Alexandre Dayer in his lab, 2014
Photo: Christian Lüscher

EDITORIAL

Dear Colleagues,

It is with a profound grief that we are writing the editorial of this issue of the NCCR Synapsy Newsletter. As you certainly all know, Alexandre Dayer, the Director of the NCCR Synapsy tragically passed away on June 28. His demise is an immense loss for neuroscience, and certainly for our Synapsy community.

Alexandre was both an outstanding psychiatrist and a passionate scientist. He stood as an example for clinicians who are interested in pursuing a career as clinician-scientist. As a clinician, he was seeing patients, trying to alleviate their suffering and as scientist, he was developing basic science experiments to test new ideas. Thanks to his scientific rigor and his exquisite curiosity, Alexandre made major contributions to the understanding of the cellular mechanisms controlling the assembly of cortical circuits and the role of psychiatric-relevant risk genes in developmental processes.

Alexandre was a thoughtful and passionate mentor and a generous and inspirational colleague. His remarkable intelligence and integrity were an example for all who had the privilege to work with him. Over the last years he had devoted his time and energy to direct the NCCR Synapsy. Alexandre committed himself to the success of the project and of all team members. He was clearly a true leader who didn't hide behind his authority and the way he respected and connected with others inspired loyalty and trust.

We will think of him often and when we will conduct our research, mentor students and drive the NCCR towards new horizons, his way of accomplishing these tasks with intelligence, creativity, immense generosity and enthusiasm will continue to guide us.

For many of us, his death has left a void that is difficult to fill. Alexandre, we will miss you every day, and thank you for what you have given to our community.

Camilla Bellone, Carmen Sandi
and Philippe Conus

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NEWSLETTER

NATIONAL CENTRE OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY

synapsy
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National Centre of Competence in Research

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BUDDING CLINICIAN SCIENTISTS

Synapsy model imitated worldwide

The translational graduate program at the International Max-Planck Research School for Translational Psychiatry – which is similar to Synapsy's – is used to teach physicians and researchers. Two PhD students tell us about their approach and training.

Synapsy researchers and clinicians joined forces in 2010 to study the biological basis of mental illnesses with the aim of improving diagnosis and treatment. One of the goals of this innovative combination of neuroscience and psychiatry is to train a new generation of psychiatrists who are fluent in neuroscience. It is an approach to training that has proved successful, and has inspired Munich's highly-reputable Max-Planck Institute with its international school. The International Max-Planck Research School for Translational Psychiatry (IMPRS-TP), created in 2016, is a doctoral studies program that provides an interdisciplinary training in molecular, cellular and systemic psychiatric research. The program offers its 50 or so current students a wide range of courses, including molecular medicine, neuroscience, psychiatry, neuroimaging and stereology, not to mention clinical studies. In addition, the IMPRS-TP runs an integrated doctorate / residency program in psychiatry for physicians.

By focusing on the translational, doctoral students receive an overview of the clinical aspects of illness, and young physicians gain research expertise while developing their clinical skills. A delegation of students was present in Geneva at Synapsy's last Neurobiology of Mental Health conference, which gave us an opportunity to learn all about the training with two of the attendees, Yi-An Liao and Lucas Miranda (see bios on page 3).

Synapsy: The profile of students is also a source of wealth for a school. What is the situation regarding psychiatry in your home countries?

Yi-An Liao: Psychiatry in Taiwan is heavily geared towards biology, because we don't have a Freudian or Lacanian tradition. Technology already has a solid presence.

Lucas Miranda: In Argentina – without generalizing, and given that I'm not even a psychiatrist myself – I think the approach is quite traditional and still focuses on psychotherapy and patient care, especially at the University of Buenos Aires, which is the country's largest university.

Synapsy: Why did you choose translational psychiatry as your respective careers?

Yi-An Liao: I chose psychiatry because it's the least understood branch of medicine. It's the only field where there aren't any biomarkers yet for diagnosing patients: clinical examination is based exclusively on symptomatic criteria. It's fascinating! There's still so much to explore, unlike in other areas of medicine. And, since I've always been interested in how the brain works, psychiatry was the best option for satisfying my curiosity.

Lucas Miranda: Coming from genetics and computer science, I'm pretty new to neuroscience. I was attracted by the same things as Yi-An, namely that there is still so much to discover and huge amounts of data to analyze. What's more, the prevalence of psychiatric disorders is higher than people think. I like to feel useful to a lot of people by helping research and knowledge progress.

Synapsy: What is the IMPRS-TP approach?

Yi-An Liao: The program tries to narrow the gap between clinical work and basic science. The idea behind translational psychiatry is to be in a position to apply the outcomes of basic research to clinical work. The IMPRS-TP program has a strand for physicians like me: we're sent away for several years of basic research and then come back to practice at the hospital at the Max-Planck Institute for Psychiatry. The idea is that physicians should be exposed to science so they can develop their understanding of mental illness.

In parallel, scientists and psychologists are given courses on the clinical aspects of psychiatry. The students are invited to attend interviews between psychiatrists and patients in an amphitheater. It's a two-way program, from basic science to clinic practice and vice-versa.

Lucas Miranda: The fact that it's two-way isn't just about applying fundamental knowledge to clinical work, but also about using clinical data in basic research to further our understanding of mental illness and help diagnose or develop new treatments.

Synapsy: Yi-An, as a future psychiatrist, would you say that fundamental knowledge is really helpful for your work as a clinician?

It's entirely possible to practice without knowing the research, but it does help raise your awareness about the latest discoveries and the new tools that are available. Knowing the literature means we follow established protocols

to a lesser degree. As a result, we're more able to discover something new because we know something's in the air. In a nutshell, we are more flexible. What's more, we have a wide range of treatment techniques in psychiatry: psychotherapy, transcranial electrical stimulation and various drugs. These treatments must be given with full awareness of the implications, and being involved in research – particularly clinical research – means you can better recognize the differences between patient sub-groups and so treat them more appropriately.

Synapsy: Lucas, you're on the side of basic research: does the reconciliation with clinical practice help you in your research?

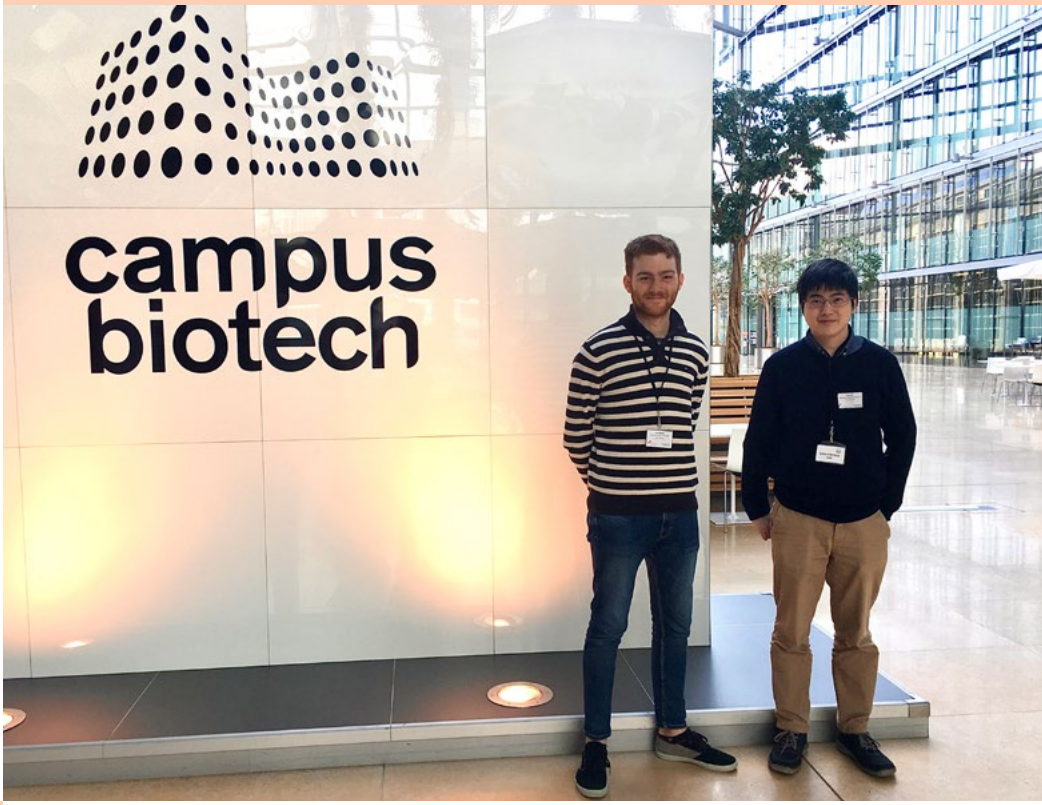
Yes, definitely, because my job is exactly about using and analyzing data that comes from patients. On the other hand, the clinical aspects covered by the IMPRS-TP training give us greater insight into our studies. It's really an opportunity to be able to "interact" with patients. Even indirectly, it's humanist and inspiring, and it feeds into our research. ●

Yi-An Liao

Yi-An, who hails from Taiwan, studied medicine and is currently doing a PhD at Ludwig Maximilian University of Munich and also works as a visiting PhD student at IoPPN (Institute of Psychiatry, Psychology & Neuroscience) King's College, London, which is linked to the IMPRS-TP. Yi-An's work is devoted exclusively to research, and he will return to clinical practice once he has finished his PhD. The subject of his dissertation is the relationship between environment, mental health and brain structure. He analyzes environmental, behavioral, clinical data and brain imaging data to study depression, anxiety and addiction.

Lucas Miranda

Lucas, who is from Argentina, has a training as a bioinformatician. He came to the Max-Planck Institute to attend the doctoral school in translational psychiatry. His thesis applies machine learning techniques to data from psychiatry. He is developing methods for clustering different types of longitudinal data, such as motion tracking from behavioral experiments, DNA methylation or fMRI images.



Lucas Miranda on the left, Yi-An Liao on the right.
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THOMAS BOURGERON

Using genetics and sharing to study autism

French researcher Thomas Bourgeron is a pioneer in genetic research on autism. The professor was also our guest at the last Neurobiology of Mental Health conference. In this article, he tells us all about his initial findings that link genes to the synapse as well as his appeal to share data.

The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association, defines autism using only two diagnostic criteria: deficits in social interaction and stereotyping. The DSM is the subject of much criticism, with Thomas Bourgeron sounding the alarm: "These diagnostic criteria leave too many other aspects in the dark! Autistic people are all different, which is why we talk about autism spectrum disorders (ASD) – with an 's' on the end!". Intellectual disability, epilepsy, sleep disturbance and anxiety are all so co-occurrent (among many other characteristics) that the French geneticist calls for them to be taken into account in the phenotyping of autism. The biggest problems for people with autism and their families are linked to comorbidities. "The definitions are used to advance research and diagnosis, but in terms of the individual it's much more complicated than that!", explains Bourgeron by way of introduction, reflecting his commitment and desire to articulate the great difficulties involved in ASD research.

The genetic line of inquiry

The first indications that a genetic factor is involved in ASD have a long

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history. As far back as 1977, studies on the heritability of autism showed that monozygotic twins had an over 80% chance of developing ASD if one of the twins was affected. Heterozygotic twins, on the other hand, had a 10% prevalence, "which is higher than the normal prevalence of 1%, a key argument for a genetic line of inquiry," explains the geneticist. In addition, there are population studies identif ying recurrences in families with ASD. Research published this year in *Jama Psychiatry* analyzing two million people across five countries demonstrated a heritability of 80%, i.e. a very strong genetic contribution.

Nevertheless, acquired types of autism do exist, as can be the case after taking certain types of medication during pregnancy. But autism is very much genetic for the vast majority of people. Professor Bourgeron states that the trajectories of individual lives influence the severity of symptoms: "For instance, a study has shown that some severe cases among children improved with the socio-economic status of the parents."

Synaptic genes

These studies do not provide any information about the genes involved or the biological pathways. In 2003, Bourgeron and his team identified a genetic mutation that induces a form of autism without any intellectual disability. They subsequently demonstrated that the genes involved coded for synaptic proteins and that harmful gene mutations were observed in the families of ASD individuals. "Neurobiologists very soon took an interest in our results, and the genes coding for proteins of the synaptic architecture such as Shank3, neuroligin and neurexin were identified as playing a role in autism with or without any intellectual disability", continues Professor Bourgeron. With the advent of genomic techniques, the researchers realized that a subset of people with autism had rare mutations in their synaptic genes. Another subset carried mutations in the genes involved in chromatin remodeling and regulating genes associated with synaptic plasticity. Over 149 genes are currently linked very strongly to autism.

When are common genetic variations present in the general population? There are three million variations on average between two individuals across the entire genome that includes over three billion letters (ATGC). These genetic variations form the genetic background, with some contributing to the emergence of a form of autism. It is the accumulation of these variations in one person that may make the difference and influence the severity of the disorder. "When it comes to autism, you have to take the person's entire genetic architecture into account since autism is not always monogenic."

Genetics and social behavior

Professor Bourgeron studies the monogenic and polygenic aspects. After identifying the role of genes in brain function, his lab generated mice with mutated genes so that the scientists could see their effect on the animals' social behavior. Bourgeron's lab developed a video analysis algorithm to do this, identifying social behaviors without human intervention. "It works well, and it's an ethologist approach that shows differences in social behaviors between the mutant mice and control mice".

Bourgeron then characterized the brain transcriptome (all the RNAs produced by the transcription of the genome) so he could define which regions are involved. All this has been done using total data sharing thanks to several online tools and platforms developed by the professor's laboratory. Transcriptome, genetic and behavioral data are systematically shared. "We share and advocate the sharing of data, including negative outcomes. That's what drives research forward, because no one wants to publish negative data even though it is important. We really want to create a sharing community to encourage everyone to do this".

The Synapsy surprise

It is a community approach, then, that is not unlike Synapsy's, which aims to bring together different environments. "It's an excellent approach, like Synapsy's. I thought that this kind of initiative was going to take off, but in reality, it hasn't much. Researchers tend to do their research on their own without organizing the sharing of data generated by their work." For Bourgeron, Synapsy is a "pleasant surprise", and he is especially pleased with the clinical-basic research combination. He quotes a sentence from Louis Pasteur: "There are no such things as applied sciences, only applications of science". ●

BUDDING CLINICIAN SCIENTISTS

What will the psychiatry of tomorrow look like?

A female student in medicine at the University of Geneva (who is keen to remain anonymous) dreams of a career in psychiatry. To achieve her goals, she is soaking up neuroscience and research, much like the new generation of psychiatrists hoped-for by Synapsy.

Preventing, diagnosing, treating and healing – from an early age, our student spent her time looking after her toys. It was something that ran in her family, where everybody is a physician. In spite of this family influence, her interest in the biology of the human body led our student in the direction of hard science rather than medicine so that, as she puts it, she could have access to "basic research". But she soon returned to follow in the footsteps of Hippocrates since medicine does not close the doors to research – quite the opposite, in fact!

Understanding psychiatry

Starting medical studies means discovering the brain for the first time. There was an initial course on neurotransmitters and receptors, followed by From Neurons to Patients by Professor Jozsef Kiss and his celebrated Neuroclub: "A very casual but intellectual evening discussing neuroscience – with drinks," as described by our student. The basics of psychiatry were examined in a little more detail in the third year with a unit on perception, emotions and behavior. Finally, there was a psychiatry internship that our young doctor did not enjoy very much, as she explains: "I had the impression that I suffered from all the psychiatric illnesses". It was thanks to another internship – in internal medicine – that she managed to overcome her fears by putting herself in the shoes of a caregiver for the first time. She was then able to seriously consider psychiatry and embark on a sixth-year internship in liaison psychiatry. It was more than a simple success: it was a real revelation!

Our student is forward-thinking, explaining her attraction to a discipline that is so particular and constantly evolving by stating that: "Psychiatry has such a wide outlook that it's really gripping. Just think of the staggering changes taking place in our society: the digital revolution, artificial intelligence and the conquest of space. The limits of our development are now more mental than physical. Knowing what the role of psychiatry and the psychiatrist of tomorrow will be is what attracts me, together with how mental disorders will evolve."

Research as an engine

Our student came to the latest Synapsy Neurobiology of Mental Health Conference (where we originally met her) for the second time with the aim of discovering the current state of research, especially its clinical aspects. "It's important for a future psychiatrist," she says. In addition, the context and the subjects addressed made her think about what she would like to tackle in her research since – before embarking on an MD or a PhD – she would like to identify her preferred topic. She adds that: "Basic research and clinical practice are a motor for practitioners and treatments," thereby confirming her membership of a future generation of psychiatrists guided by neuroscience. ●

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