Following a successful Site-Visit, Synapsy has officially entered Phase-3 in October 2018. A final decision regarding the overall funding for Synapsy’s third phase is expected from the Swiss National Science Foundation (SNSF) in January 2019. This important decision will allow us to determine the full scope of the research program we aim to achieve in this last funding phase.

At a structural level, Synapsy has two new co-Directors in Phase 3: Carmen Sandi (EFPL) and Philippe Conus (CHUV-UNIL). This structural change allows an optimal representation of the major institutions supporting Synapsy. Pierre Magistretti continues to play a key role in the Synapsy steering committee and in the WP#5.

Among the challenges that remain ahead of us, two are worth highlighting. First, the panel review made it quite clear that it expects Synapsy to better integrate genetic aspects into the clinical cohorts. For this purpose, we invited two new Synapsy affiliated members to our next annual retreat in Villars: Alexandre Reymond, Director of the Center for Integrative Genomics (University of Lausanne) and Emmanouil Dermitzakis, Director of the Genome Center (University of Geneva). A second challenge will be the implementation in Y9 of a Synapsy Data Management Plan in order to comply with the new recommendations from the SNSF. This important aspect will also be discussed in a special session at Villars in 2019.

Finally, in this Newsletter you will discover recent advances in the WP#3-Autism Spectrum Disorders by the groups of Marie Schaer, Claudia Bagni and Camilla Bellone. In addition, this 9th edition gives a voice to psychologists and clinical researchers. A heterogeneity of profiles and a diversity of knowledge crucial to Synapsy’s approach and its desire to create synergies.

Happy reading and best wishes for 2019!
The “social brains” of children with autism spectrum disorder are impaired, some compensating with a hyperconnectivity of the neural networks.

The difficulties experienced by people with autism spectrum disorder (ASD) are characterized by communication and social interaction problems as well as restricted and repetitive behaviors. Experts believe that the origins of these symptoms are due in part to a dysfunction in brain development. Researchers are trying to gain a better understanding of what lies behind the dysfunction in the hope of one day being able to treat the illness. Their strategy is based on studying brain function at an early developmental stage when the first symptoms appear and neural plasticity is at its crisis point.

Social learning disorders

Newborns are attracted by voices, faces and signs of sociability. This interest forms the basis for their social learning—in other words, their interactions with others. From the cellular point of view, it is reflected in the formation of a neural network of connections between different areas of the brain. These networks constitute the so-called “social brain.” Researchers know that infants who later develop ASD already pay less attention to social cues in their first year of life. “Some children with ASD are less attracted to ‘social’ stimuli. But we don’t know what happens in their brains at this very young age”, says Holger Sperdin, research associate in the team of Synapsy researcher Marie Schaer. Although we know the brain areas involved in processing social information, scientists are unfamiliar with the reasons for this dysfunction in individuals with ASD. The team of Marie Schaer has managed to identify differences in the connectivity in the social brains of very young children with ASD. The study, which was led by Holger, was published in eLife in 2018.

In search of the neural correlates of autism

Synapsy researchers have set up a state-of-the-art, tailor-made experimental paradigm in an attempt to pinpoint these differences. This experiment records neural activity using electroencephalogram (EEG) and measures eye movements. Children aged two to four years—they with ASD—were shown videos containing social stimuli. They were shown sequences of short films featuring social stimuli such as faces or children playing. It’s a passive observation, because their young age means we can’t ask them to perform more complex tasks”, explains Holger. These two techniques EE and eye tracking were used to try to find out how ASD children see the world, what neural correlates are involved in the visual exploration of the social stimuli, and whether early differences are observable.

Innate or acquired hyperconnectivity?

The researchers noticed that the way young children with ASD explored the videos was very different to that of children with typical development. “We were struck at first by the differences in how stimuli were explored. When a face appeared, children with typical development all focused their eyes on it, while the explorations of ASD children were more scattered”, says Holger (Fig. 1).

The team also observed a higher degree of connectivity in ASD children between certain areas of the social brain and increased activity in two specific brainwave frequencies (alpha and theta). “We know from other studies that theta frequency is an important part of the social brain, with alpha frequency playing a role in visual attention. Here we found that there was a hyperconnectivity in the waves and between certain cerebral regions of the social brain in young children with ASD compared to those with typical development,” continues Holger.

By correlating eye-tracking data with the EEG, Holger Sperdin and his colleagues have shown that among the very heterogeneous population of ASD children, those whose visual exploration is closest to that of children with typical development have the highest EEG hyperconnectivity. This seemingly counter-intuitive outcome suggests that neuronal hyperconnectivity is a compensatory mechanism. In other words, the data appears to indicate that some children manage to correct the dysfunction of the social brain via hyperconnectivity. This paves the way for early intervention therapies since nothing seems permanently fixed in the social brain of ASD children. Nevertheless, long-term studies are needed to find out how these correlates develop and whether early therapies can correct them.

Fig. 1 - Eye-tracking experience

Each dot indicates the position of the gaze while viewing a video showing a child playing. Left: the blue dots are the areas targeted by a child with typical cerebral development. Right: the red dots are targeted by a child suffering from autistic disorders.
Tonia Rihs
A full and meaningful working life

Tonia Rihs, a trained psychologist, has banked on perseverance and curiosity to pursue her career as a neuroscience researcher.

Tonia Rihs opted for clinical psychology at the University of Fribourg for her university education because she was curious to know more about behavior, emotions and human cognition. Tonia then tackled neuroscience for her master’s degree on transcranial magnetic stimulation (TMS) in collaboration with the University of Bern. She understands how important research is for identifying the effects of non-invasive brain stimulation on cognitive processes. Moving between research and clinical work fuels Tonia’s desire and thirst for knowledge.

Research, clinical work and EEG

Following her master’s, Tonia lived her dream; to discover the world, landing a job as a clinician and scientist in Sydney, Australia. Here she combined research in neuropsychology with the sides effects of pharmacological treatments against HIV. Her eagerness to broaden her skills in neuroscience then led Tonia to take part in Holger Sperdin and Marie Schaer’s study on autism, helping the team use EEG with very young patients. It was a real challenge for the researchers because the children were at such a young age. “The collaboration was incredible because at first I thought it would be impossible. Eventually, though, we found a good strategy for success”, she says, underlining the potential for collaborative synergies within the Synapsy network.

Creating a link

Tonia Rihs works in a world of neuroscientists and psychiatrists. How do other people view her training as a psychologist? “Because neuroscience and medicine are multi-disciplinary by nature, psychologists have a lot to bring to research because they have so many tools and so much experience: their solid foundations in statistics, or their knowledge about designing experiments helps them to enter a dialogue with both worlds,” explains Tonia. Bringing disparate worlds together is exactly the approach Synapsy takes as it seeks to advance research into mental illness. Tonia thinks this is an important, but delicate endeavour. Everyone has to understand the other’s needs for it to succeed. “The dialogue with basic researchers can be complicated. The domains are so specialized that sometimes it’s hard to find a common language”. Tonia believes that Synapsy has a valuable card to play but that even greater interaction is needed between the different members. “One idea would be to set up hackathons or workshops on Synapsy topics and push the participative and interdisciplinary aspects within the group,” suggests Tonia. These are all approaches that would undoubtedly stimulate the plurality of views within the Synapsy network.

Values as a goal

Tonia Rihs is not looking to follow a clearly-signposted path; for her, the key lies elsewhere. “Ideally, I’d like to continue my work between research and clinical work. But since no path is pre-defined, my ambition is to keep my curiosity and continue to do meaningful work that makes a significant contribution to society”. Armed with this ideal, Tonia’s career could lead her to an independent project or a role in a team. It does not matter that much, because for her: “The important thing is to build something”.

Tonia Rihs tells us what she thinks about gender biases in the world of academia.

What are the most glaring gender inequalities in research?

Our visibility! Men make up 90% of the programs for conferences and seminars, and they’re the main spokespersons in the media. And science-related communication, more often than not, displays a picture of a male researcher – and the same goes for advertising directed at children. But it goes beyond issues of gender, because research is often presented in the media as being the workplace for western men. All of this leads to deep biases that give rise to inequalities.

What needs to be done to improve the quota of women in research?

Well, it’s very difficult. I think that the SNSF needs to be prepared to give more support, especially during the hardest times, which is the post-doctoral period. And some of the initiatives that are designed to encourage women may act as potential deterrents if they’re seen as being stigmatizing. So, we need to find ways to support women’s careers effectively and which are evidence-based, if that’s possible.

In Switzerland, I think the underlying problem has also to do with society. It’s true that it’s very complicated to have a family and be a female researcher the same time... but why doesn’t the same question arise for men? The way around this is to introduce mentoring programs, highlight examples of female success and empowering women to encourage them to pursue their careers.

What would you say to future generations of women researchers?

You have to be robust, find your way and persevere! It’s extremely difficult because the world of academia has an antiquated pyramidal structure that’s based on competition.

“I’ve noticed that the women who have the most success and find their place have often played sport at a very intense level at some point in their lives. It’s possible that sport gives them a kind of armor that helps them persevere when times are hard or when they get knocked down. I don’t have the answer but it would be an interesting subject to study. Personally, I’ve never been very motivated by sport; I am passionate about music instead.”
Disturbed social relationships are an autistic trait. Dopaminergic neurons are implicated in these highly-complex interactions.

Social interactions are one of the difficulties experienced by people suffering from autism spectrum disorders. To get to the root of this social disorder, the laboratory led by the researcher Camilla Bellone at the University of Geneva’s Medical Center is trying to understand which neural networks are involved. Social interactions are considered highly complex because the behavior of other people is difficult to predict, and our brains have to continually adapt to the situation by making decisions. Given that dopaminergic neurons are known to be involved in decision-making, and more specifically in social behavior, it is natural that this choice led Clément to Synapsy and Camilla Bellone’s laboratory at UNIGE, where he is doing a doctoral thesis on autism. Thanks to a collaboration with former Synapsy member Peter Scheiffele, the scientists either used a mouse in which the Neuroligin-3 gene was absent from the entire body or a virus allowing the downregulation of the Neuroligin-3 gene only in the VTA dopaminergic neurons. All that remains for Camilla Bellone’s research team is to demonstrate that reward prediction error—the true digital fingerprint of dopaminergic neurons—occurs during a social interaction. This would show that the latter is a kind of social prediction error and would irreversibly confirm the social role of dopamine and its involvement in autism.

Clément Prévost-Solié is currently working hard on this area and the results, he points out, are promising.

Social dopamine

Clément Prévost-Solié is driven by the need to understand human beings in their entirety, from the body to the mind via our molecules and initially decides to tackle all of these different aspects during his studies.

But, when Clément couldn’t find a tailor-made training, he signed up for a course in biology and psychology, studying the subjects in parallel in two different institutions in Paris.

What was it like wearing these two hats? “The experience of human beings is very useful for fundamental neuroscience, especially when the goal is to find treatments”. It was only natural that this choice led Clément to Synapsy and Camilla Bellone’s laboratory at UNIGE, where he is doing a doctorate in neuroscience on autistic animal models.

Clément will defend his thesis in early 2019, after which he plans to explore private research.
Aurélie Bochet
A “made-in-Synapsy” clinician-scientist

Synapsy’s clinician-scientist grant helped Aurélie, a young doctor, land MD-PhD funding. Synapsy took the opportunity to ask her about her motivations and how she sees child psychiatry research.

Where does your interest in medicine come from?
Pediatrics, psychology and psychiatry all interested me back when I was in secondary school, which is why I suggested that the topic for my maturity fédérale certificate should be Rett syndrome. My thesis consisted of investigating the syndrome’s genetic aspects. That brought me into contact with Hilary Wood, a psychologist and director of the Autism Early Intervention Center in Geneva, as well as Stephan Eliez. Meeting these two people influenced my decision to join the Faculty of Medicine at the University of Geneva.

What motivated you to go into child psychiatry research?
When I started my studies in medicine, I wanted to do neurology but then the idea of child psychiatry gradually began to take hold. I think I needed something other than the uniquely somatic approach you find in neurology. Without really understanding why, I felt more drawn to human relationships, and hence psychiatry. The psychiatrists and everyone involved in care inspired me. During my internship in child psychiatry, I spent some time in Marie Schaer’s laboratory, and I think that’s where my desire to do research became more concrete: the environment was more dynamic than in the clinic world and I fitted in well there.

You received a Synapsy clinician-scientist grant in 2016. Tell us what that was like.
I applied during my final year of medicine so that I could get some research experience before applying for the MD-PhD grant from the Swiss National Science Foundation (SNF). The selection process for the Synapsy grant wasn’t really an easy thing for me. I hadn’t been around a long time, so I didn’t have much experience and my case wasn’t strong. So, when I found myself in front of these well-known researchers defending my project at the Villars retreat, it was a bit anxiety-provoking. Afterwards I was able to start in Marie Schaer’s laboratory on a half-time basis with the clinic at the Autism Consultation Center.

Since autumn 2018 and the MD-PhD grant from SNF, you’ve continued to divide your time between clinical work and research. Is that important for you?
The SNF grant actually means I can spend 85% of my time on my research project and 15% on clinical work. It’s essential to keep the clinical part, especially for following up patients with whom I began consultations before starting my MD-PhD. Although Marie Schaer’s laboratory is very clinically oriented, it’s important for me to keep the relational aspect with patients. Clinical work means you can have an entirely different relationship with families, and it calls for versatility. The research involves more specific tasks, such as taking or analyzing data.

What is the topic of your research project?
The original cohort at Marie Schaer’s laboratory covers children aged two to four with autism spectrum disorder (ASD). As the children are getting older, the goal now is to expand the cohort to school-age children over four years of age. The idea is to open up the existing cohort to attention deficit hyperactivity disorders (ADHD). As the children are getting older, the goal now is to expand the cohort to school-age children over four years of age. The idea is to open up the existing cohort to attention deficit hyperactivity disorders (ADHD). The aim is to track the occurrence of attention deficits in children with a neuro-developmental disorder, and – if possible – define specific neurobiological markers or even early predictors of attention deficits in these children.

What are your career plans?
After getting my MD-PhD, I will probably start my clinical training to obtain an FMH in child psychiatry. I will then need one year of adult clinic, one year in somatic medicine and 4 years in pedopsychiatry. This will be an asset if the research options close or if I would no longer be interested in it. All this will depend, of course, on the course of the next three years.

What do you think of Synapsy’s approach, which is designed to link medicine and basic science?
It’s highly relevant, especially in the context of psychiatry and neuroscience. Neurobiology, psychiatry and genetics are branches that have to be unified. The Freudian concepts found in psychoanalysis are very far-off when tackling neuro-developmental disorders in children. I think it would be a good idea if there was a specialization in child neuropsychiatry in Switzerland or that child psychiatry looked at more genetic aspects.

The main goal of Synapsy is to bring together neuroscience and psychiatry and for that purpose promoting a new generation of psychiatrists with neuroscience skills.
Since 2012, Synapsy supports scholarships aimed at young psychiatrists with an interest — but no experience — in research. The Departments of Psychiatry organize positions where trainees work 50% as a clinician and 50% in a Synapsy lab.

Clinician-in-lab program
Synapsy organizes rotations in order for these clinicians to work in the clinical domain on which the research is based, and to promote a good blend between clinical and research work.

Interested in joining one of these programs?
Synapsy collaborates closely with the Chairmen of the departments of psychiatry in Geneva and Lausanne. This is to ensure that the careers of these scientific clinicians can evolve in an environment conducive to their academic progression.

For Lausanne-CHUV
Candidates need to send their application letter and CV to Prof. Philippe Conus (philippe.conus@chuv.ch)

For Geneva-UNIGE
Candidates need to send their application letter and CV to Prof. Stephan Eliez (stephan.eliez@unige.ch)

Calls are open until Friday, 1st March 2019.

More details on our website: https://nccr-synapsy.ch/training/programs/
Genes encoding for proteins involved in synaptic protein synthesis seem to contribute to the development of Autism Spectrum Disorders. They are now suspected as early biomarkers.

Eleonora Rosina, a PhD student in Claudia Bagni’s laboratory, is looking for molecules that may represent a first sign of Autism Spectrum Disorders (ASD). The latter are recognized as heterogeneous neurodevelopmental disorders characterized by impaired social interaction and communication, as well as restricted and repetitive behaviours. “The molecular mechanisms responsible for autistic behaviour remain largely unknown,” says Eleonora. Despite this fact, several leads exist.

**Genetic origins**

Since many monogenic diseases associated with autism are caused by mutations that regulate protein synthesis, Claudia Bagni’s group undertook an analysis of the expression of key components of these two signaling pathways. For this purpose, they teamed up with Professor Paolo Curatolo, past President of the International Child Neurology Association and current Director of the Pediatric Neuroscience Unit at the “Tor Vergata” University Hospital in Rome, collected peripheral blood mononuclear cells (PBMC) from 33 children with idiopathic ASD and 22 healthy control subjects. “We have identified key components of both pathways that are differentially expressed between ASD patients and healthy control individuals. However, we should take into account the heterogeneity of the patients in order to identify common biomarkers according to the clinical phenotype”, says Eleonora Rosina. For that reason, the expression of the MAPK and mTOR pathways were then analyzed according to the clinical features of the patients.

**Strengthening cohort**

Their data suggest that components of protein synthesis signalling pathways could be considered as a molecular signature of clinical severity in Autism Spectrum Disorder. A publication validating the approach used to find molecular biomarkers in ASDs as evidence has recently been accepted in the journal *Translational Psychiatry*. “We are aware that the term “biomarker” has major implications and a large number of individuals have to be studied before any claim can be made”, states Eleonora. Therefore, Claudia Bagni’s team now hopes to recruit more patients across Synapsy’s cohorts and collaborations.

---

**Who is Eleonora Rosina?**

Interested in medicine, research and the physiological aspects of the human body, Eleonora Rosina completed a Bachelor’s degree in human biology at the University of Rome Tor Vergata. This training, a real bridge between medicine and biology, allowed her to integrate the two approaches. She then discovered neuroscience during an Erasmus internship in Paris where she worked on Down Syndrome and decided to pursue her studies in this field. She returned to Rome to study neurodevelopmental diseases in mice and humans and obtained a Master’s degree in medical biotechnology, which then opened the doors for her doctorate.

Since 2016 Eleonora has been a PhD student in Claudia Bagni’s group working between the University of Lausanne and University of Rome Tor Vergata, where she studies putative biomarkers of neurodevelopmental diseases. Working in Lausanne has been for her a great opportunity to discover Synapsy and the patient-oriented research. “In 2018 I attended the annual meeting in Villars as well as the meeting on occasion of the 8th site-visit of the NCCR Synapsy review panel in Geneva. I presented a poster which allowed me to meet and discuss our findings with basic scientists and clinicians. A closer interaction with clinicians and patients is fundamental to better understand the complexity and heterogeneity of the diseases we study. These interactions further galvanized my motivation and commitment to this research which aims at bridging the two aspects of ASD and Fragile X Syndrome: the molecular mechanisms and the clinical features,” she says.

---

**The WP#3 is setting the tone**

A new Synapsy era has emerged with the entry into Phase-3. Its success will depend, among other things, on Synapsy’s ability to transfer technologies. It didn’t take long to hear about a great example of technology transfer!

Last October, the Swiss Federal Council (SFC) took steps to improve the integration and care of people with ASD. A striking example in which Synapsy has played a key role through the important work of two of its principal researchers: Professors Marie Schaar and Stephan Eliez. The SFC intends to encourage people with ASD so that they can participate as fully as possible in social life. To this end, it has set three priority areas for intervention: early detection and diagnosis, counseling and coordination, and early intervention.

To achieve the objectives, the SFC takes into account the multiple possible manifestations of the disease and the situation that Switzerland is currently facing with a general lack of appropriate services. The SFC’s report indicates in which areas the Confederation, the cantons and the service providers are primarily responsible and which measures they should implement. It told all relevant actors to take stock of the current situation and to encourage the implementation of concrete measures on the basis of this report.

To this end, the SFC instructed the Federal Department of Home Affairs to contact the cantons and initiate the implementation of measures falling within the Confederation’s competence. The emphasis is on joint financing of intensive early intervention by the cantons and the Disability Insurance.
**WP#3 selected publications performed during Synapsy Phase-2**


Tora D, Gomez AM, Michaud JF, Yam PT, Charron F, Scheiffele P; **Cellular functions of the autism risk factor PTCHD1 in mice.**


Franchini M, Zöller D, Gentaz E, Glaser B, Wood de Wilde H, Kojovic N, Eliez S, Schaar M; **Early adaptive functioning trajectories in preschoolers with ASD.**


Bariselli S, Hörnberg H, Prévost-Solié C, Musardo S, Hatstatt-Burklé L, Scheiffele P, Bellone C; **Role of VTA dopamine neurons and Neuroligin-3 in sociability traits related to nonfamiliar conspecific interaction.**


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

---

**SAVE-THE-DATE**

**World Autism Awareness Day**

April-2

Events are organized all around the world during that special day. Do check our calendar approaching that date for HUG and CHUV events.