

N°1 / MARCH 2011

NEWSLETTER

NATIONAL CENTER OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY



bringing together
brain research and psychiatry

EDITORIAL



Dear readers,
It is a great pleasure for me to present you this first Newsletter of the NCCR "SYNAPSY – the synaptic bases of mental diseases"

which started on October 1st 2010.

The aim of this NCCR is to understand the synaptic bases of mental diseases, from molecules to circuits and functions. About 100 scientists and clinicians from Geneva, Basel and Lausanne are members of this NCCR. The project is organized around 6 workpackages, 4 Clinical projects and 3 platforms (see schematic on last page).

The ambition of this NCCR is to understand the molecular bases of mental diseases in order to improve their early diagnosis and develop novel preventive and therapeutic approaches.

A distinctive feature of the NCCR SYNAPSY is a program specifically dedicated to support

the training of clinicians/scientists to promote the emergence of a new generation of psychiatrists with strong competences in basic neuroscience who will be able to translate progress in research into new applications and therapies.

The NCCR also aims at destigmatizing mental illnesses by way of a strong commitment for communication to the public and society.

In this first edition we present Marie Schaar a clinician/scientist who exemplifies the type of career we intend to promote. You will also find the outline of a clinical project (22q11 Deletion Syndrome) as well as a basic research project in which the role of synaptic proteins, which could be implicated in the 22q11 syndrome, will be studied.

I hope you will find this newsletter of interest and we look forward to keeping you regularly informed about the developments of the NCCR SYNAPSY.

Prof. Pierre Magistretti, MD, PhD
Director

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CLINICAL PROJECT : 22q11.2 deletion syndrome

A translational model to study the endophenotype of psychosis

From mice to humans.
From genes to brain development and functions.

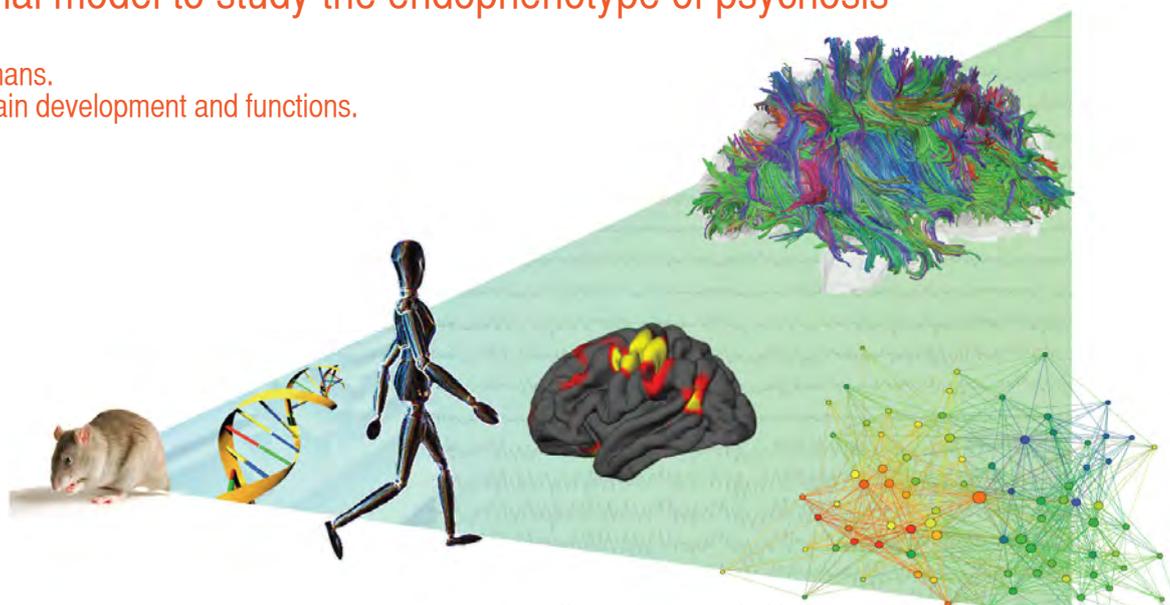


Illustration provided by Marie Schaer, scholar of excellence, NCCR SYNAPSY

Since the early 90's, the study of the 22q11.2 deletion syndrome (22q11DS), an autosomal dominant disorder that affects 1 in 4000 people in the general population, has appeared as a unique opportunity to understand the emergence of psychosis. Indeed, a child with this diagnosis runs a risk 25 times higher than average of developing schizophrenia in late adolescence or adulthood. Due to the strong impact of biological determinants in this neurogenetic disease, psychosis generally unfolds during adolescence, and its evolution is more severe, with a stronger resistance to medical treatment. 22q11DS is the cause of 1 to 2% of schizophrenic disorders in adulthood and of 7% of schizophrenic disorders beginning before the age of eighteen.

Scientists have rapidly caught on to the value of longitudinal study designs combining genetic, neuro-developmental, cognitive and environmental factors to investigate the unfolding of psychosis in 22q11DS. It appears that clinical factors such as anxiety disorders, depressive disorders or psychotic symptoms during childhood and early adolescence are good predictors of the emergence of psychosis at later stages of adolescence and early adulthood. Risk assessment is substantially improved by integrating measure of cognitive functioning, as well as structural and functional indices of brain develop-

ment. Other neurobiological markers, such as particular genetic polymorphism, expression of certain proteins, synaptic morphology, cortical neuronal density, or even microstates derived from EEG exam, could each constitute neurobiological markers of a predisposition to or of an increased risk for psychosis : a psychosis endophenotype. Amongst the cognitive endophenotype markers, both bottom-up and top-down mechanisms are thought to contribute to the emergence of early symptoms of psychosis. For example, children or adolescents with dysfunctions in the monitoring of self-generated mental content more likely report experiencing aberrant perceptions such as transient auditory verbal hallucinations. Similarly, alterations in the basic cognitive building blocks of social cognition, such as facial and emotion perception, set the stage for faulty attributions of others' emotions and intentions. Such perceptions of interpersonal and social threats are known to promote social withdrawal and contribute to generating delusional thought content.

Through the continuous support of the Swiss National Science Foundation since 2001, Pr Stephan Eliez has constituted and followed a unique cohort of children with 22q11DS, which today includes more than a hundred participants examined at three year intervals, employing protocols that combine ge-

netic, structural and functional neuroimaging measurements, as well as detailed cognitive evaluations and structured clinical assessments at every time point. The momentum gained during the last decade makes this cohort the largest and most extensively examined longitudinal 22q11DS cohort worldwide.

At this point in time, the fantastic collaborative opportunity offered by the NCCR SYNAPSY will provide research on 22q11DS unprecedented access to Swiss expertise in domains that have yet to be chartered in the scientific examination of psychosis development in 22q11DS. The additional skills, resources and scientific collaboration make for this project a unique platform of translational research at the cutting edge of research on schizophrenia.

Within this project, NCCR Genetic platform will enable to sequence the entire 22q11.2 region on the non-deleted allele, and link gene polymorphisms involved in this region with the endophenotype expression associated with 22q11DS (S. Antonarakis). Neurostructural and neurofunctional investigation methods are available by means of the Imaging platform. The EEG methodology (C. Michel, Unige) will allow the analysis of micro-resting states, whilst integrating imaging and functional resting state data. The aim is to understand how emerging cognitive alterations and psychotic symptoms result from the alteration of structural and functional networks (Olaf Blanke, EPFL, Unige) as well as reduction of synchronicity in functional network subtypes. The Imaging platform will also make available structural cerebral imaging protocols aimed to study probabilistic prediction methods of psychosis, on the base of neurostructural and neurofunctional markers (B. Draganski and R. Frackowiak, Unil). The schizophrenia cohort included in the NCCR framework will enable necessary comparisons between these different patient populations.

Most significantly, this translational research project reunites leading scientists from a range of different fields of investigation around a common starting point: a congenital microdeletion on the long-arm of chromosome 22. This starting point further extends translational opportunity to a mouse model equivalent to this human disorder, as the deleted area of the

human chromosome 22 almost perfectly overlaps with an homologous region on chromosome 16 in mice. In the NCCR framework, several research groups (P. Bezzi – Unil, A. Carleton – Unige, P. Caroni – Uni Basel, D. Muller – Unige) will study, at a cellular and synaptic level, the structural brain development in mice. The aim of these studies will be to link structural and functional alterations to candidate genes in the deleted area, and to understand their contribution to pertinent endophenotype psychotic markers. Because the animal model allows for the examination of cerebral maturation stages during childhood and adolescence, it also represents a way to study the dynamics of brain development and facilitates the investigation of cellular factors that could be at the origin of the cortical dysmaturation observed in humans with 22q11DS.

The 22q11DS cohort project in the NCCR framework represents the creation of a vibrant and tightly connected web of scientific collaborators building bridges between clinical psychiatry, cognitive neuroscience, genetics, neurophysiology and fundamental neuroscience. The contribution of murine models will bring a new window of understanding focusing on cellular and synaptic dysfunctions, and will provide critical evidence on the contributions of functional and structural cerebral alterations in the emergence of psychosis in 22q11DS. This multi-level enterprise constitutes an essential step, necessary for the development of neuroscientific evidence-based interventions and treatments susceptible to target the very mechanisms underlying risk of psychosis in these youths. Furthermore, the comprehension of a homogenous genetic model will carry important implications to the more general understanding of complex relationships between genes, cerebral structures and functions, as well as clinical and psychiatric endophenotypic symptomatology of a disorder, schizophrenia, which affects 1 to 2% of the world's population.

Prof. Stephan Eliez, Unige

Martin Debbané, MER, Unige

Prof. Dominique Muller, Unige

INTERVIEW

NCCR SYNAPSY excellence fellowship awarded to Marie Schaer

The interview of the second recipient, Philipp Baumann, will be featured in the next edition appearing in fall 2011.



Marie Schaer, you are an MD, how did you become interested in psychiatry?

I have always been interested in understanding how the brain works. How do these 1300 grams of cells acquire the ability to produce complex cognitive functions?

How come that the fine-tuned cascade of brain development sometimes goes awry, with the emergence of abnormal mental functioning? With the help of neuroscience, we increasingly get the tools to approach these fundamental questions. I am willing to bet that the field of psychiatry will dramatically evolve over the next decades, with the ability to increasingly understand mental disorders, and hopefully to prevent part of them. I feel that we are very lucky to be able to contribute to this revolution.

What is your motivation in research?

I want to learn; research provides me the time to read, think, and develop ideas. I love solving small questions, like puzzle pieces that will fill in the gaps between neuroscience and psychiatry. In particular, I like the technical aspects of image analysis: neuroimaging is half way between medicine and engineering and I really enjoy playing with the MRI and the algorithms. To answer specific clinically-relevant issues, one must sometimes be able to question the methods. For that purpose, I learnt enough programming to be independent in almost all the research questions that I may have.

What is in your eyes the benefit of the NCCR Excellence Fellowship?

Most of all, the NCCR Fellowship allows me to dedicate a consequent time for research. Being otherwise constrained with the clinical work, this grant permits to secure time for the production of scientific work. As such, it represents an inestimable support to help me building my career.

Another advantage of this Fellowship is to benefit from the stimulating setting provided by the NCCR Core, with the opportunity of many fruitful discussions. More specifically, having

worked on 22q11 deletion syndrome since a few years, I find the close collaboration with new groups very profitable and the translational approach from mouse models to humans particularly exciting.

Do you have an advice for young clinicians interested in research?

I would like to stress the need to start relatively early. For instance, interested medical students should take advantage of their elective (e.g. during the last year) to experiment the everyday work in a research laboratory. And if they like research, just head down for a PhD! Research is highly competitive, and it's probably much easier to start with research and come back later to clinical work than the other way around... And even without the goal of an academic carrier, a PhD is always a constructive experience to get a better sense of where medical knowledge comes from, and to build a structured thought.

My second advice would be to carefully select your advisor. Take a place where you can learn, where you can express yourself while being supported, where you can publish and progressively become independent. German-speaking colleagues use to name their advisor "Doktorvater", which nicely reflects how much an advisor will influence your research career.

The full version of the interview is available on our webpage :

www.nccr-synapsy.ch/fellowship_marie_schaer

where you will find the answers to the following questions:

- Could you kindly tell us about your training and career so far?
- What are the characteristics of the disorder you are studying and how can imaging techniques help to better understand the disease?
- You developed a specific method in that field, could you describe it?
- What is your long term goal?

RESEARCH PROJECT

Synaptopathies in developmental psychiatric disorders

Synaptopathy is an increasingly popular term used to define key features of neurodegenerative and psychiatric diseases. It implies that disruption of synaptic structure, function or plasticity is potentially the major determinant of these brain diseases. The argument is based on the recent progress carried out in the last two decades in the identification of genetic and molecular alterations that implicate genes coding for synaptic proteins or proteins involved in the regulation of synaptic properties. Analyses of the underlying mechanisms using gain and loss of function approaches have further revealed that these defects often lead to alterations of spine morphology, density or plasticity.

One of the most studied example of synaptopathy is probably the fragile X syndrome (FXS) linked to a genetic defect of the fragile X mental retardation protein (FMRP). The FXS is the most common inherited form of mental retardation, affecting approximately 1:4000 males and 1:8000 females (Pfeiffer and Huber, 2009). Subjects with FXS display learning difficulties and delayed language acquisition, but also impairments of fine motor skills, and behavioural deficits reminiscent of autism such as repetitive behaviour, decreased attention, and poor eye contact. Seizures are another common feature of FXS, affecting approximately 20% of patients. The genetic defect responsible for SFX is an expansion of a CGG repeat in the 5' untranslated portion of the *fmr1* gene. In subjects with over 200 repeats, the gene is silenced resulting in loss of FMRP, a protein that is highly expressed in the brain (neurones and glia) and localized at synapses. FMRP is an RNA binding protein that functions primarily as a regulator of translation. It is associated to RNA granules that travel along microtubules to dendrites and spines where the protein is believed to regulate mechanisms of protein synthesis.

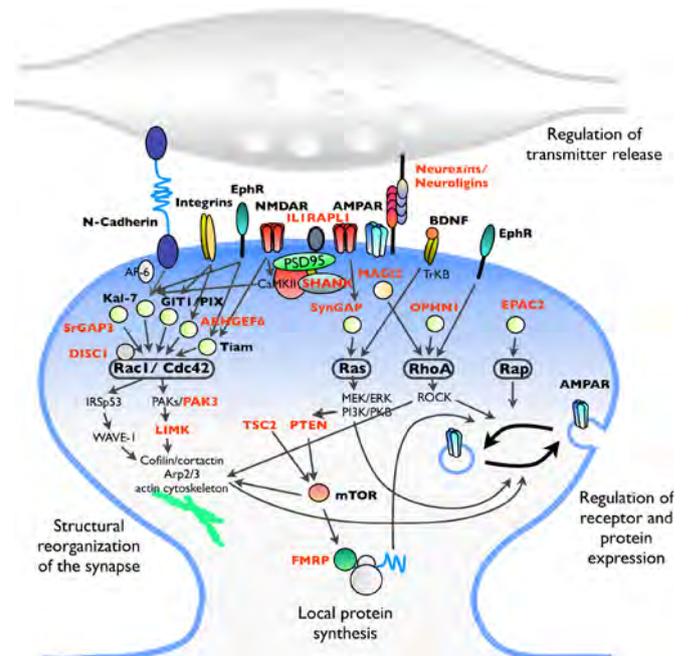


Figure 1

Figure 1. Schematic diagram representing some of the synaptic proteins implicated in intellectual disabilities, autism spectrum disorders and schizophrenia (proteins in red). Note the predominant role played by Rho GTPases (Rac1, Cdc42, Ras, Rap, RhoA) in regulating major synaptic mechanisms (*modified from Boda et al., 2010*).

Studies carried out in *fmr1* knockout mouse have identified numerous synaptic defects including abnormal morphologies of dendritic spine, altered synaptic plasticity and impaired learning and memory (Pfeiffer and Huber, 2009). A current hypothesis is that the loss of FMRP could result in an excess of mGluR receptor signalling, leading to increased long-term depression of synaptic transmission (LTD) and reversal of spine maturation (Bear et al., 2004). If correct, this hypothesis suggests that the synaptic defects could be reversed by mGluR antagonists, a possibility supported by some recent findings (Dolen et al., 2007) opening new hopes in the treatment of the disease.

Many other forms of intellectual disabilities have been identified as associated to mutations of synaptic proteins. More than 90 genetic defects linked to the X-chromosome have thus far been implicated in intellectual disability and autism spectrum disorders and many others further concern autosomal genes

(Ropers, 2008). Among these, proteins associated to signaling by GTPases play an important role. GTPases form a large family of proteins characterized by their ability to bind and hydrolyze GTP. They generally act as molecular switches affecting various biological activities regulating growth and migration of many cell types. At synapses, they participate to the regulation of three major postsynaptic functions: the organization and dynamic of the actin cytoskeleton, the control of the local translation machinery and the trafficking of synaptic proteins and specifically of receptors (Boda et al., 2010). Several members of the Rac/Cdc42/PAK signalling pathway, which regulates cofilin phosphorylation and actin dynamics, are critically implicated in spine morphogenesis, synaptic plasticity and the development of synaptic networks. Other GTPases of the Ras/Rap family, including their regulatory proteins SynGAP or Epac2, regulate the expression and trafficking of AMPA receptor subunits, affecting in this way spine maturation. Oligophrenin and the RhoA/ROCK signalling pathway also play an important role in regulating AMPA receptor endocytosis at excitatory synapses leading in this way to abnormal spine morphologies. Pathways implicating GTPases constitute therefore key signalling mechanisms at synapses.

Another group of proteins particularly implicated in autism spectrum disorders is the neuroligin/neurexin complex. Neuroligins and neurexins are synaptic cell-adhesion molecules that connect presynaptic and postsynaptic neurons at synapses, regulating in this way synaptic properties. Initial studies showed that expression of neuroligins or neurexins in non-neuronal cells could induce the formation of presynaptic or postsynaptic specializations, more recent data point to a role of the neuroligin/neurexin complex in the control of synaptic functions. Mice lacking neuroligin 1 showed impairments in NMDA-receptor signalling whereas mice defective for neuroligin 2 had deficits in inhibitory transmission. A plausible hypothesis is therefore that trans-synaptic cell adhesion mediated by neurexins and neuroligins triggers pre- and/or postsynaptic signal transduction events that affect synaptic properties. Without this signaling, synapses assemble but do not work properly (Sudhof, 2008).

The role of synaptopathies is not limited to intellectual disabilities or autism spectrum disorders, but it has also been considered in relation to schizophrenia and degenerative disorders. In the context of schizophrenia, an interesting protein is DISC1 (disrupted-in-schizophrenia 1), one of the most recent susceptibility factor for schizophrenia, genetically disrupted in cases of familial psychosis in a large Scottish family. DISC1 codes for a protein enriched in postsynaptic densities, which regulates the activation of the Rho GTPase Rac1 and thus affects spine morphogenesis and plasticity. This raises therefore the possibility that a synaptopathy could participate to the pathogenesis of schizophrenia (Hayashi-Takagi et al., 2010). Another condition in which patients are at high risk of developing schizophrenia is the 22q11.2 deletion syndrome. In this syndrome, several affected genes could regulate synaptic functions. An interesting candidate is a palmitoylation enzyme regulating the synaptic expression of a number of synaptic proteins including PSD-95, a prominent scaffold protein of excitatory synapses, and Cdc42, a Rho GTPase implicated in the control of the actin cytoskeleton.

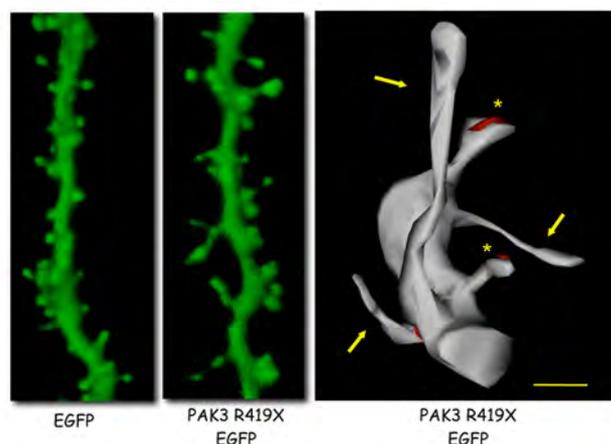


Figure 2

Figure 2. Illustration of spine morphology abnormalities observed in hippocampal neurones transfected either with the green fluorescent protein EGFP (left) or with EGFP and a mutated variant of PAK3 gene implicated in intellectual disability (center). The right panel shows a 3D electron microscopic reconstruction of elongated, thin spines that characterize various forms of intellectual disabilities (*Images provided by A. Dubos and I. Nikonenko*).

All together, these studies point to the possibility that disruption of activity-mediated regulation of processes such as spine formation, receptor trafficking, synapse maturation

and stabilization could result during critical periods in specific alterations of properties of synaptic networks. Among plausible consequences are synaptic dysfunctions, but also hyper- or hypoconnectivity of neurons within a network, non selective connectivity where connections are not established between the right partners, or imbalance between excitatory and inhibitory mechanisms that could impair the generation of oscillatory activity or synchronization. All these alterations are susceptible to affect the processing capabilities of synaptic networks and thereby account for intellectual disabilities, autistic features or other endophenotypes characterizing developmental psychiatric diseases. A major challenge for the coming years will be to understand how exactly alterations of specific synaptic proteins implicated in synaptopathies may result in synaptic network dysfunctions and how such dysfunctions could relate to the behavioural phenotypes observed in animal models. A better understanding of these issues will certainly open new avenues for the search of compensatory mechanisms that might be of therapeutic interest.

Prof. Dominique Muller, Unige
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HIGHLIGHTS

Recent publications from the NCCR SYNAPSY members

Ruediger, S, Vittori, C, Bednarek, E, Genoud, C, Strata, P, Sacchetti, B, and **Caroni, P** (2011) *Nature*, in press Learning-related feedforward inhibitory connectivity growth required for memory precision.

Deguchi, Y, Donato, F, Galmberti, I, Cabuy, E, and **Caroni, P** (2011) *Nature Neuroscience*, in press Temporally matched subpopulations of selectively interconnected principal neurons in the hippocampus.

Bednarek, E, and **Caroni, P** (2011) *Neuron*, in press b-Adrenin is required for stable assembly of new synapses and improved memory upon environmental enrichment.

Ciocchi, S, Herry, C, Grenier, F, Wolff, SB, Letzkus, JJ, Vlachos, I, Ehrlich, I, Sprengel, R, Deisseroth, K, Stalder, MB, Müller, C, **Lüthi, A.** (2010) *Nature* 11;468(7321):277-82. Encoding of conditioned fear in central amygdala inhibitory circuits.

Matyas, F, Sreenivasan, V, Marbach, F, Wacongne, C, Barsy, B, Mateo, C, Aronoff, R, **Petersen, CC.** (2010) *Science* 330(6008):1240-3. Motor control by sensory cortex.

Kalinovsky A, Boukhtouche F, Blazeski R, Bormann C, Suzuki N, Mason, CA, **Scheiffele P.** (2011) *PLoS Biol* 9(2):e1001013. Development of Axon-Target Specificity of Ponto-Cerebellar Afferents.

Kochubey O, **Schneggenburger R.** (2011) *Neuron*. 69:736-48. Synaptotagmin increases the dynamic range of synapses by driving ca(2+)-evoked release and by clamping a near-linear remaining ca(2+) sensor.

Han Y, Kaeser PS, Südhof TC, **Schneggenburger R.** (2011) *Neuron* 69: 304-16. RIM determines Ca²⁺ channel density and vesicle docking at the presynaptic active zone.

Allaman I, Bélanger M, **Magistretti PJ.** (2011) *TINS* 34:76-87. Astrocyte-neuron metabolic relationships: for better and worse.

Suzuki A, Stern S, Bozdagi O, Huntley G, Walker R, **Magistretti PJ, Alberini CM.** Astrocyte-Neuron Lactate Transport Is Required for Long-Term Memory Formation. *Cell*, Volume 144, Issue 5, 810-823

Arzy S, Mohr C, Molnar-Szakacs I, **Blanke O.** (2011) *PLoS One*, 18;6(1):e16154. Schizotypal perceptual aberrations of time: correlation between score, behavior and brain activity.



Ansermet F. and Magistretti P.J. (2010) *Les énigmes du plaisir*, Odile Jacob, Paris

SAVE THE DATES!

14-15 March 2011

EPFL, Lausanne

Symposium on "Stress, the Social Brain and Psychopathology"

<http://ssbb2011.epfl.ch/>

14-20 March 2011

Brain Awareness Week

www.lasemaineducerveau.ch

26 March 2011

Annual Meeting Basel

Swiss society of neuroscience

<http://www.swissneuroscience.ch/>

1-2 April 2011

NCCR SYNAPSY annual retreat

Eurotel Victoria, Villars

24-27 May 2011

10e Colloque - Marseille 2011

French Society for Neuroscience

<http://www.neurosciences.asso.fr/>

14-18 July 2011

8th IBRO World Congress

Florence, Italy

<http://www.ibro2011.org/>

12-16 November 2011

Annual meeting - Washington, DC

American Society of Neuroscience

<http://www.sfn.org/>

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PROJECT LIST

WP1: Genes and environment

Leader: Andreas Papassotiropoulos / Associate: Carmen Sandi

WP2: Building synaptic networks in autism spectrum disorders

Leader: Dominique Muller / Associates: Alan Carleton, Henry Markram, Peter Scheiffele, Ralf Schneggenburger, Alexandre Dayer

WP3: Network interactions in anxiety and addiction

Leader: Christian Luscher / Associates: Carl Petersen, Pico Caroni, Anthony Holtmaat, Andreas Lüthi

WP4: Astrocyte function and neuron-glia metabolism

Leader: Andrea Volterra / Associates: Pierre Magistretti, Rolf Gruetter

WP5: Cortical integration

Leader: Christoph Michel / Associates: Olaf Blanke, Carl Petersen, Stephan Eliez, Stephanie Clarke, Michael Herzog, Micah Murray

WP6: Regulation of system homeostasis

Leader: Pico Caroni / Associates: Pierre Magistretti, Dominique Muller, Andreas Lüthi

CP1: Endophenotypes of mood disorders

Leader: Martin Preisig

CP2: Schizotypy and gene deletion syndrome

Leader: Stephan Eliez / Associates: Alan Carleton, Paola Bezzi, Pico Caroni, Christoph Michel, Dominique Muller, Dominique de Quervain

CP3: Biomarkers of first episode psychosis

Leader: Kim Do / Associates: Philippe Conus, Marco Merlo, Laurent Holzer

CP4: Developmental stress

Leader: François Ansermet

Clinician/scientist program

Leader: Pierre Magistretti

Platforms

Leaders: Dominique Muller, Pierre Magistretti / Associates: Richard Frackowiak, Stylianos Antonarakis

Pilot project

Leader: Panteleimon Giannakopoulos

Tech. Transfer : Bernhard Bettler

