N°3 FALL/WINTER 2013

NEWSLETTER

NATIONAL CENTER OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY

synapsy
bringing together brain research and psychiatry
National Center of Competence in Research

CONTENT

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UNIVERSITÉ DE GENÈVE
Unil UNIL | Université de Lausanne

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HUG Hôpitaux Universitaires de Genève
FMI Friedrich Miescher Institute for Biomedical Research
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TRANSLATIONAL APPROACH TO THE IDENTIFICATION OF NEUROBIOLOGICAL MARKERS IN THE EARLY PHASE OF PSYCHOSIS

Professors Kim Q. Do and Philippe Conus

BACKGROUND

Early detection of psychotic disorders has recently become a major focus for research and service development, leading to a considerable conceptual shift in psychiatry and to the development of a preventive approach to main psychiatric disorders.

Based on the evidence that treatment delay has a negative impact on outcome, specialized programs to reduce duration of untreated psychosis and set up specifically adapted treatment have developed around the World; the TIPP (Treatment and early Intervention in Psychosis Program)[1] was launched in Lausanne in 2004. Since then, over 400 early psychosis patients (EP) have been treated at this specialized clinical and research center. Since March 2013, TIPP widened its focus to take care of ultra high risk (UHR) patients who present with prodromal manifestations of psychosis.

In the frame of such programs, the approach to mental disorders is changing in a major and promising way as the concept of clinical staging is gaining momentum, with the aim to develop stage specific treatments where earlier phases of illnesses are treated with more benign and more efficient approaches. However, improvement has so far been hampered by a major lack of evidence based knowledge of the mechanisms involved in the development and progression of psychotic disorders. Stages are currently defined almost exclusively on the basis of imprecise clinical dimensions with established but unfortunately limited validity. Therefore there is an important need for basic neurobiological research in this domain, in order to uncover neurobiological mechanisms which may lead to the identification of reliable biomarkers of such disorders.

THE PROGRAM

In this context, a translational research program, implemented in 2009 at the Department of Psychiatry-CHUV between TIPP (P Conus) and the CNP (Centre de Neurosciences Psychiatriques; K Do), has gained considerable momentum thanks to the first phase of NCCR Synapsy. The research program is based on three axes: (1) Cross sectional multimodal (clinical assessment, brain imaging, EEG, neurobiological) assessments of patients in the various stages of the disorder (prodrome, first episode, early relapse and chronic phase); (2) Longitudinal multimodal assessment of patients through the successive stages of the illness starting from the prodrome and (3) Bi-directional translation between human and animal models with experiments leading to similar endpoint assessments being conducted in both.

EDITORIAL

PIERRE J. MAGISTRETTI / NCCR SYNAPSY DIRECTOR

The present issue of the Synapsy Newsletter features one of the founding translational programs of the NCCR Synapsy which is concerned with the identification of neurobiological markers in the early phase of psychosis. The project leaders are Professor Kim Do and Professor Philippe Conus both in the Department of Psychiatry at CHUV-UNIL. This project is the result of a long-term collaboration started over a decade ago between a basic neuroscientist (KD) and a psychiatrist (PC) in a translational effort supported by the Directions of CHUV and of the Department of Psychiatry. In a way this collaboration has provided a model that has produced some of the guiding principles of the NCCR Synapsy. The developments that have been made over the last three years thanks to the support of the NCCR are quite remarkable and have opened new strategies for clinical interventions.

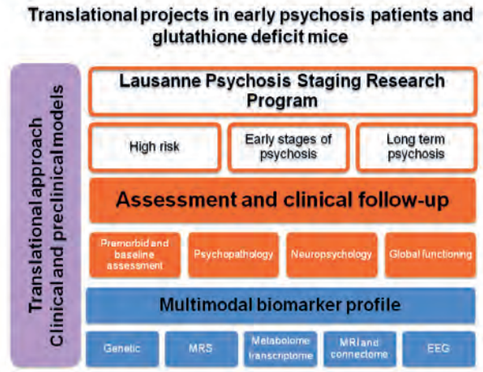
"I wish that I will never have to chose between research and clinical work". This is what Camille Piguet, MD, PhD has to say about her career. Camille is one of the first recipients of the NCCR Synapsy Clinician-Scientist program, one of the original programs supported by our NCCR. Camille's project combines advanced imaging techniques developed at UNIGE with Prof. Vuilleumier with clinical follow up of patients in the Mood disorders program in the Department of Psychiatry at HUG (Prof. Aubry). She combines with great skills her clinician scientist career and her personal life as she just gave birth to her second child. She is definitely a role model for her younger colleagues and the NCCR Synapsy is delighted to support such a remarkable career.

Finally I would like to mention that we have recently received the report of the Review panel, which reviewed the NCCR Synapsy in mid-September. The main good news is that in principle the Panel recommends extension of the support to the second four-year phase (2014-2018). The review is quite positive and at certain points even enthusiastic, particularly as far as the effort of bringing together psychiatrists and neuroscientists around meaningful common research projects is concerned. Quoting from the report "The panel agrees that the NCCR's approach is establishing a remarkable precedent in the field. The panel experts are not aware of similar State sponsored initiatives in Europe, in the United States or elsewhere that integrates so well clinical psychiatry and basic neuroscience. … The NCCR is therefore truly world leading, having created a model that other centres throughout the world can (and should) follow."

In the years to come we will have to keep up to this very positive assessment and continue to work hard towards the goals of the NCCR. The Panel made also comments on specific projects for which a better integration with the rest of the NCCR is suggested. We will work in the coming months to address these issues.

On behalf of the Steering Committee, I would like to take this opportunity to thank all of the members of the NCCR Synapsy for their efforts towards the success of the NCCR. We still have considerable work ahead of us to prepare the second phase: we will have to prepare a final proposal by June 2014. But all these efforts are worthwhile given the impact that the NCCR will have, and is already having, on Swiss neuroscience and psychiatry.

– PJM



WHERE WE WANT TO GO

The main aims of the project are: (a) To identify and validate stage specific biomarker profiles in order to allow early detection and monitoring of the efficacy of new drugs, both in animal models and humans; (b) To identify potential new treatments and preventive targets based on new critical pathophysiological molecular signaling pathways. In order to do so, biological correlates have been assessed with non-invasive technologies such as EEG (M Murray, CIBM) and brain imaging (MRS, MRI, DTI; R Gruetter, CIBM; P Hagmann, Radiologie-CHUV; J-P Thiran, LTS5-EPFL) as well as blood and fibroblasts transcriptomics and metabolomics (OMICS), both in humans and animal models where ever possible. The tight partnership between preclinical and clinical components which are both based on a precise hypothesis will ensure effective translation from bench to bedside and vice versa.

ONGOING PROJECTS

A CORE NEUROBIOLOGICAL MECHANISM IMPACTING LOCAL MICROCIRCUITS AND LONG RANGE CONNECTIONS.

Based on converging evidence pointing at redox imbalance and oxidative stress in blood, fibroblasts, CSF and brain of patients suffering of schizophrenia[2] (including association with the disease of common variants and CNV in genes involved in GSH metabolism[3]), we proposed that redox dysregulation represents one hub on which converge various causal genetic and environmental risk factors during neurodevelopment, leading to structural and functional connectivity impairments[2].

The genetic vulnerability factors involve either redox regulation genes directly affecting glutathione (GSH) metabolism, or genes which indirectly lead to oxidative stress, including DISC1, PROD, G72, NRG, DTNBP1. Environmental factors known to favor major psychiatric disorders generate ROS as well, which, if the redox regulation is impaired, could perturb the developing nervous system in a time and region specific manner. As a consequence, two key systems, essential for cognitive and affective functioning, will be particularly affected: local microcircuits and long range connections. The critical role of oxidative stress has been validated in a GSH deficient animal model (GCLM-KO mouse model) reproducing numerous schizophrenia phenotypes including NMDA receptor hypofunction, impaired parvalbumin fast-spiking GABA interneurons (PVI)[4, 5], neural synchronization[5, 6], and related behavioral anomalies.

Highlights of some translational aspects of the project

A metabolomic profiling performed in fibroblasts (baseline and oxidative stress) of 30 EP and 20 control subjects revealed an abnormal reactivity to oxidative stress. Indeed, besides abnormalities in the regulation of redox/anti-oxidant system and in the phospholipids metabolism, we found alterations in the regulation of arginine and extracellular matrix related metabolism which should be further investigated as potential early markers in SZ (Fournier et al, SfN 2013). These findings are in concordance with experimental data from GSH deficit mice (GCLM-KO) in which the perineuronal net, a specialized extracellular matrix surrounding the parvalbumin interneurons, is impaired until late adolescent[4, 5]

REDOX REGULATION IN MYELINATION AND WHITE MATTER INTEGRITY IN EP AND MODELS

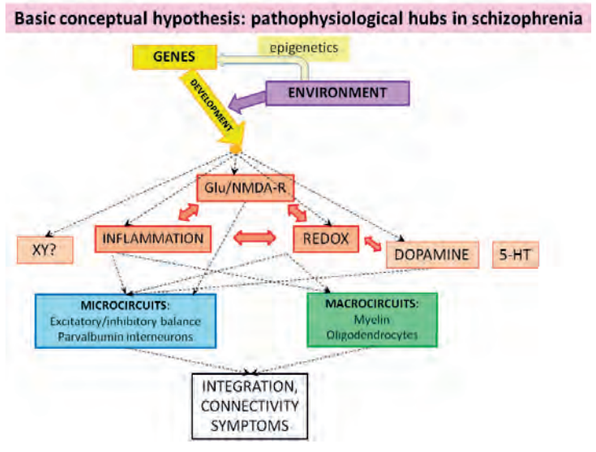
We explored with multimodal imaging the interplay between GSH levels measured through MRS in PFC (L Xin, R Gruetter), and structural and functional connectivity measures at both local and global brain network levels (DSI) (P Baumann, A Griffa, J-Ph Thiran, P Hagmann). A positive correlation between GSH levels and gFA along the cingulum was found in controls but absent in EP patients. These findings indicate a potential dependence between GSH levels, white matter integrity in the young adult and which is disrupted in EP.

To substantiate the relationship between GSH and myelin, we investigated myelin-associated proteins in GCLM-KO mice (A Monin, J-H Cabungcal, M Fournier). Immunoreactivity of myelin markers was decreased in PFC at peripubertal age. GSH deficit reduced oligodendrocyte progenitor cell proliferation, a process mediated by an increase of Fyn kinase activity. Consistently, fibroblasts of GCLC-high-risk genotypes presented an abnormal regulation of Fyn expression in response to oxidative stress. All together, these data indicate a critical role of glutathione and redox regulation in myelination processes and white matter maturation in prefrontal cortex of rodent and human, a mechanism disrupted in schizophrenia. They also highlight dysregulation of Fyn kinase as potential marker in early psychosis (Monin et al, SfN 2013).

A REVERSE TRANSLATION STUDY: DTI IN GCLM-KO MICE AND EARLY PSYCHOSIS PATIENTS

DTI imaging was successfully developed at 14.1 T. and FA was analyzed in 27 brain regions (A Corcoba, J Duarte, Y Van de Looij, R Gruetter). Volumetric analyses were assessed in parallel. We found lower FA values in juvenile GCLM-KO compared to WT mice throughout white matter. These differences were significant in the anterior commissure and in the fimbria-fornix of the hippocampus. Juvenile KO mice also showed an enlargement of the ventricles. Our results highlight the relationship between impaired redox regulation and myelination deficits during development and point to potential white matter integrity impairment in the anterior commissure and fornix-fimbria in schizophrenia. These data have led to the assessment of white matter integrity in fornix with DTI in chronic and EP patients (P Baumann). Consistently, preliminary results in EP patients showed an impairment of fornix white matter integrity which correlated with hippocampal volume loss. These results highlight the potentiality of a reverse translation aspect of the project. Moreover, the presence in the GCLM KO mouse of white matter deficiencies together with ventricular enlargements, two of the most replicated anatomical phenotypes in schizophrenia further supports its validity as a model for the disease.

– Kim Q. Do/ Ph. Conus



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PORTRAIT

CAMILLE PIGUET / NCCR SYNAPSY CLINICIAN SCIENTIST

"I HOPE I NEVER HAVE TO CHOOSE BETWEEN RESEARCH AND CLINICS"

Camille Piguet is supported by a grant for clinician researchers from Synapsy. She works part-time (50%) in the laboratory of Neurology and Imaging of Cognition headed by Prof. Vuillemier at the University of Geneva (UNIGE) and dedicates the other 50% of her time to working in the Mood Disorder program directed by Prof. Aubry in the Department of Psychiatric Specialities at the University Hospital, Geneva.

In the middle of October, Camille Piguet gave birth to two babies: a little sister for her 3 year old and a rather big research project to investigate susceptibility to bipolar disorder, to be carried out with the NCCR Synapsy. While the first baby rounded her tummy, the second was launched with a serious push …… and then she left on maternity leave. Camille Piguet doesn't want to give up anything; and so, she lives three lives: that of a clinician, a researcher and a mother.

' I always wanted to study medicine. But then, I also wanted to know how things work.' In the sixth year of medical school, Camille started an internship in the Neurology and Imaging of Cognition laboratory, run by Prof. Patrik Vuilleumier at the University of Geneva. It was here that she discovered the reality of imaging research: '8 hours a day in front of a computer'. Even so, she became enthusiastic about this exciting field of research, close to human beings and how they function. From this moment, the relationship between psychiatry and cognitive neuroimaging gels, and the doctor becomes a researcher, carrying out her MD-PhD on correlating neuronal function in thought disorders in mood disorders in the same laboratory, thanks to a grant from the Swiss National Science Fundation.

Four and a half years later, Camille is both a Ph.D and a mother. She obtains a clinician-researcher laboratory grant from Synapsy that enables her to continue in her research theme and embark on two professional careers: half-time in the laboratory and half time in the Mood Disorder program in the Department of Psychiatric Specialities, directed by Prof. Jean-Michel Aubry. 'Being able to work in this clinical department allows me to carry on in the same vein as my thesis work, while bringing new, exciting perspectives to my research, states the clinician-researcher.

Right before going on maternity leave Camille feels unruffled. 'A deep-rooted collaboration has been set up between the clinical department and the researchers and I feel happy that the project will carry on while I'm away'. Things could get more complicated later. Although very organised, Camille Piguet, doesn't want to play superwoman. 'With my three lives, it's often difficult to find a good balance'.

Conducting two careers in parallel means specialising in psychiatry on the one hand (6 years full-time), and an academic career on the other, which inevitably involves work experience in a laboratory abroad. This may not be easy with two small children and a husband who is already established as a doctor. 'For the moment I haven't had to choose between doing one career or the other and I really hope I never have to make that choice as I am so passionate about them both' maintains Camille Piguet. 'I think it will be rather a question of how much time I can spend on each'.

Anyway, what drives Camille is to contribute one way or another to the understanding of psychiatric disorders. 'I'm really happy that I could take advantage of the opportunities that arose and feel so lucky to have such a stimulating and interesting career, and I must say I never hesitated for a moment to have my wonderful children'.

Anne-Muriel Brouet,
NCCR SYNAPSY media officer

SAVE THE DATES!

LEMANIC WORKSHOP ON SCHIZOTYPY
December 6-7, 2013 – Geneva

BRAIN AWARNESS WEEK
March 10-16, 2014 – Switzerland

NCCR SYNAPSY ANNUAL MEETING
April 4-5, 2014 – Villars

3RD NCCR SYNAPSY SYMPOSIUM ON "MOOD DISORDERS"
May 16, 2014 – Lausanne

4TH NCCR SYNAPSY SITE VISIT
August 21-22, 2014 – EPFL

4TH NCCR SYNAPSY SYMPOSIUM ON "AUTISM"
Fall 2014 – Geneva

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