.1016/j.neuron.2017.10.002

CONTENT

home institutions

UNIVERSITÉ DE GENÈVE

EPFL ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

UNIL

partners

CHUV Centre hospitalier universitaire vaudois

HUG Hôpitaux Universitaires Genève

FNSNF Fonds national suisse Schweizerischer Nationalfonds Fondo nazionale svizzero Swiss National Science Foundation

UNI BASEL

FMI Friedrich Miescher Institute for Biomedical Research

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