

N°2 / DECEMBER 2011

# NEWSLETTER

NATIONAL CENTER OF COMPETENCE IN RESEARCH (NCCR) SYNAPSY



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

bringing together  
brain research and psychiatry

## EDITORIAL



The NCCR SYNAPSY was officially launched just over a year ago, on October 1st 2010. The projects in the various workpackages and clinical cohorts have been launched as planned and the emphasis now is on strengthening the interactions and collaborations between basic scientists and clinicians.

Accordingly, a major effort of the NCCR has been to support initiatives that aim at a culture of sharing data and competences in particular by establishing common platforms that could be applied to the different clinical cohorts. A first initiative was launched to establish a common platform for characterizing the patients included in the different cohorts that would include common imaging modalities and protocols as well as neuropsychological tests. The NCCR has now established a sort of "pipeline" with specific imaging modalities and protocols both for fMRI and EEG as well as neuropsychological tests. In this issue of the Newsletter, Professor Bogdan Draganski describes some of the main features of this platform. We feel that this effort represents a significant achievement that has brought together basic scientists and clinicians who now share common resources and competences for the characterization of endophenotypes of the patients in the different cohorts. Furthermore,

in particular, as far as the imaging data are concerned, the uniformity of data acquisition through this standardized and commonly shared "pipeline" of tests will allow us to create a common database that will be shared amongst all the participants of the NCCR. This achievement represents a quite significant cultural change in the current practice of research and is certainly in line with the main objectives of the NCCR. Another defining feature of this NCCR is the establishment of a clinicians/scientists program. The goal of such a program is to provide a rigorous neuroscientific training to young psychiatrists with the ultimate goal of establishing a new generation of clinicians with research expertise who could strongly contribute to the future of the departments of psychiatry in Switzerland. Two young fellows, one in Geneva and one in Lausanne, were selected as the first members of the clinicians/scientists program. The first Newsletter featured an interview of Dr Marie Schaer, from the Department of Psychiatry at the University of Geneva, who works on the 22q11 cohort. In the present Newsletter we present the second fellow, Dr Philippe Baumann, who works on the early psychosis cohort. A third facet of the present Newsletter is a brief description of the project carried out by Professor Christian Lüscher in the context of Workpackage 3 which deals with the investigation of the molecular mechanisms of drug addiction and their relevance to the understanding of compulsive behaviors. We hope that you will find these articles of interest.

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# RESEARCH PROJECT :

## Drug-evoked synaptic plasticity: A key to understanding addiction?

Certain drugs can induce profound, long-lasting behavioral changes that ultimately lead to the diagnosis of addiction. Much evidence supports the hypothesis that compulsive decision making, which is a hallmark of the disease, comes about by reorganization of neural networks. Our lab has over the last five years studied drug-evoked synaptic plasticity as a possible cellular mechanism underlying network adaptations that eventually lead to behavioral changes that in their most extreme form are termed addiction.

**All addictive drugs increase dopamine (DA) in the mesolimbic system.**

The addiction liability of drugs is conferred by their pharmacological effect on the mesolimbic DA system. While the physiology of the ventral segmental area (VTA) is much more complex, involving a diverse population of VTA neurons, a two-neuron circuit model of the VTA can best explain pharmacological effects of addictive drugs (1), in which GABAergic interneurons control the firing rate of DA projection neurons (Figure 1).

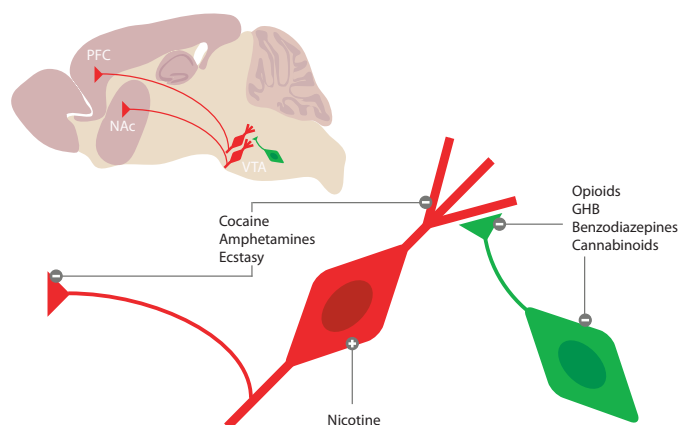


Figure 1

Addictive drugs thus fall into three classes based on the cellular mechanism engaged to cause the increase on DA levels (2). A first class works indirectly by inhibiting GABA neurons and thus causing the disinhibition of DA neurons. Such a scenario had been proposed for the opioids and the cannabinoids, and our lab has actively contributed by unraveling the molecular underpinnings for Gamma-Hydroxy Butyrate (3,4) and benzodiazepines (5), which now allows their classification in this group. Drugs in the second class (e.g.

nicotine) directly stimulate the DA neurons. Members of the third class (e.g. amphetamines, cocaine and ecstasy) interfere with the reuptake of DA in the target regions as well as the VTA (DA neurons in the VTA also release DA from their dendrites).

**VTA dopamine neuron activity is sufficient to cause adaptive synaptic plasticity**

Dopamine is a modulator of glutamatergic and GABAergic transmission and it is therefore of no surprise that adaptive changes affecting excitatory afferents persist long after the drug has been cleared from the system. In DA neurons of the VTA already a first dose of an addictive drug will decrease synaptic NMDA receptor currents and lead to concomitant insertion of calcium permeable AMPA receptors (6,7). That this observation results from the convergence of all addictive drugs on the mesolimbic DA level is demonstrated by the observation that optogenetic stimulation of DA neurons is sufficient to cause the same synaptic adaptations and that these changes can be blocked with a dopamine receptor agonist directly applied into the VTA (8).

### Cascade of several forms of drug-evoked synaptic plasticity

In the VTA, synaptic changes in response to a single drug exposure last about five days, after which synaptic transmission returns to baseline, provided metabotropic glutamate receptors (mGluR1) do their job (7,9). In fact mGluR1 through Gq signaling, phospholipase C (PLC) and the mammalian TOR (mTOR) pathway initiate local synthesis of AMPA receptor subunits required to restore normal transmission (10). This is particularly interesting because similar mechanisms are engaged during the postnatal maturation of this synapse (11). While in neonatal mice calcium permeable AMPA receptors and calcium impermeable NMDARs predominate, these immature receptors disappear during the first two weeks provided mGluR1 function normally. In other words the drug-evoked synaptic plasticity in adults constitutes the reopening of a developmentally critical period. Whether this “rejuvenation” of the synapses is only “bad” “remains to be seen; in any case it strongly suggests that the changes in the VTA represent a form of metaplasticity. Addictive drugs switch synapses into

a different mode of function, for example by changing the rules for activity-dependent plasticity (6,12).

There is direct evidence for the permissive role of drug-evoked plasticity in the VTA. In fact, manipulations of the persistence of the synaptic changes in the VTA have an effect on longer-lasting adaptations in the nucleus accumbens, one of the primary target region of the VTA (13). These observations lead us to believe that with repetitive drug exposure more and more parts of the mesolimbic system undergo adaptive changes, which makes reversal more and more difficult and behavioral changes more and more permanent (14). In other words chronic drug use overwhelms endogenous defense mechanisms that normally would be able to restore baseline transmission, eventually affecting decision-making behavior.

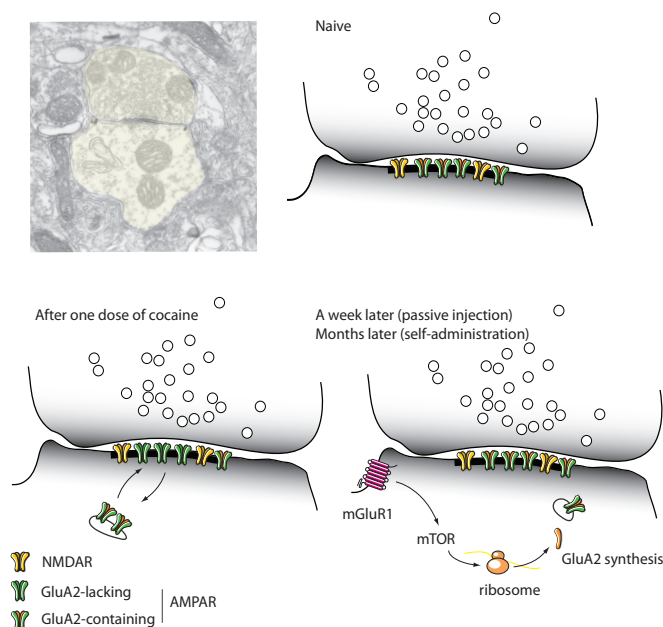


Figure 2

### Blueprint for mechanistic addiction treatments

Based on the above model novel therapeutic strategies emerge. Two complementary approaches consist of blocking drug-evoked synaptic plasticity or boosting compensatory mechanisms to restore normal transmission.

A promising strategy may be to amplify mGluR1 function thus efficiently removing calcium permeable AMPA receptors and restoring normal NMDA receptor function. Recent data suggest that this mechanism may not be limited to the VTA, but may also work in the nucleus accumbens where calcium permeable AMPA receptors have been shown to be instrumental in cue-induced relapse (15). Selective inhibition of calcium permeable AMPA receptors may be another strategy, but this pharmacological approach is still in its infancy (14).

In addition to pharmacological approaches, neuromodulation using DBS or

TMS may be promising. With the advances in our understanding of network remodeling we may take advantage of optogenetic in vivo protocols to restore baseline transmission after drug exposure. For example, if cocaine potentiates certain synapses, it may be possible to apply an LTD-protocol to depotentiate the transmission in question, which then may affect drug-related behavior. Obviously translation into humans is still far off, but proof of principle studies in rodents are appearing and clinical centers are actively exploring novel targets and stimulation protocols. Since it is likely that cortical control of striatal structures plays a crucial role, TMS may be just as efficient as DBS and much less invasive.

Clearly curing addiction is a daunting task, but the high individual, social and economical burden motivates researchers in the field to explore truly novel therapeutic approaches. It has been too long that addicts have been marginalized, which has scared away public health authorities and industry alike. Hope comes from the affirmation that addiction is truly a brain disease and the realization that addiction is one disease, no matter which drug (or behavior) causes it. This may unite forces.

### Prof. Christian Lüscher

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University of Geneva

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## INTERVIEW

### NCCR SYNAPSY clinician/scientist fellowship awarded to Philipp Baumann



**Philipp Baumann, you are an MD, how did you get interested in psychiatry?**

During my medical studies, I became fascinated by the relationship between mind and brain. When I had to decide on a clinical specialization, I chose psychiatry because I liked the fact that it was more people and relationship oriented than any other medical disciplines. During my stay in Australia, I had the opportunity to work with psychiatrists who were combining clinical work with research, especially brain imaging. I found this very captivating and decided to get involved with research as a way to explore not only the mind, but also the brain as well as their relationships through translational research.

**What are the characteristics of the disorder you are studying and how can imaging techniques help to better understand the disease?**

In the TIPP program, we treat patients experiencing first episodes of psychosis and our purpose is to optimize care and hopefully improve outcome. Psychosis is a generic term which includes several diagnoses and some patients have just one episode of psychosis while others progress towards illnesses such as schizophrenia. Patients typically develop symptoms during adolescence and early adulthood.

The illness often interferes with the development of different aspects of the individual, including identity, relationships, schooling and education. The TIPP program lasts for 3 years and, in addition to offering intensive follow up, it is also a unique opportunity to document and study how patients evolve. We realize however that our limited knowledge of the neurobiological aspects of such disorders hampers the implementation of more efficient early intervention strategies and that medications we use may not be specific enough to really target stage specific mechanisms of the illness. This is why we need to develop translational research projects. We therefore work in

close collaboration with the Unit for Research in Schizophrenia (led by Prof. Kim Do) that developed important expertise in the pathophysiological mechanisms of schizophrenia and proposed a novel and integrating hypothesis that implicates redox dysregulation as a vulnerability factor in schizophrenia. This interdisciplinary project has been growing over the last few years and I'm currently coordinating the structural imaging part.

Schizophrenia is a multisided and complex disorder characterized by disturbances in perception, speech, cognition as well as delusions and more subtle changes such as basic symptoms. Converging evidence points towards an interaction between biological and environmental factors occurring in the developing brain and leading to neural disconnectivity. The nature of this faulty connectivity is of multiple origin and certain aspects of it can be measured by brain imaging. Subtle but important changes occur in the brain of patients especially during the first years of illness. While concerning, it is also an opportunity for intervention. The non-invasive nature of MRI imaging makes it the perfect tool to better study this dynamic process and understand trajectories of brain modifications in relation to clinical and biological changes.

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

<http://www.nccr-synapsy.ch/interviews>

**where you will find the answers to the following questions:**

- What is your long term goal?
- What is in your eyes the benefit of the NCCR excellence fellowship
- Could you kindly tell us about your "parcours"
- What is your motivation in research?

## NEUROIMAGING PLATFORM

### Coordination of imaging protocols for the NCCR

**The aims of the Neuroimaging Platform within the NCCR project “SYNAPSY” are to provide the tools for acquisition and analysis of brain imaging data i) taking advantage of the latest in quantitative neuroimaging techniques, and ii) in a consistent manner across all patients’ cohorts.**

The overall goal is to integrate imaging data (structural magnetic resonance imaging (MRI), functional MRI) with other multi-modal patient data (electroencephalography recordings, genotype, neuropsychology, and clinical phenotype). Ultimately, we aim to establish generative models of mental disease pathophysiology, weighting the impact of anatomical changes, genotype and clinical phenotype.

In the last two decades neuroimaging research aimed at elucidating the pathophysiological basis of mental disorders by looking at functional and structural alterations within a steadily expanding network of brain areas involved. In the computational anatomy domain, experiments focused mainly on characterisation of relative changes in brain volume and cortical thickness using non-quantitative imaging techniques leaving room for speculative interpretations. This problem could be exemplified by dorso-lateral prefrontal cortex (DLPFC) *post mortem* findings in schizophrenia patients showing no evidence of neurodegeneration (e.g. gliosis), however increased pyramidal cell numbers paralleled by reduced dendritic spine density. The complexity of underlying histopathological changes is reflected by the diversity of computational anatomy results, which demonstrate inconsistently DLPFC volume changes in both directions – increase or decrease.

*New strategies needed:* It becomes clear that only new imaging strategies utilizing multi-modal MR sequences sensitive to microstructural tissue properties characteristics could contribute solving the problem of ambiguous interpretation of findings and establish *in vivo* the link to findings of *post mortem* histological

assessment of brain tissue. Based on technical developments in recent years, whole-brain high-resolution multi-parameter mapping of the major contrast parameters reflecting water physical properties that govern MRI contrast (i.e.  $R_1$  and  $R_2^*$  relaxation and magnetization transfer – MT) can be performed in clinically feasible acquisition times. According to the common biophysical notion the rate of longitudinal relaxation ( $R_1$ ) depends mainly on the mobility of water within its microenvironment, the effective transverse relaxation rate ( $R_2^*$ ) is sensitive to the iron content and MT reflects the macromolecular content of tissue with myelin having the largest contribution to measured MT in the brain. Each parameter map, namely  $R_1$ ,  $R_2^*$  and MT saturation, reflects characteristic aspects of tissue micro-architecture and has the potential to detect regional changes in tissue properties in particular mental disease and demonstrate their differential trajectories over time. Based on a multi-parameter mapping method, the neuroimaging platform NCCR SYNAPSY provides a comprehensive approach combining morphometric and quantitative MRI offering complementary information regarding brain architecture in mental diseases.

NCCR SYNAPSY relies on imaging data acquisition in different centres over long period of time, which requires standardization of MR techniques to avoid dependency on scanner software and hardware. Unlike the widely used in computational anatomy T1-weighted MR data, the Neuroimaging platform builds on the fact that multi-parameter mapping is a truly quantitative technique, by definition insensitive to inter-scanner variability and robust to software upgrades on MR platforms.

*Challenges to address:* Considering the complexity of the established quantitative MR protocol we face challenges both at practical and methodological level of data processing and statistical analysis.

Because the current multi-parameter protocol generates more than forty 3D volume datasets per subject ( $\sim 1\text{GB}$  of data), the necessity for intuitive and automated data processing is evident. We adapted algorithms within the world-leading software for brain image analysis (Statistical Parametric Mapping - SPM) to create a toolbox specifically dedicated to data processing of multi-parameter data and following the methods suggested by our group in previous publications.

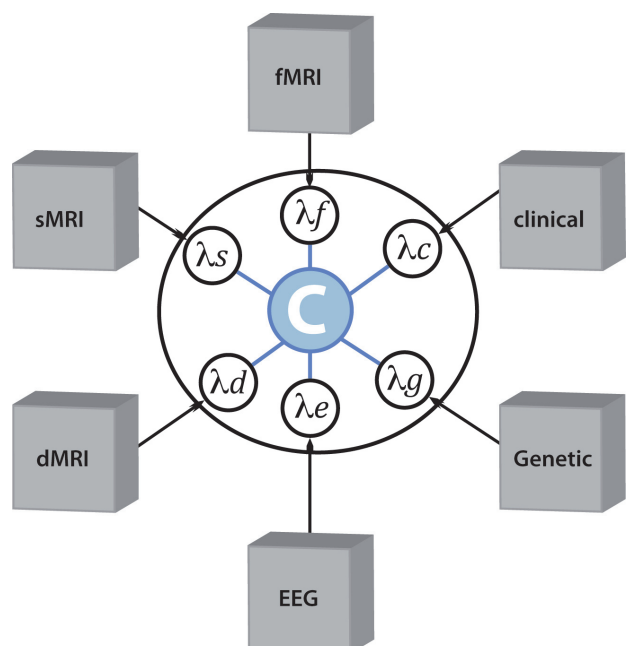
At the data analysis and modelling level, our objective is two-fold. First, develop a unified methodological framework that extends existing statistical tools to account for the high-dimensional, multivariate and multimodal nature of our imaging data. The aim is to derive combined biomarkers for predictive models specific to particular mental disorder that can be used for research and also in a clinical environment. Secondly, we aim to assess and improve the generalisability of the predictive models across centres to be able to control for subject heterogeneity within and between clinical cohorts. Critically, we further develop methods helping with decision-making for extraction of relevant features from the vast amount of multi-parameter data for subsequent mass-univariate analyses.

We also further develop analytical methods to take full advantage of the multi-parameter data in a comprehensive manner by accounting for its high-dimensional, multivariate and multimodal nature. Recent advances in multivariate analysis of brain images allow for the classification of individual anatomical data based on pre-learned characteristic patterns using support-vector machines (SVMs). SVMs are based on principles in the context of machine learning where individual MR images are treated as points located in a high dimensional space. In principle, images of subjects within the same diagnostic group should be more similar to each other, than they would be to images of subjects from another group. Other methods are based on the Gaussian Mixture Model and Principal Component Analysis (GMM/PCA). The GMM/PCA approach extracts subject groupings from the data. Therefore, this approach does not depend on *a priori* knowledge of subgroups, but uses a probabilistic classification method to find the probability that a particular subject belongs to one or another subgroup. Patterns are assumed to be similar within a subgroup but vary be-

tween subgroups.

Computational models of brain structure and function represent the most compact form summarizing complex neuroimaging and clinical data. The overall scientific aim of the Neuroimaging platform is to create biologically plausible generative models of specific mental diseases allowing for early diagnosis and prediction of clinical outcomes. The models define the combination of brain areas that best predict disease related changes or a continuous behavioural variable. The predictive ability of a model can be tested in an unbiased way by applying the model to a new independent data set. Simulation based approaches can be conducted using *a priori* hypotheses about which brain area plays an important role in the dysfunction of interest.

Considering that each imaging, neurophysiology, psychology and clinical modality generates a vast amount of data, we further offer expertise in data fusion approaches (i.e. "MetaVariate Analysis"), which are able to combine several thousands of variables for the purpose of generating reliable predictive models. A good predictive model is a model that is able to predict data of one modality using data from another modality (e.g. predicting clinical outcome from structural data, see figure 1).



**Figure 1.** Data fusion model:

We assume that a particular mental disease is due to an unknown underlying cause (C). However, C is expressed in each class of data (via some latent variables). By finding common or shared variance, C can be identified.

In summary, the Neuroimaging platform presented here offers expertise on well-established methods for quantitative multi-parameter MR data acquisition, standardised processing and analysis. Critically, we implemented state-of-the-art methods for user-friendly data handling and statistical package that is open to all participants in the NCCR consortium, alongside teaching modules and properly defined standards for assessing statistical significance.

The combination of multiple sources of information will increase the sensitivity of our methods in detecting trait- and state- related features between mental diseases cohorts. We also expect that a predictive model that leverages information across modalities can be used as biomarker for particular pathophysiological features in psychiatric disorders with significantly increased sensitivity and specificity.

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## HIGHLIGHTS

### Recent publications from the NCCR SYNAPSY members

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**Brain Awareness Week**

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<http://ssbb2012.epfl.ch/>

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**PUBLISHER** Management Team NCCR  
SYNAPSYPierre Magistretti, Dominique Muller, Beatrice Roth, Gabriele Grenningloh, Emilie Pralong  
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