



The Synapsy group
Villars, March 2019

EDITORIAL

by Alexandre Dayer

Synapsy and Genetics: an Adventure Ahead

From a historical perspective, early hypotheses about risk genes in psychiatry were based on candidate gene approaches and were largely incorrect. These studies were performed in small-sized cohorts and led to a replication crisis. However, in the past few years, genome-wide association studies of psychiatric phenotypes have been performed in large-scale collaborative cohorts and led to the successful identification of polygenetic risk scores (PRS). PRS are the result of the combination of hundreds of common variants and are considered to be robust. Whether PRS derived from large-scale cohorts can be used successfully in smaller cohorts such as the ones studied within Synapsy research groups remains an open question. More specifically it remains to be

determined whether PRS will have sufficient power to stratify Synapsy clinical cohorts in a biologically relevant manner and whether they could contribute to delineate high-risk states and predict disease conversion.

For Phase 3, Synapsy has decided to tackle these timely questions and this will be the topic of the current newsletter. By teaming up with Emmanouil Dermitzakis, Director of the Genome Center at Campus Biotech (University of Geneva) and Alexandre Reymond, Director of the Center for Integrative Genomics (University of Lausanne) Synapsy will have sufficient methodological support to begin to investigate genetic variants in clinical cohorts. More specifically, new postdoctoral researchers trained in genetics and

working under the supervision of Prof. Dermitzakis and Reymond will interact with Synapsy clinicians and begin to interrogate the use of PRS in clinical cohorts. The focus on genetics will initially be put on Axis-1 cohorts, which are more genetically-driven than those found in Axis-2.

Finally, Synapsy has continued to grow and has recently incorporated into its network new affiliated members. In this newsletter, you will discover six additional profiles of psychiatric researchers in the Lemanic area working in the fields of genetics, brain development, early-life stress and high-risk states. These newcomers will continue to enrich the network in the coming years and hopefully lead to new synergies. ●

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NEWSLETTER

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INTERVIEW – AFFILIATED MEMBER

Emmanouil Dermitzakis

“Producing Something Together is so Rewarding!”

Emmanouil Dermitzakis is from Heraklion in Greece. After studying biology at the University of Crete, Emmanouil completed a PhD in genetics at Penn State University. He then joined the University of Geneva as a post-doctoral fellow in the laboratory led by Stylianos Antonarakis. Emmanouil left the Swiss City in 2001 to set up his own laboratory at the Sanger Institute, a leading genomics center based near Cambridge, before returning to Geneva in 2009 as a full professor in the Department of Genetic Medicine and Development in the Faculty of Medicine. Emmanouil's laboratory works on genetic variants and their causality link with complex diseases such as diabetes or cancer. He has been an

affiliated member of Synapsy since 2018 and is keen to help the consortium with his expertise on genetic variants. We met him on the margins of his seminar during the last annual retreat in Villars.

Why did you choose to study genetics?

I have always been very interested in DNA structure. When I was in last year of high school, I focused all my attention on a book about genetic engineering. There were two pages in the middle that described how to clone genes into vectors and how to transform cells and flies. I realized that doing engineering with DNA was possible! Since I was hesitating between biology and architecture, I found this amazing. So, that's why I decided on biology, and I knew genetics was going to be my primary focus.

Do you have any interest in the brain?

Not particularly, to be honest. My “organ” of interest is DNA! My initial studies concentrated on thinking about DNA function and how that function is modified by genetic variants. I was trying to find the simplest possible model where you can study this, and the brain is not the simplest possible model, either in terms of complexity or the availability of samples. The first experiments in our lab were done with cell lines and, progressively, with tissues and organs. I've been working for a while on type 2 diabetes, cardiovascular disease and cancer. In the same way that a cardiologist studies the heart, geneticists study genomes. But the genome is everywhere, brain included.

Does working on psychiatric

disorders with Synapsy members inspire you?

Producing something together is so rewarding, I'm very excited. I like to work with a lot of people who have complementary ideas and complementary expertise. I'm just stating the obvious but it's not good when you're the smartest person in the room. You need to be in a group where you're constantly intellectually challenged. I am not talking about intelligence but about expertise and the information people can bring to the table. Initially, things are going to be very hard because we won't share the same language. I'm very excited because I'm going to learn more, and learning is always the scientist's intention, my intention.

Collaborations and synergies are important for research; what more should be done to stimulate them?

Funds are always a good motivation for doing things; they force people to work together because that's where they get the money. It's a kind of top-down approach for saying: “Show me that your collaboration is fruitful and here's the money” but it's actually a good thing. The Swiss community, while extremely strong in basic science and individuality, is not so strong when it comes to team science. Switzerland has not traditionally funded projects where a team has to work together on a single problem. Even the Synergia grant from the SNSF has not been as good because it's not large enough. The SNSF and other organizations should force more people to work together because that's the way you can make the money



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INTERVIEW – AFFILIATED MEMBER

Alexandre Reymond Puzzled About the Way Nature Works

produce more knowledge. You bring different minds together, they bring different perspectives and you get more out of it! Scientists are selfish, and their instincts push them to be the first to discover something. The adrenaline shot of seeing something in a cell that nobody in the world has ever seen is amazing! However, the speed at which you can get these results increases massively when you do team science. ●

Alexandre Reymond has a dual biochemical and biological background with undergraduate studies at the University of Lausanne (UNIL). Alexandre entered research via a PhD at the Swiss Institute of Experts on Cancer Research (ISREC) before continuing with a post-doctoral fellowship at Harvard Medical School. He built his first lab in Italy, at the Telethon Institute of Genetic Medicine, where he was studying human genetics. From there, Alexandre went back to Switzerland to the Department of Genetic Medicine at the University of Geneva before joining the Center for Integrative Genomics (CIG) at UNIL in 2004 as a tenure track professor. Alexandre is now a full professor and the current CIG director.

How did your fascination for genetics develop?

I am a passionate bird and mammal watcher, fascinated by the different facets of nature. I've always been quite puzzled about how nature works. In that sense, genetics was just a natural step. For my studies, I could have chosen zoology but I realized that genetics actually offered the best tool for zoologists. At that time, I was more intellectually challenged by genetics, keeping zoology as a hobby.

Do you have any interest in neurosciences and psychiatry?

Yes, I have always run projects related to the brain. More particularly, I am used to working on the genetics aspects of intellectual disability. In fact, mutations causing intellectual disability are quite frequent because a lot of genes are important for the proper functioning of the brain and of cognition.

Is the genetics variant approach well perceived by neuroscientists and psychiatrists?

I think so. Of course, we bring a new perspective. If it allows us to really begin to understand why one patient is different from another, it might be a step in the right direction. If we can do this, we will certainly be perceived well because we will facilitate the work of neuroscientists, psychologists, psychiatrists and neurologists.

Is this an ambitious approach?

Yes, it is a challenging approach but a fun one. I think that's also why we are doing this job. It's always changing because technology is advancing, allowing us to ask new and challenging questions. ●



INTERVIEW – AFFILIATED MEMBER

Antje Horsch

Deciphering the Inter-Generational Transmission of Stress and Trauma

Antje Horsch holds the position of assistant professor at the Institute of Higher Education and Research in Health Care at the University of Lausanne (UNIL) and in the Women and Children's Department at Lausanne University Hospital (CHUV). Professor Horsch, who is a clinical psychologist by training, graduated from Humboldt University in Berlin and the University of Toronto, Canada. She undertook her doctoral training at Oxford University, where she split her time between research and clinical work in one of the UK's major national trauma centers.

How did your fascination for the brain develop?

I decided to study psychology because I've always been interested in understanding how humans function and, in particular, how they respond to a traumatic event. This type of event can happen to anybody at any time. I've always been very interested in factors that might contribute to the development of post-traumatic illnesses as well as the protective factors that might help people adjust, cope and carry on.

What are your research interests?

My group is interested in the perinatal period. We are studying the impact of stress and trauma on family mental health. For example, what is the impact of pregnancy on parents, and what is the link with the mental health, development and well-being of the child? This is what we call the intergenerational transmission of stress and trauma. We're interested firstly in a better understanding of the underlying mechanisms of this transmission, including physiological and social mechanisms.

Secondly, my group is developing early intervention protocols in order to try and interrupt this intergenerational transmission of stress and trauma.

When treating the parents, we also work with the future generation. This means that it is crucial to have a systemic approach that looks at the whole family.

Could you tell us more about your approach?

Following a traumatic childbirth, such as an emergency caesarean or a preterm birth, between 3 and 6 percent of women develop a post-traumatic stress disorder when there are no obstetric complications. However, if there's a threat to the life of the mother and/or her baby, the prevalence rates can be up to one third. We're investigating what to do during the first few hours after a traumatic childbirth to prevent the development of these post-traumatic stress disorders. For instance, we asked mothers following

an emergency caesarean to engage in a visual spatial task within the first six hours after the birth. In comparison to a control group, these mothers had significantly less traumatic intrusions in the following week and were less likely to develop post-traumatic stress disorder in the month afterwards.

Is this kind of intervention only applicable to traumatic childbirth?

No, we think it could be a universal intervention. It could also be relevant to other populations who have experienced traumatic events. For example, hospital professionals who are exposed to traumatic events in their daily work. This is something we would also like to pursue in the future, to see if we could roll it out across a wide range of other types of traumatic events.



INTERVIEW – AFFILIATED MEMBER

Denis Jabaudon Synapsy is Developing a Common Culture

How could your affiliation with Synapsy help your research?

I'm very excited to be an affiliated member and I'm hoping that this might open opportunities for future collaborations with the Synapsy network. I'm also very interested to hear more about the very impressive amount of work that has been carried out.

I think that the way forward in clinical research is interdisciplinarity. I firmly believe that all of the projects I'm working on can only be carried out with the collaboration of different professionals from different backgrounds. If we want to address complex questions, such as mental health, we need to join forces. So, I'm very committed to the mission of the NCCR-Synapsy. That's where the future lies in achieving the translation from fundamental to clinical and applied sciences. There's no doubt about it! ●

Denis Jabaudon is a professor of neuroscience and current director of the Department of Basic Neuroscience at the University of Geneva. He is also an attending physician in the Department of Neurology at the University Hospital of Geneva (HUG). Professor Jabaudon trained as a medical doctor at the University of Lausanne before doing a PhD at the University of Zurich. He subsequently undertook his internal medicine and neurology residency before becoming a post-doctoral fellow at Harvard University. Denis came back to Switzerland in 2008 to launch his own lab, trying to combine his interest in neuronal circuits, synaptic physiology and brain development.



What are your research interests?

My lab is interested in the development of the cerebral cortex. More specifically, we're trying to understand and identify the genetic programs that generate neuronal diversity in the cerebral cortex. This is a cellularly highly heterogeneous structure. Neurons project from one part of the cortex to the other, to the spinal cord and other regions of the brain. Neuronal projections are very specifically wired and this is defined by gene expression. My lab is trying to understand how, from a seemingly relatively homogeneous pool of progenitor cells, this diversity

can emerge. The aim is to understand not just how genes control the generation of different neurons and circuit types but also the other way around. It's a two-directional interaction: genes influence the building of circuits but the wiring of circuits influences the expression of genes also.

What is the link with psychiatric disorders?

I think it relates to the interactions between genetic and environmental factors, I mean susceptibility genes and their interactions with the environment.

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Of course, there's more and more evidence that the cell death that occurs at relatively late ages in neurodegenerative diseases might reflect the susceptibility factors that are present very early on, maybe even during embryonic or early postnatal development.

What does your work as a clinician bring to your research approach?

A few years ago, as a pure clinician, I was always interested in basic research so that I could have a bigger picture. While interacting with patients, I really felt the need to go a little bit deeper into the mechanisms of what was going on. That's what drives my research interest today. I still have a 20% clinical commitment but it has no direct relationship with my research work. I believe that this is a strength in that it gives me two perspectives to ask questions from. Also, from the point of view of the clinics, I get a realistic idea about how drugs could be translationable as a therapeutic approach. From the basic research point of view, I get a realistic understanding of what we can actually do with human beings.

How did your fascination for the brain develop?

Compared to other fields of medicine, the exciting part is that you can study the same organ from a very detailed molecular perspective

to a more cellular point of view as well as in terms of a network and a cognitive point of view. I think that's what's exciting about the field we're in. What's more, you can interact with very different kinds of people from very different backgrounds. That brings a lot!

What do you expect from your affiliation with Synapsy?

I'm learning a lot from the patient-cohort type of approach that I'm not particularly familiar with. In the same way, it's important that clinicians learn how things are going on in basic research. I think it's important, for those of us who are not directly exposed to basic research, to understand the limitations of the cohort approaches, the diversity of patients and the type of information that can be gathered – even in single case studies as proof of principle or examples of what can happen in a disease.

Synapsy is quite rich and, again, it's developing a common culture. The development of this culture – in the “neuroworld” in particular and, I would say, in medical studies in general – is absolutely critical and undervalued. A good way to promote scientific progress is to promote human interactions – very simple human interactions, so that people feel comfortable with each other and confident about what the other person is saying. I think Synapsy does that in a remarkable way. ●

Nathalie Ginovart uses neuroimaging as a research tool to investigate mental disorders and as a way of bringing the clinical and fundamental worlds closer together.

Nathalie Ginovart started by studying biology before continuing with a master's in pharmacology followed by a M.Phil. in integrated biological systems – which is when her interest in the brain began to deepen. “I was exposed to studies on epilepsy, depression and schizophrenia. I soon wanted to do neuroscience so I could have a better understanding of the brain mechanisms involved. The brain seemed to me to be like a black box that wasn't very accessible.” A thorough training combined with a passion for the brain meant that Nathalie decided to undertake a doctorate in neuroscience at the University of Lyon in France.

Clinic-based biologist

Even as a young doctoral student, Nathalie was aware of the difficulties involved in translational research. “There were problems in dialoguing with each other: most basic researchers don't understand the challenges of clinical research and most clinicians don't have the time, training and resources to venture into basic research.” Ginovart adds that she has always been interested in neuropsychiatric research because it can be used to apply basic research concretely. And that's why Nathalie decided, as part of her post-doctoral internship, to do a clinical neuroscience training at the Karolinska Institute in Sweden where she was trained in clinical positron emission tomography (PET) imaging.

INTERVIEW – AFFILIATED MEMBER

Nathalie Ginovart

Translational Research Using Neuroimaging

She was later called back to the place where she had done her doctorate, Lyon CNRS, to “bridge the gap between clinical and fundamental work,” as she puts it. She then applied to the Center for Addiction and Mental Health at the University of Toronto, which was looking for her kind of profile, so she could act once more as the interface between the two worlds. She stayed in Toronto for five years as an assistant professor before joining the Department of Psychiatry in UNIGE’s Faculty of Medicine. Based at HUG’s Belle-Idée psychiatric hospital, she was surrounded by clinicians and worked on developing animal models to complement the clinical areas. “We have a multidisciplinary approach and conduct operant behavioral testing, PET imaging and chemogenetics in animal models. Clinical studies in humans are carried out in parallel, and PET imaging provides the translational bridge between the animals and human studies”.

Using a translational approach to help understand addiction

In particular, her research goal is to gain a better understanding of the factors that predispose individuals to addictive behaviors and to identify their neurochemical mechanisms and the neuronal circuits involved. Impulsivity, risky decision-taking and the search for novelty are prominent characteristics of addicted individuals. “For instance,” says Nathalie, “although deficits in dopaminergic receptors are correlated with high levels of impulsivity, we don’t know whether these factors pre-exist drug abuse or if they’re abnormalities that arise from repeated drug exposure.” As a result, Ginovart

is carrying out research on a rat strain (RHA / RLA) used as an addiction vulnerability model to determine these factors with the help of observations made in humans.

Ginovart and her team are also looking at clinically relevant issues, such as research into environmental factors that may reveal pathological behaviors later in adulthood. She is studying early environmental effects: “Addicts tend to have lived in a poor social environment, suffered abuse or experienced negligent parenting behavior when they were young. And that’s thought to increase vulnerability to addiction.” Thanks to tight collaborations with psychiatrists from the Department, clinical studies are also underway in patients with cannabis use disorder and in young people suffering from internet gaming disorder because, as Ginovart points out: “We aim to extract the predisposing factors and potential brain abnormalities common to these two types of addiction

and dissociate them from those linked to drug-taking.”

Gaining access to the network

Nathalie’s research group got co-affiliated to the Department of Basic Neuroscience and moved to the UNIGE’s University Medical Center in 2019, with the promise of having closer and easier access to the neuroscience network in Geneva. “I’m really delighted as this gives me and my students new opportunities for closely interacting with neuroscientists through events such as seminars, meetings and lunch events.” Furthermore, Nathalie is also delighted with her closer relationship with Synapsy since it will give her more visibility in the Lemanic neuroscience community and will help her to be informed of recent advances in the field as well as to develop new research collaborations. ●



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INTERVIEW – AFFILIATED MEMBER

Kerstin Von Plessen Treatments Based on Self-Regulation

Kerstin von Plessen studies early biomarkers and potential resilience pathways for treating neurodevelopmental illnesses - areas that require a translational approach.

As well as being a full professor in the Faculty of Biology and Medicine at the University of Lausanne (UNIL), Kerstin von Plessen is director of the Division of Child and Adolescent Psychiatry (SUPEA), Department of Psychiatry at CHUV. Professor von Plessen joined UNIL / CHUV in 2017 after medical school and an MD-PhD in Norway followed by an international career spent at Columbia University, the University of Bergen and Copenhagen University. Kerstin is a child psychiatrist especially interested in Attention-Deficit/Hyperactivity disorder (ADHD) and Tourette's syndrome (TS), as well as in detection, prevention and treatment programs for children with parents with mental disorders.

Studying self-regulation

The clinical researcher aims to study mental illnesses by investigating their neurobiological basis during development in a transdiagnostic approach. Her goal is to identify biomarkers, genetic factors and endophenotypes at an early stage in order to enable early diagnosis and treatment. Professor von Plessen is also studying the self-regulating factors that help to recover certain cognitive abilities. "Lots of children with a neurodevelopmental illness have reduced self-regulation capacities. Self-regulation is an important part of resilience, which is the ability to develop normally in spite of a trauma or adversity with a high risk of a negative outcome. There are few data on the subject even though we could develop specific cognitive training and other

more general facilitating approaches to correct the malfunctions," explains the professor.

To do this, Professor von Plessen intends to examine resilience factors during brain development. "These are factors the children could learn to master, such as cognitive control, the importance of self-efficacy or other factors, such as the importance of strong relationships and "sense" in life and we can help them develop these factors which we know determine their mental health in the future. It's important to strengthen these children with neurodevelopmental problems during development because they are disadvantaged both academically and socially." Professor von Plessen advocates cognitive mediation, neurofeedback and any approach that allows the child to regulate him or herself.

Treating without disrupting

Finding a way to care for children so they can take back control of their lives is what motivated Kerstin to practice medicine as a young child (she is the daughter of a psychiatrist and a logopedist). "It's definitely down to the encouragement I received from my parents that I noticed at a very young age that some of my classmates had behavioral problems, without anyone really knowing what they were about. Later, it was a great discovery when understanding that those are related to their human development and related to the brain, which is why I took an interest in psychiatry. Many small things that can happen during a lifetime and have an important impact on the brain development of a child— this appeals to me due to the potential that a child has and the importance of their experiences". The



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EQUAL OPPORTUNITIES

Empowerment Three Questions for Bitā Moghaddam

researcher thinks that priority should be given to non-drug treatments when caring for children, because, we do not know sufficiently about the effects of medication on the brain's development and because studies that compare both approaches, show a superior sustainability of behavioral approaches.

Mixing disciplines

Kerstin von Plessen's approach requires extensive translational work since much fundamental knowledge has been accumulated without being put in place in the clinical approaches to treat children. Translational research on its own justifies her affiliation with Synapsy. "We can't work in separate silos! We have to mix different branches so we can put all the data together and formulate a common equation," she concludes. ●

Bitā Moghaddam is a full professor at Oregon Health and Science University where she holds the Chair of the Department of Behavioral Neuroscience. In the past 26 years, she focused her research on the modeling aspects of psychiatric disorders. Last March, she participated in the Synapsy-LWiN career lunch with students of the Department of Basic Neurosciences of the University of Geneva and took time to answer our questions about gender bias in academia.



What are the most obvious gender inequalities in the world of research?

Inclusion at all levels: academic positions, awards, research resources, papers in high profile journals, and many more things.

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

I wish I had a good answer but we need to do many things. We need to find out why women are leaving research and find ways of supporting them. We need to identify younger women – and not just a token few – who have the potential to become successful researchers and mentor them better.

What would you say to the next generation of women researchers?

Please do not leave research! We need you! Find mentors – emphasis on plural – to support you. And find ways that are comfortable for you to fight and speak out about inequalities. ●

REPORT

Genetics and psychiatry Using Genetic Variants to Stratify the Enormous Heterogeneity of Patients

Genetic variants have an effect on our appearance, functioning and health. Synapsy is taking a detailed look at their association with psychiatric illness phenotypes.

Following the success of the first two Synapsy phases, the time has come to begin to apply genetic analyses to the wide range of clinical data that has been collected throughout the years. In recent years, polygenic risk scores (PRSs) calculated from genome-wide association studies (GWASs) have proved useful in predicting the risks of complex illnesses and analyzing genotype-phenotype relationships for a better stratification of illness subtypes. Synapsy recently acquired the resources to use this type of analysis to begin to genetically stratify its clinical cohorts and thus possibly improve the diagnosis and prevention of psychiatric illnesses.

Revamped genetic approach

Since being set up in 2010, Synapsy has aimed to identify the genes involved in vulnerability to mental disorders by assessing the biological factors that influence brain development. Why has Synapsy waited for the third phase of the program to implement genetic analysis in clinical cohorts? Alexandre Dayer, director of Synapsy and professor in the Department of Psychiatry and Basic Neurosciences at the University of Geneva (UNIGE), explains that, from a historical perspective, the early hypotheses about risk genes in psychiatry were largely incorrect. "One of the reasons is that these hypotheses were derived from an approach focusing on candidate genes, which were chosen on the basis of various assumptions related to the biological foundations of psychiatric phenotypes, rather than on unbiased association studies." This methodology gave rise to a substantial number of publications that concentrated on the potential significance of a given polymorphism in a complex psychiatric trait.

However, with the vast majority of these publications, it has

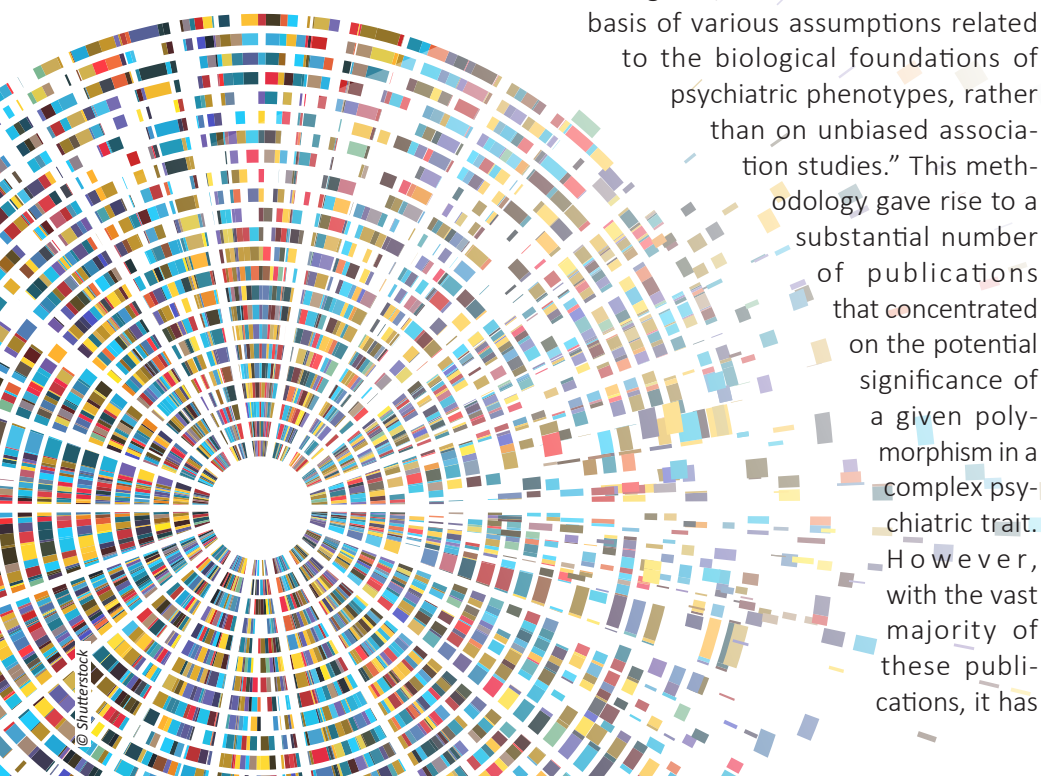
not been possible to verify the reported discoveries, suggesting that most of the candidate genes used in earlier studies could actually be false positives.

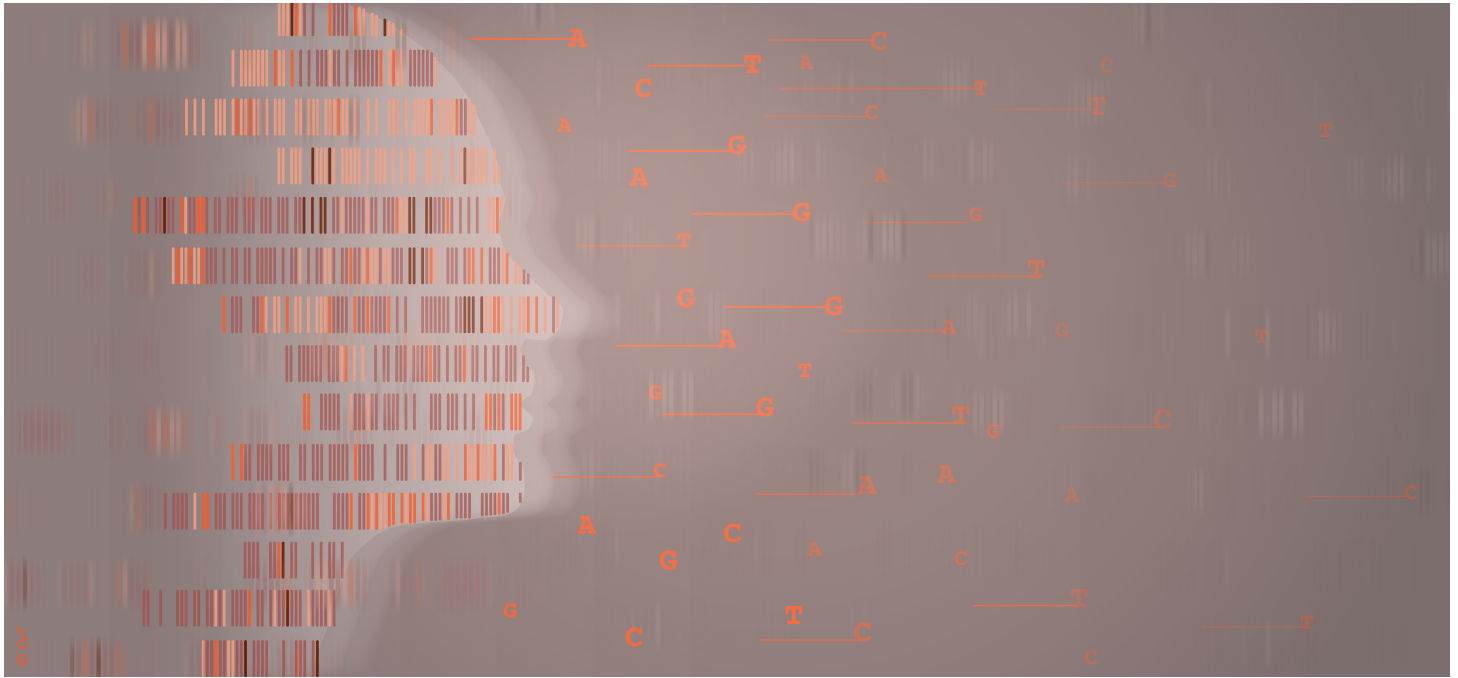
Emmanouil Dermitzakis, director of the Health 2030 Genome Center and UNIGE professor, adds that this conventional approach supposed that the genetic effect only occurred in the organ that was affected: the brain for psychiatric illnesses, for instance, or the pancreas for diabetes. "Although that was correct in part," he explains, "the initial cause does not always come from the diseased tissue. For example, the brain is a causative tissue for diabetes because it controls appetite, meaning that the pancreas isn't responsible for everything when it comes to diabetes."

The overall vision and approaches have changed in response to this genuine genetic crisis, and have now given enough guarantees to be applied to psychiatry. "The current view is that the genetic architecture of psychiatric phenotypes is complex and includes a wide variety of common polymorphisms. Taken individually, each genetic variant has only a very small effect and only accounts for a very small fraction of the variance of a given trait. It's the combination of a wide variety of risk genes that can constitute a more general genetic risk factor with possible clinical implications," says Synapsy's director.

Stratifying by gene risk

People with psychiatric disorders are currently grouped into categories such as autistic spectrum disorder (ASD), schizophrenia, bipolar disorder, major depression, etc. These categories,





however, are composed of highly heterogeneous patients suggestive of several subcategories or possibly different types of illnesses. Patients in each category clearly share common behavioral traits but probably have further phenotypes that are not yet sufficiently understood to differentiate them in biologically relevant categories. If researchers could better understand the etiology of these illnesses — which may be genetic, environmental or a combination of both — it would be possible to better stratify patients and identify biological pathways differentially affecting distinct subgroups of patients. “We’d then be in a position to understand what differentiates one subgroup of patients from another. Using genetics as a starting point, we’ll obtain the first unbiased indication about what isn’t working properly because a given gene is affected”, adds Alexandre Reymond,

director of the Center for Integrative Genomics at the University of Lausanne.

The idea is then to analyze the genetic variants that are common to patients. In fact, each human cell contains the entire genome, which is made up of 6.54 billion nucleic bases. There are on average 20,000 single nucleotide variants between individuals, 500 of which are rare and half linked to a loss of function. “It’s estimated that 50% of the risk of developing an illness stems from the variability of the genome”, says professor Dermitzakis. These genetic variants can be used, therefore, to understand the illnesses.

Common or rare

There are two main ways to proceed depending on the extent of the effect of the variants on the body. Genetic variants with limited effects can be identified through large studies called

GWASs, which correlate a position on the genome with the phenotype variants. Researchers can extract probabilities and risk factors — PRSs — for the development of an illness by employing genotyping on large cohorts consisting of tens of thousands of individuals. “Once this work has been carried out, it’s theoretically possible to return to the patient and identify his or her variant alleles to diagnose a disease or identify a predisposition. It’s also a way of stratifying patients,” points out professor Reymond.

The second approach is based on rare variants that have a significant effect on cognition. “They can only be rare from an evolutionary point of view, because the carriers will tend to have fewer children than normal,” continues

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professor Reymond. “In a situation like that, you can’t only examine unique positions on the genome through genotyping to derive a PRS but all the positions in detail, including in non-coding regions.”

A special situation for Synapsy

Both approaches will be used by Synapsy with a common goal in mind: to identify the genetic origins of the clinical phenotypes observed in patients and to derive risk factors for each individual. “That means there will be a personalized vision of risk, as opposed to the average for the population,” explains professor Dermitzakis.

The question of whether PRSs are clinically useful is still very open according to professor Dayer. Synapsy’s clinical cohorts will contribute to answer this question, he says. “Synapsy clinical cohorts are particularly attractive since the genomes can obviously be extracted from the blood of patients to be sequenced

and analyzed, and the clinical variables including high-quality multi-modal imaging data are available” says professor Dermitzakis. In the first instance, it will be necessary to determine whether imaging can be integrated into PRSs to define the risks and predict the onset of disease. Finally, “the modest size of the Synapsy cohorts, a hundred or so patients compared to several thousand for the GWAS, could be an obstacle,” tempers professor Dayer.

The Synapsy researchers, with the help of a post-doctoral fellow supervised by the two affiliated geneticists, will compute PRS profiles and stratify the genetic risk in the 22q11 deletion syndrome cohorts (WP 1), early psychoses (WP 2) and ASD (WP 3). Genetic data from the WP 1 and WP 2 clinical cohorts are already available through international consortia. Finally, additional private funding has been obtained by Marie Schaer, a UNIGE professor and Synapsy member, to carry out whole genome sequencing on the ASD cohort. ●

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Home Institutions



Partners



26-27-28 FEBRUARY 2020

3rd Conference on the Neurobiology of Mental Health

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