



Do/Conus Team Members. From left to right, front: Sara Camporesi, Gloria Reuteles, Iles Khadimallah, Adeline Cottier, Kim Do Cuénod, Martine Cleusix, Margot Fournier, Lijing Xin; behind: Clémentine Vincent, Raoul Jenni, Guillaume Mariner, Pascal Steullet, Paul Kläuser, Philipp Baumann, Gilles Allenbach, Michel Cuénod, Philippe Conus, Jan-Harry Cabungcal.

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EDITORIAL

by Alexandre Dayer and the Management Team

Synapsy sets its course for 2022, borne along by rising synergies

Synapsy members have recently spent time writing up the annual report and preparing the research proposal for its third Phase. The Synapsy Newsletter is a chance to focus on the research done in a specific work package and get to better know their leaders.

This newsletter, our 8th issue, focuses on Work Package 2 (WP#2). WP#2 has been in the spotlight since the beginning of the year with its two leaders, Kim Do and Philippe Conus, recently receiving prestigious awards for their overall scientific achievement. In their portraits, you will learn about their careers in a different light –without losing sight of their translational research at the heart of the Synapsy project. Their ongoing project on the role of oxidative stress in high-risk individuals for schizophrenia exemplifies that the transition to the third phase of Synapsy will generate strong collaborations on the national and international scale, together with extensive synergies between WPs.

The newsletter also features an interview with the American psychiatrist

and researcher Carol Tamminga, a key figure working in the field of schizophrenia using translational approaches. In another article, Ghislaine Dehaene-Lambertz, a specialist in human brain development and distinguished guest at the recent Synapsy conference on the Neurobiology of Mental Health, describes her career path and the challenges that remain for clinicians aiming to bridge clinical care and research. Last but not least, Synapsy was present at the special conference marking the third anniversary of the passing of its former co-director, Dominique Muller, and we take this opportunity to pay Dominique a final tribute.

We would like to wish you a great beginning of the academic year and look forward to seeing you again at the Site-Visit, September 26-27. □

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NEWSLETTER

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

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Early Psychoses

Synapsy reviews the highlights and discusses the future of its work package on early psychosis for which the similarities between early-stage psychoses are calling to synergies.

Psychoses develop in stages. In the early phases, the various psychotic syndromes overlap as they gradually evolve towards well-defined clinical features and disabilities. The initial stages of schizophrenia, which are the central subject of the second Synapsy work package (WP#2), are characterized by the heterogeneous nature of patients with multiple clinical symptoms. Since distinct neurobiological mechanisms seem to underlie these successive stages, researchers think that specific treatments should be used for each of them. Some of these mechanisms have been identified during the first two Synapsy phases, and are now opening up new strategies for clinical intervention.

Discovering a phenotype

To understand how the neurobiological mechanisms involved in the early phase of schizophrenia were discovered by WP#2, we have to go back to the initial work carried out by Kim Do and her collaborators. Before the beginning of Synapsy they showed that glutathione deficiency was observable in schizophrenic patients (see interview with Kim Do). As glutathione is part of the antioxidant defense system, it has dramatic consequences on neuronal function and survival if it is deregulated. Why? Because the brain requires a highly efficient antioxidant system to counteract

the production of free radicals generated by its high oxidative metabolism leading to high oxygen consumption (25% of the body’s oxygen).

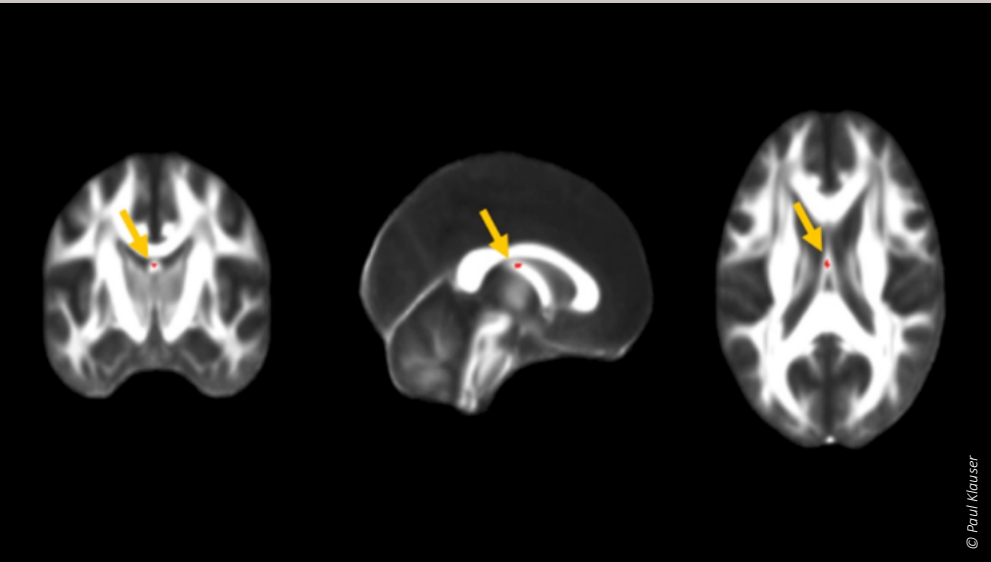
Once the teams led by Kim Do and Philippe Conus came together under the Synapsy umbrella, they focused on the neurobiological and clinical consequences of this glutathione deficiency and how to counter them. They first observed that polymorphism of the glutathione synthesis genes was more prevalent in schizophrenics and that it resulted in a functional effect. Using studies on transgenic mouse models, Kim Do’s team observed that the parvalbumin interneurons in the ventral part of the hippocampus –a region involved in emotions– are the most affected when oxidative stress rises. These neurons are critical for neural synchronization and cognitive function. More importantly, according to her: “Anxiety problems have appeared in our animal models without any disturbance to the spatial memory, a function that is performed in the nearby dorsal hippocampus.” This is an interesting observation since it suggests that glutathione deficiency underlies a specific phenotype in the early stages of schizophrenia.

The influence of trauma

Although it is fundamental, the genetic basis of pathological mechanisms

does not explain the environmental component. For example, traumas that occur during childhood are known to influence the development of psychoses in at-risk patients. According to the literature, stress generates increased levels of dopamine, and this is thought to play a part in the development of psychoses. To demonstrate the link between trauma and schizophrenia, Kim Do’s team succeeded in mimicking the increase in dopamine due to trauma-induced stress by using reuptake inhibitors in targeted brain regions at various stages during neurodevelopment. This approach, says Kim Do, allowed to identify a critical period during which the dopamine increase is an aggravating factor for schizophrenia. When observed in mice, this period corresponds to peri-puberty and childhood in humans. Kim Do was then able to demonstrate that an increase in dopamine in the anterior cingulate cortex heightened oxidative stress, leading to an impairment of parvalbumin interneurons, their neural synchronization, and producing an impact that persists until adulthood. “If the same manipulation is carried out after this sensitive period, there is no long-term impact,” says the researcher. In short, the Synapsy researchers have discovered one of the neurobiological mechanisms underlying the interaction between genetic and environmental risks, on the basis of schizophrenia.

Fig. 1
NAC improves fornix integrity in parallel to the increase of brain glutathione and cognition improvement. 6-month longitudinal gFA changes : NAC vs Placebo. Coronal, sagittal and axial views show voxel-wise analysis results indicating location (body of the fornix) of time interaction.



Back to the patient

This breakthrough goes hand-in-hand with the discovery of biomarker-based approaches. The mechanisms observed in mice were subsequently confirmed in patients. They now provide new perspectives for therapeutic targets. “It’s important not just for early diagnosis but also for developing novel treatments. Current pharmacological treatments—i.e. antipsychotics—do not improve the negative symptoms of schizophrenia nor the cognitive deficits. In addition, they have various negative side effects. Alternative solutions are therefore urgently needed,” says Kim Do.

The second great achievement of phase 2 was a clinical study focused on the add-on treatment with a glutathione precursor, N-acetyl-cysteine (NAC),

which Philippe Conus and the translational team tested in early psychosis patients. Although the results should be confirmed in a larger sample of patients, the clinicians, in collaboration with Rolf Gruetter’s group, observed that NAC crosses the blood-brain barrier and increases cerebral glutathione. A significant improvement in the cognitive state was observed, together with an improvement in the structural connectivity of the fornix (Fig. 1) and the functional connectivity of the cingulum. Moreover, NAC improved positive symptoms such as hallucinations and delusions in a subgroup of patients with high blood oxidative status.

These highly promising clinical trials pave the way for biomarker guided treatments for patient subgroups. “We would like to be able to boost the studies into the early phase of the disease,”

explains Philippe Conus. The Synapsy network and the synergies between its working groups will be very useful in phase 3. The WP2 researchers are now collaborating with Stephan Eliez and Marco Armando to strengthen the cohort and the recruitment of high-risk patients prior to the first psychotic episodes. The idea is to create an open longitudinal program for young people aged 12 to 25, the period during which psychiatric disorders develop. “Since psychiatric disorders have overlapping dimensions, we’re going to build more bridges between the different working groups and ensure that international collaborations begin,” says Philippe Conus. The success of the third Synapsy phase will therefore depend on pooling data and resources, and on the ability of researchers to form local and international synergies. □ YB

CAREER

Kim Do “Knowledge frees mental illness from stigma”

Kim Do has devoted most of her career to understanding the origins, effects and potential opportunities linked to an observation she made in patients suffering from schizophrenia. As a pioneer of the translational approach to psychiatry, Kim Do’s determination, commitment and expertise could end up delivering concrete treatments. At a time when her global approach has just earned her a prestigious award, Kim Do presents her work to Synapsy.

The young Kim Do always thought she would make a career in medicine. But her exam results –which were particularly brilliant in basic science– made her change her mind and turn instead to chemistry and molecular biology. It was after her PhD thesis in molecular biology in the field of enkephalins and a stay in Paris to study endorphins that Kim Do shifted to neuroscience and basic research in neurobiology. She then started her research at the Brain Research Institute of the Swiss Federal Institute of Technology in Zurich, where she studied excitatory amino acid neurotransmission. In 1994, Kim Do discovered that glial cells are able

to release transmitters. She identified *inter alia* that astrocytes are capable of releasing agonists of NMDA receptors, such as glutamate and homocysteate.

Between neurochemistry and psychiatry

After spotting the link between glia and neurons, Kim Do thought that

alterations of gliotransmission could underlie certain mental illnesses associated with neuronal hyperexcitability. It was while looking for traces of homocysteate and glutamate in the cerebrospinal fluid of schizophrenia patients that she found that there was a reduction in the levels of glutathione and its metabolite, namely gamma

glutamylcysteine. “A drop of almost 30% of glutathione was clearly visible in the cerebrospinal fluid of schizophrenia patients! Glutathione could only be involved in this pathology,” explains Kim Do. She then set about working on a method for detecting glutathione using magnetic resonance spectroscopy (MRS) to determine whether such decreases in glutathione could reflect the same abnormality in the brain. She was able to demonstrate that schizophrenia patients have similar decreased levels of glutathione in the prefrontal cortex. Kim Do thus envisions to bridge neurochemistry with psychiatry: “It was the starting point for setting up a translational research laboratory.”

Combining neuroscience and psychiatry was not an easy thing in the 1990s. Kim Do managed to find a sympathetic ear and an open mind at the CHUV psychiatric hospital in Cery, where she set up a laboratory for psychiatric neuroscience in 1999. Her idea was to start with observing patients and then move towards animal models. The task was not simple, recounts Kim Do: “I was given premises formerly used by patients: there was plenty of free space but otherwise nothing.” The immediate priority was to set up a small animal facility. “The mice were delivered to the cafeteria, and the chef asked us: ‘how would you like us to prepare these delicacies for you?’” says Kim Do with a smile on her face.

Once the laboratory was up and running, the aim of Kim Do’s research was to investigate the origins of glutathione deficiency and its effects on animal models in order to identify underlying mechanisms, allowing the back translation to patients. The collaboration with Philippe Conus was crucial for linking research to a clinical cohort. The subsequent integration into Synapsy as a work package (WP#2-Biomarkers of early psychosis) meant that funding was available for the cohort alongside extensive opportunities for brain imaging and systematic phenotyping. “The contribution made by Synapsy has been major and we are very grateful,” says Kim Do. Today, the connection between impairments of glutathione, antioxidant defense, oxidative stress, neural networks and psychoses has been established. Remarkable clinical trials are now underway, focusing on personalised treatments for patient subgroups with a disrupted redox system. Everything is taking shape with promising outcomes during Phase-3.

The recipe for success

How was this success achieved? Our translational approaches, says the Synapsy researcher, are highly rational and often bear fruit: they start from observations in patients and progress through mechanism based experimental research before being fed back to the patient. Kim Do further explains

that, although consortia of researchers and clinicians are imperative for translational methods, “the human aspects and an open mind” are even more important than stated intentions, and lead to productive collaborations. She adds that Synapsy has made it possible to train young clinician-scientists, who strive to bridge the gap between basic neuroscience and psychiatry, even though each is a specialty in itself. “It’s this bridge that makes the whole difference,” says Kim Do.

An award-winning career

Kim Do received the prestigious *2018 SIRS Outstanding Basic Science Award* from the Schizophrenia International Research Society (SIRS) in recognition of her contribution in advancing schizophrenia research. When asked about this –or about her career as a whole and her recent nomination as full professor– Kim Do says the same thing: her finest hour was during an *open-door* visit of the laboratories, when a patient’s mother took her in her arms, telling her that “this knowledge has relieved me from the feeling of guilt.” “Research and knowledge help to destigmatise mental illnesses,” she says, before adding: “This award should be given to our whole translational team; I am only the *chef d’orchestre*. I am so lucky to work with such motivated and talented students and researchers.” □ VB

Kim Do receiving the 2018 SIRS Outstanding Basic Science Award, and Professor René Kahn



Dominique Muller leaves behind an indelible imprint

Dominique Muller, the former Synapsy co-director who passed away three years ago, was commemorated in a one-day conference on April 19, when the lecture theater at the Louis Jeantet Foundation played host to family members, old colleagues and a number of scientists.

The microscopist Irina Nikonenko, a long-standing member of the laboratory of the late Dominique Muller, strongly supported the project of a commemorative day conference, which was organized by several professors from the Department of Basic Neuroscience at the University of Geneva, including Prof. Kiss, Prof. Holmaat and Prof. Lüscher. In choosing the title *From Synaptic Structure to Neuronal Dysfunction*, the organizers hoped to attract international speakers to discuss scientific themes that

were dear to Dominique Muller. “We wanted to remember him in an informal way,” explained Muller’s friend and former colleague Jozsef Kiss in his introduction to the conference.

The air crackled with emotion as participants arrived at the conference: for some members of Dominique’s laboratory, it was one of the first times they had met since tragedy struck three years ago. But it was also an opportunity to share memories of the golden period they enjoyed together under the aura of their late mentor.

Muller’s erstwhile colleagues queued up throughout the day to attest to the success of his career and his scientific discoveries. They also mentioned his obliging nature; his lifestyle, so idiosyncratic on occasion when it came to eating and driving; and, of course, the huge legacy Dominique bequeathed to the neuroscience community, both locally and on the international stage. These first-hand accounts and anecdotes were interspersed with exclusively scientific presentations, whose rich

content would doubtless have fascinated Synapsy’s former co-Director.

“The day was a great success,” said Jozsef Kiss, still overcome with emotion. “Dominique’s family was delighted and very grateful to all the researchers who made the journey in memory of their dad and husband.” There is no doubt that Muller changed the physiology and structure of the synapses of anyone who took the same road –and far into the future, too. □ VB

Remembering Professor Dominique Muller



REMEMBERING

CAREER

Philippe Conus “The unexpected plays a part in jazz as is does in psychiatry”

As he receives the Alphen Award for his global clinical approach, Philippe Conus tells Synapsy about the rich and novel path that led him to psychiatry.

Between music and psychiatry

Philippe Conus dreamt of a career as a jazz clarinetist when he was 18, attending a school of classical music in New York. But this year-long experience was not entirely satisfactory: there was no jazz training. Philippe decided to go into medicine instead, where his interest in psychiatry was very quickly satisfied when he performed night shifts and internships to earn a little money. “It was a very literary interest because psychiatry was ever-present in novels,” says Philippe. Even in those early days, the future psychiatrist particularly enjoyed the close patient contact that can be found in psychiatric hospitals. Nevertheless, as he admits, things were *complicated* – a reference to the challenge of getting in touch with people who are very much out of touch. “It’s the doctor’s personality that is key in forming a relationship; it’s not just a question of technique like it is in surgery.”

After leaving medical school, Conus went back to music and jazz “so that I could know for sure what I wanted to do and in order to acquire a level that would allow me to enjoy playing with others.” This time he left for Boston – the Berkley Jazz School – where he rubbed shoulders for 18 months with future monsters of jazz such as Diana Krall and the saxophonist Joshua Redman (who were both 17 years old at the time). When Philippe himself was all of 26, he was confirmed in his choice to keep music as a hobby when he saw numerous very young kids with extraordinary talent and musical maturity. He returned to Switzerland to continue his career in medicine. Today his love of music – he plays the piano, double bass and saxophone – helps him in his role as a psychiatrist. “First and foremost, it’s all about how you breathe. Jazz also helps me with my psychotherapy, where there’s always the fear that you’re going to make a wrong interpretation. When you make a mistake, you use it to find

a way out that works, as you do in improvisational jazz.”

When the interpersonal aspect leads to psychiatry

Philippe Conus has learned how to leave room for doubt when it comes to both psychiatry and music. He experimented with a range of specializations before making a definitive choice: “I started with a year of surgery, because I was afraid that psychiatry is too marginal. The medical part is still controversial and stigmatized, which has an impact not just on patients but also on psychiatrists and students.” Since the elitist environment of surgery did not fit in with Philippe’s values and expectations, he turned to internal medicine: emergency and cardiology. After obtaining an FMH, paths that opened up for him were intensive care, infectious disease or cardiology. “They were branches that left little room for the individual and I missed the relationship side of things.” As a result, Philippe returned to psychiatry.



Philippe playing in a Jazz band - 2017

This was at a time when the CHUV was beginning to form specializations for its psychiatric units, with one specialization for mood disorders, another for personality disorders and a third for schizophrenia, with the latter being particularly attractive to the psychiatrist from Vaud. The different clusters created fields of interest that generated research, to which Philippe devoted himself, starting with *tinkering*, as he himself admits.

But Philippe’s interest in research predates all this: his initial desire lay in an academic understanding and curiosity in this branch where the causes of schizophrenia were largely unknown. “In the beginning, I organized my clinical research around the question of how to structure patient care. We had to organize a care system that had been very blurred and lacking in rigor, since it was an area very much geared towards psychotherapy.” Conus first introduced procedures that were designed to compare the effectiveness of interventions.

Detailed mechanisms for keeping up with the international behemoths

Philippe Conus left for Australia so he could be exposed to new research horizons. There he discovered the exciting professionalism of clinical research and the breadth of the Australian cohorts through his collaboration with Prof. Pat McGorry in Melbourne. This experience meant that when he returned to Switzerland he was able to set up early-intervention clinical programs and start real collaborations

with Kim Do: this was a pivotal meeting for Conus and the development of his clinical research. “We were able to counterbalance our clear deficit in terms of the patient pool compared to Australia or America with our local capacity to study the mechanisms in detail.” Synapsy later brought about a major shift when it helped finance the WP#2 cohort, which now numbers nearly 700 patients.

In addition to its financial support, Synapsy’s clinical scientist positions have created a new generation of researchers and a community of interest, explains Philippe. “The agenda for translational neuroscience research has been extended, and we have been able to teach neuroscience from the third year of medicine and in the psychiatry training. This attracts candidates and is a real driver for research in the field of psychiatry.”

A clinical approach that has been rewarded

Conus was the recent recipient of the Alphen Prize, which recognized his work in various areas: his efforts to establish clinical research programs in his institution; his advocacy for including neuroscience training in the medical curriculum; and his own



research in schizophrenia. In spite of this prestigious award, the bottom line for Philippe is the impact that such prizes have internally on the cause of clinical neuroscience. “The deanship now acknowledges our psychiatry research, and that’s important because we have had to fight really hard over the years to gain institutional recognition.” Conus also admits that there is something flattering about winning such an award but steers clear of any complacency: “It’s not just about me, this prize rewards the type of research we do and helps move things forward, and, at the end of the day, that’s what is important.” □ ▮

INTERVIEW

Carol Tamminga
“Synapsy is setting the stage for what needs to be done in the future”

Carol Tamminga is conducting translational research on psychosis at the University of Texas with the goal of understanding the mechanisms underlying schizophrenia, especially psychosis and memory dysfunction. She explains her shared vision of translational research with Synapsy and her interest in psychiatry.

Where does your fascination with the human brain come from?

I was always interested in the brain and in the products of brain functions—cognition, affect and movement. When I was a teenager, I wondered how can one person act in one way and another person in another. I thought it must be because of brain differences and I was curious about how we could look at the brain to really understand behavior. When I went to medical school, I thought that if I wanted to understand the brain and if I wanted to really understand its function, I would have to choose between neurology and psychiatry. By looking at neurology, I realized that neurologists were very concerned about neurodegeneration and that they were taking care of people who were about to die. On the other hand, psychiatrists were taking care of very interesting disorders like psychosis, schizophrenia and

depression. It became fascinating to me how the brain would make hallucinations and delusions, symptoms that were so distorted. I choose psychiatry with the goal of finding out about brain pathophysiology that could explain something so behaviorally bizarre as psychosis.

When you started out in psychiatry, what was the understanding of psychiatric disorders?

The picture we had was the brain, a black box, and then the disease. We knew very little about what was in that black box. Over the last decades, our knowledge of neuroscience has just exploded. Of course, the brain is so complex that we still don't know nearly everything we need to. But we have started to learn a few things and basic neuroscientists are making very important discoveries about how the brain functions. You really need to understand this before you can go back and understand what the

diseases of the brain that alter behavior could be.

Today, what is known about psychosis?

I see psychosis as a learning and memory disorder and more specifically as a disorder of memory formation. Brains of psychotic patients are full of memories but they are made in a very odd and unusual ways. In fact, it's an exuberant memory system from which comes the trouble because patients mistakenly associate things. On the top of several altered brain areas and a hyper-connected brain, the hippocampus, which is important for memory formation, is very abnormal.

What brings you from clinical work to research?

I was interested in basic science from the beginning. It was a bit accidental that I got an MD degree but I was happy with it because it allowed me to discover the clinical determinants of disease and the clinical treatment environments for people with psychosis. There are so many important aspects of human disease that you have to take into account in doing clinically oriented research that I think every research group needs one or two clinicians so that they can be involved in steering the research in a clinically relevant way.

At the time I graduated, I started my research work with a fellowship to do basic science. Once you get the basics of fundamental science information, you have to continue new discovery by yourself to acquire new knowledge. One difficulty is that laboratories doing translational neuroscience have to use many different complex methodologies. I could never be equipped to do well without a lot of very talented collaborators.

Professor Carol Tamminga during the Synapsy conference



WOMEN IN SCIENCE
PORTRAIT

Ghislaine Dehaene-Lambertz
“An infant’s brain is not made of soft clay!”

Ghislaine Dehaene-Lambertz was destined to become a pediatrician in a regional medical office, but her curiosity—together with a series of chance meetings—led her to a career as a researcher. And not just any researcher : she is the figurehead of the human brain development research. Her work is part neuroscience and part psychiatry, and belongs to what she describes as cognitive psychology. Synapsy met Ghislaine at the last Neurobiology of Mental Health conference, where she was the principal guest.



Professor Ghislaine Dehaene-Lambertz during Synapsy's Conference

Investigating babies

Dehaene-Lambertz's instincts as a researcher began to flourish during her medical internship and her stints in neonatology and neuropediatrics. “We were resuscitating very early premature infants but what did we know about the impact of this hostile neonatal environment on their brains?” she asked herself. Science and medicine in the 1980s knew only a few things about the cerebral development of newborn children. Given this situation—not to mention her own investigations and growing interest in child psychiatry—it was only logical that Ghislaine would cross the threshold of a cognitive science laboratory. “It was a revelation! I discovered questions that I had never been introduced to. How babies manage, for instance, to recognize their mother tongue, or a face, or a name? And how do you ask them these questions?” she says.

The young French-born pediatrician was bowled over by this scientific approach because, as she recalls: “At the time, child psychiatry in France was dominated by the concepts of Françoise Dolto. In other words, if you suffered from a psychiatric disorder during childhood, it was always the mother who was to blame.” Moreover, our understanding of child development in France (as elsewhere) still centers heavily on psychoanalysis. It is an approach that is too narrow for Dehaene-Lambertz, (cont'd>)

What is your translational approach?

We observe the pathophysiology of individuals with psychosis in postmortem human tissue and search for the detailed molecular and genetic mechanisms first in the tissue, then translated to mice; we also use human neuronal precursor cells now in vitro. There are only a few researchers who are currently applying this cellular approach and the methodology is very early. We also do brain biomarker studies in live individuals with psychosis in large patient studies. For most of the patients from our large cohort study, we are collecting fibroblasts and transforming them into stem cells and neuronal precursor cells. We believe having cells from a specific individual would allow us to find out what medications are useful. Our goal is to do personalized medicine in psychiatry.

What do you think about the Synapsy approach which is to bring psychiatry and neuroscience together?

It's more than a nice, it's inspiring! Moreover, it is a necessity. This is the transition that cancer, heart disease and diabetes went through. Nowadays, it seems as though we have always known about the science of those diseases but, in fact, we have not always known it. I believe this transformation is what is going to happen with psychiatry. We are going to take people with psychosis and pull out specific diseases and their neurobiological basis. Psychiatrists will be able to understand pathophysiology only by applying basic neuroscience principles. I think Synapsy is truly setting the stage for what needs to be done in the future when psychiatrists, neuroscientists, psychologists and other brain scientists will sit side by side in order to pull together the entire story.□VB

Budding Clinical-Scientists

Vincienne Naef, Grace Kurian and Marc-Aurèle Adler are third and fourth year medical students at the University of Geneva. All three attended the Neurobiology of Mental Health conference, an ideal opportunity for Synapsy to meet up with the future generation of putative psychiatrists.

(cont'd)

although she does not reject it out of hand: “It’s important to think about the whys and wherefores of the psyche when you look at it in the context of family. On the other hand, when someone says that a child’s dyscalculia is down to the fact that their parents aren’t interested in them as a person, I don’t agree. You have to examine the child to understand how he thinks from the information that is available to him and not from the adult.” It follows that when Dehaene-Lambertz began life as a researcher almost thirty years ago, she was driven by a desire to lay the foundations for our understanding of the nascent human brain.

All for research

Doctors such as Ghislaine Dehaene-Lambertz who are involved in research are often faced with a dilemma: do they give up patients to help advance knowledge or do they abandon research in favor of diagnosis? Ghislaine felt this tension between research and clinical work and managed to circumvent it. “When there’s someone sitting opposite you, you don’t listen the same way if they’re a patient or if they’re a healthy individual who is volunteering for research. It is difficult to think at the same time about your role as a researcher and the person you interact with. I didn’t want to neglect patients because of what they could tell me about how the brain functions. So, I very soon decided not to try to wear two hats at the same time and to only do research on healthy subjects.” Nevertheless, Ghislaine has been aiming to return to studying pathologies for over 20 years but: “As long as I don’t know how a six-month-old child learns how to speak, it is difficult to put in place appropriate protocols to understand language disorders and help children who suffer from them.”

Partly innate, partly acquired

Ghislaine Dehaene-Lambertz’s research has shown that newborns possess many innate capacities. It is likely that the extensive neuron networks observed in adults are already in place after six months of pregnancy. In short, a baby’s brain is prewired and signs of cerebral asymmetry are clearly visible, as they are in adults. Ghislaine’s findings clearly call into question the idea that we learn everything from birth. In other words, our behavior is not attributable solely to acquire knowledge. Dehaene-Lambertz stresses that in the great debate between nature and nurture : “The glass is half-full and half-empty. Pre-wired systems are used to make some stimuli –such as faces or speech– more interesting than others so that a baby is actively learning straightaway. The environment will promote (or not) these learning experiences that are partly based on acquired knowledge. The brain of an infant is not made of soft clay that is simply waiting to be shaped!” Among other things, Ghislaine has been able to demonstrate very clearly that frontal activation exists in newborn babies, which is suggestive of voluntary attention and high-level prediction. “It was a genuine surprise! The only difference with adults is that frontal activation is three times slower in babies.” □ ▯

It is hard to tell what the clinical researchers of tomorrow will be like. When it comes to mental health, Synapsy hopes that they will come from psychiatry and will have a strong background in fundamental neuroscience. But what do those directly concerned think?

A breeding ground for psychiatrists

Synapsy got down to business by taking a look at the student’s respective interest in research, psychiatry and neuroscience. Neuroclub was partially responsible for pointing them in the right direction, as has been the case for many medical students of the University of Geneva (see our Newsletter No. 5, November 2016). When Vincienne started off in medicine, she had no interest in the three disciplines. But the wide array of events put on by Neuroclub – together with lectures and chance discoveries– began to draw her towards research and psychiatry. “As a means of making a financial contribution to my medical studies, I look after people suffering from autistic disorders. I also did a research internship on autism with Marie Schaer, and now I would like to find out more about it. Research is a complicated world that calls for so much investment that it’s a bit frightening at the moment,” says Vincienne.

Grace was prompted to embark on a career in medicine by the public health aspect, even though she has always had an interest in neuroscience. Neuroclub helped Grace discover a facet of medicine that was unfamiliar to her research. “Various speakers talked about the links between research and medicine, especially the role of clinician-researchers.” Grace’s curiosity in research, neurology and psychiatry was heightened during an internship in an immunology research laboratory as well as by

progressive learning courses (APPs) on neurological subjects. She also worked for three years in child guidance, where “a fascinating new world was opened up by being in close contact with child psychiatrists, speech therapists and psychologists.” Despite this, it is still hard for Grace to look too far into the future at the moment.

Marc-Aurèle discovered the brain for the first time in his compulsory biology classes. He wanted to *know how it works*, which motivated him to go into medicine with the aim of studying neurology or neurosurgery. Psychiatry is also an interest, although he is seemingly put off by the clinical aspects. “I think it’s fantastic to look at mental illnesses from a pathophysiological perspective but the problem is that the practical side of psychiatry is currently limited to giving medication and patient care due to our lack of understanding of the neurological basis. This current empirical practical approach makes me feel uncomfortable, even if I understand that recent advancement of knowledge is slowly changing this reality.”

Left behind but not dropped completely

Synapsy wondered what level of knowledge students had after studying medicine for three or four years. For instance, were they equipped to follow the themes addressed at the mental health conference? The three budding doctors said that they were delighted and proud to have attended the debates. Although none of the trio encountered any difficulties in catching the basic principles, they found that they did not have a broad enough perspective to think critically about the topics. With knowledge on autism, Vincienne had a particular understanding about –and appreciation of– related subjects. But for the other topics, she admits that

she had to concentrate enormously to “grasp all the subtleties of the experimental paradigms.” Grace noted that to understand the content of lectures, “you had to be used to dealing with technical details and results being presented in the form of curves and graphs.”

A more basic curriculum?

Should there be more courses geared towards basic research as part of the medical curriculum? The students were divided when asked this question. Grace considered that the curriculum

Vincienne, the courses where students have to read and present articles should be obligatory because “they sharpen the critical regard doctors have on certain treatments.”

Grace also believes that it is vital for doctors to appreciate what is happening in research and to have a solid base since: “They have to keep in touch with all the latest developments. The opposite would be reprehensible!” Knowing about molecular mechanisms is not crucial for doctors, suggests Marc-Aurèle: “Clinicians have to know whether their



Vincienne Naef, Grace Kurian and Marc-Aurèle Adler

is not the right place for teaching the practicalities of research and that medicine should remain focused on the clinical aspects. The solution, she said, is simple: “Students who are interested in research can do internships.” Marc-Aurèle pointed out that students are already taught a huge range of subjects which, depending on their specialization, they will never meet again. His view is that “research should be included in the teaching of basic medicine”, even if it is not continued afterwards. For

treatment is effective against a particular pathology or not. All the work trying to understand and validate the drugs must be done upstream. Clinicians can’t know everything because the different fields are so vast.” All three students acknowledge that they do not fully know whether an understanding of the most basic mechanisms is essential for treating patients properly. They do agree, however, that this knowledge helps their thinking and, by extension, their ability to carry out a diagnosis. □ ▯

SCIENTIFIC PUBLICATIONS

WP#2 Selected Articles Published During Synapsy Phase-2

Baumann PS, Griffo A, Fournier M, Golay P, Ferrari C, Alameda L, Cuénod M, Thiran JP, Hagmann P, Do KQ, Conus P;

Impaired fornix-hippocampus integrity is linked to peripheral glutathione peroxidase in early psychosis.

Translational Psychiatry 6(7):e589. (2016)

Steullet P, Cabungcal JH, Coyle J, Didriksen M, Gill K, Grace AA, Hensch TK, LaMantia AS, Lindermann L, Maynard TM, Meyer U, Morishita H, O'Donnell P, Puhl M, Cuénod M, Do KQ;

Oxidative stress-driven parvalbumin interneuron impairment as a common mechanism in models of schizophrenia.

Molecular Psychiatry 22(7):936-943. (2017)

Retsa C, Knebel JF, Geiser E, Ferrari C, Jenni R, Fournier M, Alameda L, Baumann PS, Clarke S, Conus P, Do KQ, Murray MM;

Treatment in early psychosis with N-Acetyl-Cysteine for 6 months improves low-level auditory processing : Pilot study.

Schizophrenia Research 191:80-86. (2017)

Geiser E, Retsa C, Knebel JF, Ferrari C, Jenni R, Fournier M, Alameda L, Baumann PS, Clarke S, Conus P, Do KQ, Murray MM;

The coupling of low-level auditory dysfunction and oxidative stress in early-phase psychosis.

Schizophrenia Research 190:52-59. (2017)

Shaqiri A, Roinishvili M, Kaliuzhna M, Favrod O, Chkonia E, Herzog MH, Blanke O, Salomon R;

Rethinking body ownership in schizophrenia : Experimental and meta-analytical approaches show no evidence for deficits.

Schizophrenia Bulletin. (ePub Jul-2017)

Conus P, Fournier M, Xin L, Baumann P, Ferrari C, Cousins A, Alameda L, Golay P, Jenni R, Kashavan MS, Eap CB, Cuenod M, Buclin T, Gruetter R, Seidman L, Do KQ;

N-Acetyl-Cysteine in a double-blind randomized placebo-controlled trial : Towards biomarker guided treatment in early psychosis.

Schizophrenia Bulletin 44(2):317-327. (2018)

Baumann PS, Klauser P, Griffo A, Golay P, Palix J, Alameda L, Moulin V, Hagmann P, Do KQ, Conus P;

Frontal cortical thickness correlates positively with impulsivity in early psychosis male patients.

Early Intervention in Psychiatry. (ePub May-2018)

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