

Inserm 2015 Host Laboratories and Research Programs

1. Francois Tronche

Role of Brahma and BRG1 Chromatin Remodelers in Behavioral Responses to Drugs of Abuse

Clinical and preclinical research strongly suggests that the stress response is a key determinant in the appearance of addiction. Stress release of glucocorticoids activates their receptor (GR). We demonstrated that GR gene inactivation in dopaminergic neurons was sufficient to strongly reduce behavioral responses to psychostimulant (Ambroggi et al Nat Neurosci. 2009, Barik et al. Biol Psychiatry 2010) and to block the development of social aversion following repeated aggressions (Barik et al. Science 2013).

Refine anatomical dissection of GR gene functions. To dissociate the effects of GR gene inactivation in the PFC from the effects of its inactivation in the NAcc, we will generate mice deprived of GR in either one or the other of these structures, using viral delivery of the Cre recombinase.

Understand epigenetic mechanisms underlying GR function. GR controls gene expression in part by recruiting chromatin remodeler complexes containing brahma or BRG1 that shape the chromatin and may be responsible for long-lasting changes in gene expression. We established mouse lines deprived of Brm, BRG1, and both proteins in dopaminergic neurons. Their behavior will be compared to that of GR mutants in order to reveal whether the interaction of Brm and BRG1 with GR sustains responses to cocaine.

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2. Marie-Odile Krebs

Stress and Cannabis: Crossed Vulnerability During Adolescence to Long Lasting Cognitive and Behavioral Impairments in Adult

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3., 4., and 5. Jean-Paul Moatti

Epidemiology and Social Sciences in the Field of Addictions

Project 3: An epidemiological study enrolling a cohort of 800 injecting drug users with a 12-month follow-up and 3-month interval interviews to assess the impact of individual and structural factors on health and risky behaviors.

Project 4: A pharmacological study to assess the effective dose of methylphenidate (MPH) in cocaine-dependent individuals using a combination of socio-behavioral and pharmacokinetic approaches preliminarily to a randomized clinical trial to evaluate the efficacy of MPH for cocaine dependence.

Project 5: A clinical trial assessing the efficacy of intravenous buprenorphine for opioid-dependent individuals who have failed with oral opioid substitution treatment.

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6. Marcello Solinas

Role of Cognitive Training on Cocaine Self-Administration in Rats

Exposure to environmental enrichment (EE) produces profound positive effects on drug addiction. EE is comprised of different types of stimulation including social interaction, physical activity and cognitive stimulation. In this project, we will investigate whether cognitive stimulation by itself can also be beneficial in animal models of addiction. Our working hypothesis is that training rats in cognitive tasks that require inhibitory control prior to self-administration session will reduce both active drug taking and risks of relapse. We will use operant cognitive tasks that we have developed in our laboratory and self-intravenous administration of drugs. In addition, provided that positive results are obtained we will use molecular techniques to investigate the neurobiological mechanisms involved.

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7. Laurence Lanfumey

Ethanol and Epigenetic Regulations in the Mouse Brain

We have recently shown that chronic and moderate ethanol intake could regulate cell proliferation in adult C57BL/6J mouse hippocampus. This effect involved chromatin remodeling and BDNF over-expression associated with an increase in transcriptional activity due to an inhibition of HDACs (histone deacetylases) expression and a hypomethylation of the main CpG islands present within the BDNF gene. Interestingly, while neurogenesis is known to influence hippocampus-dependent learning and memory, we showed that the epigenetic-induced increase in neuroplasticity factors after ethanol intake did not increase hippocampal LTP. However, memory-related behaviors were affected by ethanol (Stragier et al. 2015, and submitted). In order to further characterize the effects of ethanol, we propose to use novel pharmacological tools, targeting either epigenetic enzymes, or BDNF/TrkB complex to dissect the effect of ethanol.

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8. Mickael Naassila

Looking for a Marker of Alcohol Addiction: Is Loss of Phasic Dopamine Release and Synaptic Plasticity Critical?

The objectives of this proposal are to determine the neural substrates of the alcohol addiction process and especially the changes in phasic dopamine release and synaptic plasticity that may represent the keystone by which alcohol hijacks reward circuits and leads to an overlearning of cues predicting drug availability. Identifying this keystone action of alcohol also targets phasic dopamine release as potential therapeutic intervention. The present project is aimed at elucidating the neurobiological bases of alcohol addiction using relevant preclinical models of alcohol addiction (using the inhalation procedure to induce both physical and psychological dependence) and the technical approaches such as *in vivo* electrochemical (fast cyclic voltammetry) and *ex vivo* electrophysiological recording techniques.

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9. Jocelyne Caboche

Epigenetic Regulation in Addiction: Role of miR128b

Addiction is a chronic disease characterized by a loss of control over use and compulsive drug taking, in spite of adverse effects on health and psychological state. It is now well established that this pathology relies on neuroadaptive processes in specific brain areas: the “reward circuitry”. This project will study the molecular mechanisms that underlie cocaine-induced neuroadaptation in the striatum, with a particular emphasis of the short non-coding RNA: miR128b. We will collaborate with Dr. Anne Schaefer (anne.schaefer@mssm.edu), Assistant Professor at Icahn School of Medicine at Mount Sinai in New York, who generated a transgenic mouse that can overexpress miR128b. This miRNA controls the neuronal excitability and locomotor activity (Tan et al., 2013). miR128b will be overexpressed in striatal neurons expressing D1 receptors specifically. We will study in these mice cocaine-induced long-term behavioral responses (locomotor sensitization, conditioned place preference). Post-mortem, on striatal slices, we will study intracellular signaling pathways (MAPkinase/ERK; Elk-1 CREB) and gene regulation induced by cocaine. This study will provide new therapeutic avenues in addiction. Tan et al., (2013) MicroRNA-128 governs neuronal excitability and motor behavior in mice. *Science*. Dec 6; 342(6163):1254-8.

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10. Jean-Louis Laplanche, Bruno Mégarbane

Addiction Properties of the New Synthetic Cathinones: A Behavioral and Molecular Approach

The use of synthetic cathinones in the recreational scene is exponentially spreading. However, only limited experimental data support their potential for abuse. The objective of this project is to investigate the addictive potential of different cathinones in comparison to cocaine and amphetamine in a rodent model of addiction and study their involvement on dopamine in reward-related behaviors through the mesolimbic dopaminergic pathway using an *in vivo* microdialysis approach. The contribution of different monoamines and specific transporters at the blood-brain barrier will be studied. In this proposal, we will combine behavioral, neurochemical and pharmacokinetic approaches after acute and repeated administration, to better understand the mechanisms involved in cathinone abuse.

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11. Jean-Louis Laplanche, Frank Bellivier

Mutation Screening, Genetic Association and Gene-Gene Interaction Modeling Studies in Addiction

Our research team is involved in clinical phenotyping and biological sampling of cohorts of drugs of abuse users (mainly cocaine and opiates). We use a variety of approaches such as transcriptional profiling, molecular genetics and genome-wide epigenetics in combination with extensive clinical characterization to study vulnerability factors to addictions as well as factors influencing illness course. Ongoing projects on cocaine addiction include next-generation sequencing of a large cohort of cocaine addicts and controls, targeting a pathway possibly involved in cocaine dependence according to pre-clinical studies. In addition, an SNP-based gene association study is ongoing in patients with complex addiction (poly-dependence) regarding subjective effects of first cocaine use. The objective of the project is to establish gene association and gene-gene interaction modeling studies in addiction based on a large and complex set of data.

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12. Jean-Luc Martinot

Outcome of Cannabis and Other Addictions: Multidisciplinary Database of Adolescents

Substances of abuse such as cannabis have deleterious effects on the brain maturation at adolescence that can be tackled by multimodal MR imaging techniques acquired in the context of an international cohort. Participants were assessed for psychometry, neuropsychology, and GWAS, and their parents completed questionnaires. INSERM Unit 100 is a partner in this unique resource database that includes multidisciplinary data from >2000 14 year-old adolescents who were followed up. Outcome data at ages 16 and 18 might be available for analysis.

Raising specific hypotheses on the relationships between these brain images and psychobehavioral or genetic data, and performing the analyses would be part of the research exchange. This might be of interest for further French–U.S. collaboration as regards brain imaging and bioinformatics applied to addiction.

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