Entering Phase-3 has been achieved following a long preparatory and competitive process involving coordinated work from NCCR members at all levels. At the end of January 2019, the Synapsy management team received from the Swiss National Science Foundation (SNSF) the funding decision for the third and final phase. The SNSF ranked NCCRs of the 3rd series into two groups: NCCRs in the top group were allocated 73% of their overall Phase-2 budget, while NCCRs in the second group about 64% of their Phase-2 budget. Synapsy was rated extraordinarily well with regards to both—the scientific and the structural—sets of criteria and is thus part of the top group. This is excellent news! On behalf of the management team, I wish to thank all members of Synapsy for this major achievement.

It is a clear indication of the competitiveness and excellency of the Synapsy project.

Although the budget allocation still represents a substantial 27% reduction in Phase-3 funding, Synapsy will maintain its five basic-clinical work packages and continue to support the clinical scientists program. As future directions, and as proposed by the panel review at our last site visit, we aim to work on new strategies to study additional genetic aspects relevant for the clinical cohorts. Hopefully, the use of polygenic risk score will help to better stratify the high-risk clinical cohorts. This will be discussed in Villars with our new affiliated NCCR members: Alexandre Reymond, Director of the Center for Integrative Genomics (University of Lausanne) and Emmanouil Dermitzakis, Director of the Genome Center (UNIGE).

For once, no single work package is the subject of this newsletter. Instead, you will discover the profiles and visions of psychiatric research of four new affiliated members as well as an article on open data, a topic that will be covered by a seminar in Villars. I strongly encourage you to read the dedicated article (p. 7-9), the subject is exciting and timely since Synapsy must prepare a data management plan by June 2019. And finally, often cited by clinicians from the Geneva medical school as the trigger for their passion for research and psychiatry, you will know everything about Jozsef Kiss’s Neuroclub by reading this tenth newsletter.

Happy reading and looking forward to seeing you at our annual retreat in Villars (21-22 March).
Stefan Kaiser became an affiliated member of Synapsy in March 2018, one year after taking up the position of head of the HUG’s Adult Psychiatry Division and following his appointment as a full professor in the Psychiatry Department in UNIGE’s Faculty of Medicine. Synapsy’s annual meeting in Villars 2018 was the ideal opportunity to learn more about this German-born psychiatrist.

Stefan Kaiser studied medicine in Heidelberg, where he obtained his medical degree before specialising in psychiatry and psychotherapy. He then joined the Zurich Psychiatric University Hospital, dividing his time between clinical work and translational research on severe mental disorders for almost eight years. As head of the division of adult psychiatry at HUG, Stefan Kaiser is responsible for a large clinical division that includes general outpatient and inpatient psychiatry for patients between 18 and 65 years of age. He also holds a university post that he devotes to teaching and research on the negative symptoms of schizophrenia.

“Research helps me a better clinician”

It was while undertaking an internship as part of his medical studies that professor Kaiser had his “eureka” moment for psychiatry: “I found the link between neuroscience, social science and psychological science fascinating!” Based on his experience, it’s clear today that Stefan’s original intuition was right: “A good psychiatrist has to be able to integrate a wide range of disciplines” – and that’s what motivates him the most in this particular branch of medicine. The desire for research and clinical work has always been very strong for him: “In psychiatry, as in medicine, it’s important not to accept everything you read in books! Clinicians develop tools when they carry out research, which gives them a critical understanding, and that’s absolutely vital! On a personal level, research helps make me a better clinician”.

An academic facing a drought in biopharmaceuticals

Psychiatry is in a difficult position vis-à-vis drug therapies: most of the biopharmaceutical industries are withdrawing from the market, with very few – if any – drugs with new mechanisms being offered. “Since nothing is moving on their side, it’s crucial that we turn to basic academic research to develop good concepts that will lead to improved treatments,” explains Stefan Kaiser. The first step is to identify the mechanisms and networks involved in mental illnesses. Against this background, it is essential that neuroscience and psychiatry come closer together: “It’s an important, very long-term job that will have to be carried on well after Synapsy!”

Stefan Kaiser sounds a warning, however, saying it would be a mistake to reduce psychiatry to mere biology. For him, the neuroscientific approach is a way forward but community psychiatry and psychotherapy are not to be forgotten. “You shouldn’t throw everything into these areas. At the same time, they do need to be developed as well. For instance, if you want to improve the social care patients receive, it’s self-evident that neuroscience won’t help much. We have to be aware of that.” To achieve success, he thinks it is imperative that psychiatrists should be trained as early as possible in three streams: biological, social and psychological science.

Understanding and treating the negative symptoms of schizophrenia

As a clinician and researcher, Stefan Kaiser is delighted that he is now affiliated to Synapsy: it will serve as a basis for future research collaborations or it will quite simply help him be more aware of the latest advances in local research. There is no doubt that Synapsy will, in one way or another, feed into Stefan’s research that is geared towards the negative symptoms of schizophrenia and other mental disorders. These symptoms include apathy and decreased expressiveness, for which treatment options are still too limited.

Stefan Kaiser’s first goal is to ensure we have a better understanding of the motivational and cognitive processes of negative symptoms via behavioural paradigms and functional brain imaging techniques. Reward systems are of particular interest to him. In this field, experimental methods derived from basic research on rodents can often be adapted to humans. “We combine these approaches with the development of clinical psychopathology tools to measure negative symptoms more effectively,” he says. His second goal is to develop psychotherapeutic and biological treatments based on his research observations.
Nicolas Toni
“Adult neurogenesis: at the root of psychiatric illnesses”

With a background in fundamental neuroscience, Nicolas Toni’s research may be successful in detecting a link between neurogenesis and psychiatric illnesses.

Memory is an area that has always fascinated Nicolas Toni: it gives us our identity as human beings, says Nicolas, because it’s the cornerstone of how knowledge is transmitted, helping us compensate for our physical disabilities compared to other species. And it’s all possible thanks to the hippocampus, the brain structure that has always been at the core of Nicolas’s investigations – during his PhD on synaptic plasticity with Dominique Muller, his post-doctorate work on adult neurogenesis in Fred Gage’s laboratory, his stints in private industry and in his current position as associate professor at the UNIL-CHUV Center for Psychiatric Neuroscience.

**Neurogenesis and depression**
Nicolas’s research is now focusing on trying to understand how neurogenesis is involved in depression. His investigations are centered on the regulatory mechanisms of adult neurogenesis by the cellular and molecular environment (the neurogenic niche) of the dentate gyrus. It’s an area that is of particular interest to Synapsy: many psychiatric illnesses are linked to a reduction in the volume of the hippocampus and neurogenesis. “No one knows whether these drops are collateral damage or whether they’re causal,” explains Nicolas. “On the basis of what we do know about hippocampal function, it’s easy to imagine that they contribute to pathological phenotypes.” By contrast, the positive role of new neurons on memory and depression is clearly established. Since many mental illnesses have depressive components and involve memory loss, it is possible that impaired adult neurogenesis may be an aggravating factor.

**The neurogenic niche as a biomarker**
Nicolas’s team is currently setting up a blood test to identify the molecular mechanisms that regulate adult neurogenesis via circulating factors. His laboratory has found that the dentate gyrus’s neural stem cells are in direct contact with the blood vessels, suggesting that they could be regulated by the neurovascular niche. The researchers plan to identify these molecules by collecting serum and testing it on stem cells in vitro. “It’s a way not just to understand the regulation of the stem cells but also to devise a test that could signal a neuropathological state,” says Nicolas. The test is at the validation stage in animals before being trialled on patients in Martin Preisig’s cohort. Nicolas is thrilled with this collaboration and his close links with Synapsy: “The Synapsy approach is an inspiration that helps us foster our own models!”

Nadia Micali was appointed head of HUG’s Child and Adolescent Psychiatry Department in late 2017, joining Synapsy in her role as a clinician-researcher immediately afterwards. Her neurodevelopmental approach to eating disorders dovetails with Synapsy’s approach.

It was Nadia Micali’s interest in medicine and social interactions that led her to specialise in child psychiatry. Born in Italy, Nadia studied for her degree in medicine in her home country before heading to Paris to try out clinical research in pediatrics. She subsequently packed her bags for the Institute of Psychiatry and Maudsley Hospital in London, attracted by the institutional conditions in the United Kingdom that were very favourable to the research – clinical work combination. Nadia divided her time in London between her clinical training in psychiatry, doing research one day a week for 3 years; and later a specialisation in child psychiatry (40%) and her PhD studies (60%) for five years. She spent a few more years in the British capital for a prestigious postdoctoral fellowship at University College London, before crossing the Atlantic to work in New York as an Associate professor in psychiatry and co-director of the Eating Disorders Program at Mount Sinai Hospital. In 2017, Nadia was appointed full professor in the Psychiatry Department in UNIGE’s Faculty of Medicine and head of HUG’s Child and Adolescent Psychiatry division. She joined Synapsy as an affiliated member six months later. She has just set up a clinical team to assess and treat children and adolescent with feeding and eating disorders at the HUG.

**Early action**
Micali’s research focuses on the biological and inter-generational risks associated with eating disorders, together with the epidemiology of these disorders in adolescents and their neurobiological risk factors. Her goal is to develop treatments to help patients and their families. She is particularly interested in child psychiatry since she shares Synapsy’s vision of psychiatric illnesses: “If we want to change pathological behaviour, we have to change it early during brain development”.

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**Learning from the network**
Nadia has split her entire career between research and clinical work. Based on the expertise she has acquired, she says: “Research impacts on our actions with patients and that’s important. Likewise, our clinical work is useful to researchers. It’s a positive feedback loop where research ideas are often generated by interactions with patients.”

During Nadia’s stint at University College London she also helped set up a master’s degree in eating disorders. This degree is unique in that it offers a mix of neurobiology and clinical skills, with a scientific approach to psychiatry that is comparable to Synapsy’s. Micali argues that psychiatry trainees should be exposed to research as early as possible in their studies to facilitate their transition. “Personally, I did my psychiatric training in an institution where everyone was involved in research. All the internships and courses included at least one day of research. It was very beneficial for my career because research is not the icing on the cake; it’s an integral part of clinical work.”

**Virtuous circle**
Nadia has a newcomer to the world of Geneva-based neuroscience and psychiatry. She plans first to learn about what is happening in the local community by creating a network, which will serve to fuel her own research, with Synapsy certainly making a large contribution. “Synapsy is a timely opportunity to find out what’s going on here. I’m amazed at the amount of work carried out by Synapsy’s researchers and clinicians,” she says.
Manuel Mameli: Giving clinicians all the tools they need

Manuel Mameli’s research is devoted to identifying the neural circuits involved in motivation. Here he explains how he sees his role as a neuroscientist helping to advance psychiatric clinical research.

Manuel Mameli is a neuroscience researcher with a background in basic biology. After a university education in Italy, he went to the University of New Mexico to train in neurophysiology. “It was an exotic destination for a scientist from Sardinia!” says Manuel of his transatlantic adventure. “It was decisive for my career because I was immersed in the American scientific environment”. After three years, Manuel decided to do a doctorate, joining Christian Lüscher’s laboratory at the University of Lausanne.

This was a period when the quality standards, convinced Manuel to extend his stay in Geneva with a postdoctorate. On subsequently obtaining a Chair of Excellence from the Paris Neuroscience Network, Manuel went to INSERM in Paris to conduct his own research before obtaining a prestigious ERC European Starting Grant. Since January 2017, he is an associate professor in the Department of Fundamental Neurosciences at the University of Lausanne.

Manuel, who is now firmly established in Vaud, believes that clinicians and scientists need to share a common language in order to stimulate the discovery of new psychiatric treatments. “Scientists must synthesise messages designed for clinicians, and clinicians have to understand what it means to do basic research. Researchers, for their part, need to have a broader view of diseases based on clinical data”. The second step, according to Manuel, is to build on the animal behavioural models used in basic research so as not to remain stuck on concepts: “Diseases must be compartmentalised and dissociated in syllables, to use a fashionable term, by means of phenotypes. The discovery of the pathways involved will then be more precise, meaning we can take things to the next level.”

Manuel Mameli’s research is devoted to identifying the neural circuits involved in motivation. Here he explains how he sees his role as a neuroscientist helping to advance psychiatric clinical research.

https://www.fbm.unil.ch/dnf/group/synapses-and-pathophysiology-of-motivational-states

SNSF data management plan for NCCRs

Researchers have long known that sharing information helps science move forward, which is why the sciences have been “open” since the first academic journals appeared in the 17th century. Three hundred years later, open science has entered a new era: the age of open data. Academic publications, and even raw data, now have to be made available in digital format and online. The bodies that fund academic research have recently called for this revolution, which is possible thanks to the digital transition and the advent of the internet.

Tackling the reproducibility crisis

The idea of open data arose in response to a series of studies showing that 50-90% of published preclinical research was non-reproducible and that 20-80% of the data disappeared after 20 years. “Since this sterility has been mainly attributed to avoidable events, journals and supporting foundations have tried to take steps to ensure that the billions invested in research do not go up in smoke,” explains Cécile Lebrand, head of data management at FBM UNIL/CHUV Library. Among the causes that were identified, the following were singled out:

- The Swiss National Science Foundation (SNSF) is adopting an openness policy for scientific data that will have a major impact on research, with the first implementation measures for NCCRs beginning in 2019.

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out: poor documentation; protocols that are kept secret; experimental details that have not been fully developed; and a lack of access to raw data.

As far back as 2013, the United States, the United Kingdom and the Netherlands insisted that scientific data should be shared. The EU followed, demanding 100% open data for its Horizon 2020 program after the "Amsterdam Call for Action on Open Science" in May 2016, and the SNSF fell into step. The policy is having a direct impact on national centres of competence in research, which must provide a data management plan in 2019.

OPEN data vs FAIR data

The SNSF now expects that data generated by funded projects will be publicly accessible in non-commercial digital databases, as long as there are no legal, ethical, copyright or other issues.

The SNSF requires that the sharing of primary data follows the principles of FAIR data. FAIR is a measured approach to open data that is particularly compatible with clinical data since it allows restricted or authorised access for sensitive data, such as data that must retain the anonymity of study subjects. FAIR data covers the ways that data is constructed, stored, presented and published so that it is Findable, Accessible, Interoperable and Reusable. The word "fair" also refers to the fairness of researchers in the sharing process. Data must be recoverable using a standard, open, free and universally-applicable communication protocol. Furthermore, the data must be enriched using appropriate metadata and should be made available under known conditions via clear, visible licences.

The impact on Synapsy

At this early stage of the process, it will not be possible for Synapsy’s researchers to make their entire raw data accessible to the general public. A plan will be developed instead to manage the data for internal – and possibly external – sharing. The procedure required by the SNSF for basic or preclinical laboratories indicates that every laboratory can independently describe what it does in terms of raw data management and must appoint a manager. For clinical data, there are a number of additional obstacles. The first stage consists of determining whether the data complies with the SNSF’s ethics rules. “If there are good reasons, such as it’s impossible to make the genetic data anonymous, or if the sharing of data has not been submitted to the patient’s consent, there is restriction to share the raw data. In this case, the reasons for not sharing the data must be justified and explained,” points out Cécile Lebrand. Accordingly, Synapsy must first define what clinical data is compatible with sharing and then identify with whom and how to grant access.

Sylvain Lengacher, Synapsy’s technology transfer officer, will oversee the entire inventory process for drafting the management plan, which will naturally be scalable to adapt to the needs of researchers.

Choosing the right servers, formats and platforms

Synapsy uses several animal models and clinical cohorts. Common mechanisms exist between pathologies and between the animal models. It will be important, therefore, to share the data across the different laboratories, whether they are clinical or fundamental. “Nevertheless, it is essential to start the data sharing strategy with a nodal point. We chose MRI imaging and EEG,” says Synapsy director Alexandre Dayer.

Patric Hagmann, a Synapsy researcher and assistant physician in CHUV’s Diagnostic Imaging and Interventional Radiology Department, was put in charge of leading discussions on setting up a system for managing MRI and EEG data for Synapsy. Patric brings with him enormous expertise in the field for neuroimaging. “The idea would be to put the clinical data on a server by adopting a common format between the five Synapsy clinical research groups, and then managing how it is shared with a dedicated digital platform.”

According to the legislation, clinical data must be stored in Switzerland. Protected areas, UNIGE’s UniDufour servers and CHUV/UNIL’s Vitality servers are available to research groups. There is no consensus on the format of the primary data and how to organise and share it. Evidence from neuroimaging and EEG data shows that it is not unusual for experimenters from the same laboratory to use different formats. Hagmann says that a simple and easy-to-adopt format known as Brain Imaging Data Structure (BIDS) would lend itself well to the situation since it is compatible with imaging, EEG and behavioural data. However, it will be necessary to define how to integrate other types of clinical data.

A platform for managing data and metadata will then have to be put into place. Unfortunately, although the technology exists, no platform that meets the requirements of FAIR data is available at present. “Exchange platforms have existed in the biomedical field for over 20 years but they can’t be used to read, trace, protect and anonymise data,” says Cécile Lebrand. The US is investing heavily but does not yet have anything concrete. Developing a digital management platform will probably be a necessity for Synapsy.

The cost of sharing

Above and beyond the technological, ethical and security challenges, science’s new era of openness will have direct consequences for researchers. In the first instance, storing data comes at a price: around CHF 400 per terabyte (TB) or CHF 40,000 for the 100 TB needed at Synapsy. “Then you need to add the administrative work and time devoted to these tasks, which is sizeable. The costs of sharing are not currently paid in full by the foundations,” explains Alexandre Dayer.

A sustainable future

The wide-scale sharing of data will undeniably have a positive impact on national research clusters and Synapsy. “Thanks to the work done today, no one will leave with the data in four years, and the consortium’s twelve years of research will be passed on to future generations of researchers,” says Alexandre Dayer.

The systematic exchange of clinical data from different cohorts in the consortium will promote cross-sectional diagnosis in psychiatry. In other words, since the various psychiatric diseases are very heterogeneous, it will be easier to identify the global mechanisms and biomarkers. “Data management will bring the cohorts together and promote dimensional rather than categorical approaches, which are the result of expert consensus and don’t constitute a scientific approach,” says professor Dayer. The purpose of sharing is not to satisfy the requirements of the SNSF but to stimulate research in psychiatry.

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NeuroClub: the “Brain Factory”

The University of Geneva’s NeuroClub, founded in 1999 on the fringes of the neuroanatomy course, introduces the world of research to budding doctors. It’s a club unlike any other, born out of professor Jozsef Kiss’s passion for teaching.

Generations of psychiatrists, neurologists and neurosurgeons from Geneva’s medical school have virtually all passed through the doors of the NeuroClub. More impressive still, most of the former students who have carved out a career in research have only one answer when asked what led them to take up research: NeuroClub! The Club can be seen as the leading recruiting ground for the clinicians-scientists who are so important to Synapsy. To understand what the NeuroClub is, you need to immerse yourself in the career of its founder, professor Jozsef Kiss. The professor, who has recently retired, was a researcher in the Department of Basic Neurosciences in the Faculty of Medicine at the University of Geneva.

Professor Kiss, you co-founded the NeuroClub 20 years ago with two medical students. What is the Club exactly?

To put it simply, it’s a beer and crisps evening! An invited speaker talks about a scientific topic to do with the brain or NeuroClub student members present a research article in the form of a journal club. It’s designed for all medical students. Every event has between 20 and 100 participants. More officially: the NeuroClub is an undergraduate organization whose aims are to promote the formation of undergraduate students in fundamental and clinical neuroscience and to recruit talented and motivated students for the MD-PhD program in neurobiology.

So, it’s a seminar and journal club—which is quite common in the academic world. What is it that makes the NeuroClub so popular?

Actually, there isn’t any journal club organised on the medicine course. But it’s a highly educational approach where participants can find out about research and the philosophy behind it. I suggest that the students work on an article with a clinical theme, and they have to present it beforehand in my office. I play at ‘deconstructing’ the presentation so they can incorporate the researchers’ approach better and think like them. The idea is to create a real-life experience, a feeling, around the meeting so the students can enhance the presentation of the article. Thanks to the involvement of the students, the NeuroClub is like a theatre where the members are sometimes the audience, sometimes the actors.

We also invite researchers to speak, when the presentation is followed by a session on careers in research. The guest of the day serves as a template for stimulating discussion and giving advice. For instance, we talk about the ideal time to do an MD or PhD or the fact that research gives you a critical mind that is very useful for the work of a clinician.

We’ve got carte blanche, really! When someone who specialises in taste is asked to give a talk, we invite a sommelier to do a wine tasting. The NeuroClub is mix of pleasure and serious experimentation: the debates are a very intense experience for participants that stays with them for life.

Why did you create the Club?

For three reasons. Firstly, the NeuroClub stands outside the standard curriculum; it doesn’t ask for or receive any financial contribution from the faculty. Its roots are exclusively in the neuroanatomy course. It’s a difficult area of expertise that makes great demands on students. Since they put so much work in, some students don’t want to let the subject drop. So, I designed something that wouldn’t simply leave them to their own devices once the course was over. Also, I’ve noticed over the years that the majority of future doctors don’t know much about the world of research. The NeuroClub gives students the chance to meet researchers and catalyse their careers. The final reason comes from my personal reflections about my role as a teacher. I think that a good teacher is someone who stays after class, someone who makes themselves available to students.

Could you say a little bit more about your approach to neuroanatomy?

I’m a neuroscientist who came from the world of medicine. I trained at the Semmelweis Medical School in Hungary in the 1970s. I was lucky enough to take the courses of very charismatic professors, Miklos Palkovits and János Szentagotai, neuroanatomists with an international reputation. Their classes were captivating and they helped nurture my romantic dream: to find the secret of life through the brain. When I came to Geneva as a researcher after a stint at NIH, I was assigned to teach neuroanatomy. I was inspired by my experiences in Hungary and I kind of made sure that the discipline was revived.

What did you revolutionise?

I try to make things appealing to the students and to enthuse them. The innovative part is teaching them how to navigate through the brain so they can construct a three-dimensional representation. Then I encourage them to use this to solve a clinical problem. I teach a method of learning that’s based on practice and the ability to think, and I ban rote learning. Doctors are like mechanics who work on humans instead of cars: they need practical work so they can gain experience. That’s why I make them handle real brains and teach them respect for the donor. In addition, I deliberately put them under stress with questions to create a real-life experience and to prepare them as best as possible for the exam. It is a very demanding oral exam where logical thought is the priority. Medicine is an art where the ability to hypothesise – rather than cramming your head full of facts—is of vital importance.

Students love and dread the course in equal measure. It’s true that it needs two months of major effort in the third year, but year after year it receives the highest ratings from the students.

Now that you are retired, who will take over?

I trained colleagues who are neuroscientists, Charles Quairiaux, Alan Carleton and Anthony Hoitmaat, in neuroanatomy for years. For the NeuroClub, if I’m not there, nothing will happen. Ideally, we need a doctor but I’m still looking for one. For as long as I’m in good health, I’ll carry on because I don’t want to leave things in a mess after I’ve gone.
3RD CONERENCE ON THE
NEUROBIOLOGY OF MENTAL HEALTH

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---|---
Attention & Cognition | Alan Carleton, Anne Churchland, Christoph Kellendonk, Francesco Papaleo
Neuromodulation & Reinforcement Learning | Patricia Janak, Christian Lüscher, Yael Niv, Naoshige Uchida
Sensation & Perception | Jennifer Bizley, Carlos Portera-Cailliau, Albert Powers
Social Interactions & Predictive Coding | Camilla Bellone, Katharina von Kriegstein, Marta Moita, Lisa Stower
Microcircuit Development & Function | Jessica Cardin, Josh Huang, Matt Jones, Beatriz Rico
Stress & Mood | Michael Bruchas, Rosemary Bagot, Nadine Gogolla, Johannes Gräff
Translational Psychiatry | Thomas Bourgeron, Nikolaos Koutsouleris, Leonhard Schilbach, Marie Schaer, Gunter Schumann

All speakers confirmed

Registration starting in September!
Stay tuned and meanwhile save-the-date in your calendar!
nccr-synapsy.ch/conference2020

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