6TH BORDEAUX NEUROCAMPUS CONFERENCE

Bordeaux / October 2nd – 4th, 2019

# Normal and pathological reward processing: from synapse to behavior

Essential feature of the human as well as the animal brain is its ability to process information on line in order to efficiently adapt behavior to a changing environment. The brain constantly integrates new sensory information and adjusts its behavioral responses to maximize reward and / or minimize unpleasant and even dangerous consequences for the organism.

The question here is to highlight brain regions that share the ability to "reward" the performance of vital functions such as feeding, exploration of new environments, initiation of new social interactions, reproduction and appropriate reaction to threat? The mesocorticolimbic dopaminergic system was the first neural circuit to be described in this context and is closely related to the whole reward system. Are there other brain reward systems? What happens in the brains of patients with autism spectrum disorders, addiction to drugs or sports, anxiety or depressive symptoms, Parkinson's disease, whose reward system is altered? Answers to these questions do not reach consensus and will be debated during the three days of this conference.

Stéphanie CAILLÉ-GARNIER, François GEORGES, Pierre TRIFILIEFF

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# Invited speakers

**Keynote lecture**

- Ivan E. DE ARAUJO, Icahn School of Medicine at Mount Sinai, US

**Invited speakers**

- Serge AHMED, Bordeaux Neurocampus, FR
- Frédéric ALEXANDRE, Bordeaux Neurocampus, FR
- Jaideep BAINS, University of Calgary, CA
- Christelle BAUNEZ, University of Aix-Marseille, FR
- Camilla BELLONE, University of Geneva, CH
- Martine CADOR, Bordeaux Neurocampus, FR
- Francis CHAOULOFF, Bordeaux Neurocampus, FR
- Elena CHARTOFF, Harvard Medical School, US
- Joshua T. DUDMAN, Janelia Research Campus, US
- Philippe FAURE, Institut de Biologie Paris Seine, FR
- Pierre-Olivier FERNAGUT, University of Poitiers, FR
- Cecilia FLORES, McGill University, CA
- Ebrahim HAROON, Emory University, US
- Thomas KASH, University of North Carolina, US
- Mehdi KHAMASSI, Sorbonne Université, FR
- Christoph KELLENDONK, University of Columbia, US
- Stephan LAMMEL, Berkeley - University of California, US
- Angela LANGDON, Princeton University, US
- Diana MARTINEZ, Columbia University, US
- Marisela MORALES, Biomedical Research Center, Baltimore, US
- Ignacio OBESO, Centro Integral en Neurociencias , Madrid, ES
- Emmanuel VALJENT, Institut de Génomique Fonctionnelle, Montpellier, FR
- Peter VANHOUTTE, Institut de Biologie Paris Seine, FR
- Kate WASSUM, University of California, Los Angeles, US

**A conference for a wide audience will also take place on Friday 27th September (6pm), at Librairie Mollat**

- Thomas BORAUD, Bordeaux Neurocampus, FR
- Cédric BRUN, Université Bordeaux Montaigne, FR

# Supports

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# Program

## WEDNESDAY, OCTOBER 2ND

8:30 – 9:00 Registration and welcome coffee

9:00 - 9:15 **WELCOMING SPEECH**

### INTRODUCTION TO REWARD: CONCEPTS / PHILOSOPHY

CHAIR: STÉPHANIE CAILLÉ-GARNIER

9:15 - 10:00 **Serge AHMED** (Bordeaux Neurocampus, FR)
*It takes two to reward*

### SESSION 1 THE EXPECTED AND UNEXPECTED BASES OF REWARD

CHAIR: FRANÇOIS GEORGES

10:00 - 10:30 **Stephan LAMMEL** (Berkeley - University of California, US)
*Dopamine circuits in reward and aversion*

10:30 - 11:00 Coffee break and posters

11:00 - 11:30 **Christelle BAUNEZ** (University of Aix-Marseille, FR)
*The subthalamic nucleus: an unexpected critical node in the reward circuit*

11:30 - 12:00 **Kate WASSUM** (University of California, Los Angeles, US)
*Corticolimbic circuitry in reward learning and pursuit*

### SELECTED TALKS

CHAIR: FRANÇOIS GEORGES

12:00 - 13:00 **Giulia FOIS -** *Cocaine use the circuit of novelty to trigger plasticity in dopamine neurons*
**Marcello SOLINAS** - *Environmental enrichment reverses the neuroadaptations produced by escalated cocaine intake*
**Enrica MONTALBAN** - *Implication of Ankk1 in the regulation of food reward-based behaviors*
**Marie Flavia BARBANO** - *Modulation of cocaine seeking-behavior by VTA glutamatergic neurons*

13:00 - 14:30 Lunch time and posters

### SESSION 2 MODELING OF REWARD

CHAIR: NICOLAS ROUGIER

14:30 - 15:15 **Angela LANGDON** (Princeton University, US)
*Model-based predictions for dopamine*

15:15 - 15:45 **Frederic ALEXANDRE** (Bordeaux Neurocampus, FR)
*A computational model to study the dynamics of representations of rewards in the orbital and medial frontal cortex*

15:45 - 16:15 **Mehdi KHAMASSI** (Sorbonne Université, Paris, FR)
*Exploiting individual differences to inform computational models of dopamine in reinforcement learning.*

16:15 - 16:45 Coffee break and posters

### PLENARY CONFERENCE

CHAIR: PIERRE TRIFILIEFF

16:45 - 17:45 **Ivan E. DE ARAUJO** (Icahn School of Medicine at Mount Sinai, US)
*Peripheral Sensory Control of Brain Reward Systems*

18:00 - 20:00 Wine and cheese around the posters

## THURSDAY, OCTOBER 3RD

8:30 - 9:00 Welcome coffee

**SESSION 3** **FUNCTIONAL AND MOLECULAR DIVERSITY OF DOPAMINE SYSTEMS** CHAIR: PIERRE TRIFILIEFF

9:00 - 9:30 **Joshua T. DUDMAN** (Janelia Research Campus, Ashburn, US)
*Dopamine neuron activity and the desiderata of learning*

9:30 - 10:00 **Marisela MORALES** (Biomedical Research Center, Baltimore, US)
*VTA neuronal diversity and motivated behavior*

10:00 - 10:30 Coffee break and posters

10:30 - 11:00 **Emmanuel VALJENT** (Institut de Génomique Fonctionnelle, Montpellier, FR)
*Functional and molecular heterogeneity of D2R-expressing neurons along dorsal ventral axis in the striatum*

11:00 - 11:30 **Peter VANHOUTTE** (Institut de Biologie Paris Seine, FR)
*Modulation and functions of dopamine and glutamate receptor heteromers in cocaine-evoked adaptations*

11:30 - 12:00 **Christoph KELLENDONK** (Columbia University, New York, US)
*Ventral striatal d2 receptors and motivation*

**SELECTED TALKS** CHAIR: PIERRE TRIFILIEFF

12:00 - 12:45 **Claire ESCHBACH** - *Multilevel recurrent architecture for adaptive regulation of learning in the insect brain*
**Frederic AMBROGGI -** *Orexin in the posterior paraventricular thalamus mediates hunger-related signals in the nucleus accumbens core*
**Léa TOCHON -** *Lack of α5 nicotinic receptors increases alcohol self-administration at high dose and reverses the pattern of alcohol-induced neuronal activity in VTA and IPN*

12:45 - 14:15 Lunch time and posters

**SESSION 4** **PATHOLOGIES AND REWARD:** CHAIR: ANNA BEYELER / BRUNO AOUIZERATE
**FACE-TO-FACE PRECLINICAL TO CLINICAL**

14:15 - 15:15 Addiction:
**Francis CHAOULOFF** (Bordeaux Neurocampus, FR)
*Neurobiological bases of the rewarding value of exercise*

**Diana MARTINEZ** (Columbia University, New York, USA)
*Imaging and treatment development for substance use disorders*

15:15 - 16:15 Anxiety/Depression:
**Thomas KASH** (University of North Carolina, US)
*Probing alcohol induced mechanisms of altered threat response*

**Ebrahim HAROON** (Emory University, Atlanta, US)
*Cortico-striatal Glutamatergic Underpinnings of Inflammation-Induced Reward Dysfunction in Depression.*

16:15 - 16:45 Coffee break and posters

16:45 - 17:45 Parkinson's disease:
**Pierre-Olivier FERNAGUT** (University of Poitiers, FR)
*Reward dysfunction in Parkinson's disease: trying to disentangle the contributions of neurodegeneration, drugs and individual vulnerability using animal models*

**Ignacio OBESO** (Centro Integral en Neurociencias, Madrid, ES)
*Dopaminergic treatment and excessive behaviours: impulse control disorders in Parkinson disease*

20:00 - 23:00 Gala dinner

## FRIDAY, OCTOBER 4TH

8:30 - 9:00 Welcome coffee

### SESSION 5 REWARD ACROSS AGE AND SEX

CHAIR: GUILLAUME FERREIRA

9:00 - 9:30 **Martine CADOR** (Bordeaux Neurocampus, FR)
*Too much sugar at adolescence: brain reward deficits at adulthood*

9:30 - 10:00 **Elena CHARTOFF** (Harvard Medical School, Middleborough, US)
*Sex differences in the reward-related effects of opioids in rats*

10:00 - 10:30 **Cecilia FLORES** (McGill University, CA)
*The reward circuitry in adolescence is still under construction*

10:30 - 11:00 Coffee break and posters

### SESSION 5 SOCIAL REWARD

CHAIR: CHRISTELLE GLANGETAS

11:00 - 11:30 **Jaideep BAINS** (University of Calgary, CA)
*$CRH^{PVN}$ neurons decode stress controllability and modify defensive behaviour*

11:30 - 12:00 **Philippe FAURE** (Institut de Biologie Paris Seine, FR)
*Individual traits and nicotine addiction*

12:00 - 12:30 **Camilla BELLONE** (University of Geneva, CH)
*Neural mechanisms underlying social motivation*

12:30 - 12:45 Closing remarks

12:45 Lunch box

# Oral presentations

## Invited speakers

| | | |
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| IS2 | **Stephan LAMMEL** | *Dopamine circuits in reward and aversion* |
| IS3 | **Christelle BAUNEZ** | *The subthalamic nucleus: an unexpected critical node in the reward circuit* |
| IS4 | **Kate WASSUM** | *Corticolimbic circuitry in reward learning and pursuit* |
| IS5 | **Angela LANGDON** | *Model-based predictions for dopamine* |
| IS6 | **Frédéric ALEXANDRE** | *A computational model to study the dynamics of representations of rewards in the orbital and medial frontal cortex* |
| IS7 | **Mehdi KHAMASSI** | *Exploiting individual differences to inform computational models of dopamine in reinforcement learning* |
| IS8 | **Ivan E. DE ARAUJO** | *Peripheral sensory control of brain reward systems* |
| IS9 | **Joshua T. DUDMAN** | *Dopamine neuron activity and the desiderata of learning* |
| IS10 | **Marisela MORALES** | *VTA neuronal diversity and motivated behavior* |
| IS11 | **Emmanuel VALJENT** | *Functional and molecular heterogeneity of D2R-expressing neurons along dorsal ventral axis in the striatum* |
| IS12 | **Peter VANHOUTTE** | *Modulation and functions of dopamine and glutamate receptor heteromers in cocaine-evoked adaptations* |
| IS13 | **Christoph KELLENDONK** | *Ventral striatal D2 receptors and motivation* |
| IS14 | **Francis CHAOULOFF** | *Neurobiological bases of the rewarding value of exercise* |
| IS15 | **Diana MARTINEZ** | *Imaging and treatment development for substance use disorders* |
| IS16 | **Thomas KASH** | *Probing alcohol induced mechanisms of altered threat response* |
| IS17 | **Ebrahim HAROON** | *Cortico-striatal glutamatergic underpinnings of inflammation-induced reward dysfunction in depression* |
| IS18 | **Pierre-Olivier FERNAGUT** | *Reward dysfunction in Parkinson's disease: trying to disentangle the contributions of neurodegeneration, drugs and individual vulnerability using animal models* |
| IS19 | **Ignacio OBESO** | *Dopaminergic treatment and excessive behaviours: impulse control disorders in Parkinson disease* |
| IS20 | **Martine CADOR** | *Too much sugar at adolescence: brain reward deficits at adulthood* |
| IS21 | **Elena CHARTOFF** | *Sex differences in the reward-related effects of opioids in rats* |
| IS22 | **Cecilia FLORES** | *The reward circuitry in adolescence is still under construction* |
| IS23 | **Jaideep BAINS** | *CRHPVN neurons decode stress controllability and modify defensive behaviour* |
| IS24 | **Philippe FAURE** | *Individual traits and nicotine addiction* |
| IS25 | **Camilla BELLONE** | *Neural mechanisms underlying social motivation* |

## IS1 - It takes two to reward


### Serge Ahmed

*Université de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France*
*CNRS, Institut des Maladies Neurodégénératives, UMR 5293, 146 rue Léo-Saignat, F-33000 Bordeaux, France*


The word “reward” has the same etymological roots as the French word “regard” from the verb “regarder” which meant “to ward against, guard.” Today, “reward” means recompense – récompense in modern French – as opposed to “punishment.” A reward is something used by someone (the rewarder) with the intent to reinforce a desirable behavior in someone else (the rewardee). “To reward” is also a transitive verb that describes the action of using a reward. One can also try to reward someone for not behaving in some undesirable way, but this typically does not work well which explains why one prefers in such case to resort to punishment. Thus, fundamentally, the concept of reward defines a specific relationship between at least two individuals (or groups of individuals). It takes two to reward: a rewarder and a rewardee. Examples abound. Parents reward their child. PIs reward their post-docs. Funding agencies reward scientists and academies do the same too. And, of course, we neuroscientists reward our lab animals, notably with the hope to decipher the brain mechanisms of reward. In each case, however, a different kind of reward is used: love; first-author position in a scientific publication; grant money; peer recognition; or palatable food. Clearly, what works well with some rewardees may not work with others. For instance, it is relatively easy to reward all kinds of behaviors in a mouse with a high-fat food pellet, but try using a high-fat food pellet to reward a post-doc. Differences in reward also exist across the sexes. And, of course, a same rewardee is differently sensitive to a given reward at different stages of her life and even at different times of the day, depending on fluctuating internal states. Thus, a reward is not inherently rewarding. How come?

Recent neuroscientific advances have revealed that a reward is rewarding in virtue of its ability to change activity in some specific structures of the rewardee brain, called variously since the 1950s “reward centers”, “reward pathways”, “reward systems”, “reward networks” and, more recently, “reward circuits” or even “reward circuitries.” What compose these brain structures at the molecular and cellular levels, how they develop and age through time, how they normally function or dysfunction in certain pathologies, how they compute and broadcast so-called reward signals in the brain, will be among the important questions that will be covered during the Conference. During my introductory talk, I will also emphasize another dimension that is often overlooked, but that is the elephant in the room. As already mentioned, it takes two to reward: a rewarder and a rewardee. Relatively recently in human history, this relationship has evolved into a novel variant in which a few rewarders get rewarded by rewarding frequently and potently a mass of rewardees, even if this generates addiction-related disorders and diseases in many. Some historians have aptly called our age “the Age of Addiction.” In this context, our increased knowledge and control of reward mechanisms in the rewardee brain, not only bring the promise of immense benefits to society, but also important risks, notably if this knowledge and control are exploited for the benefit of few at the peril of many. I will try to explain what these risks are and why we should ward us against them. Perhaps one way to resolve this issue would be to complement our sophisticated neurobiology of the rewardee brain with a neurobiology of the rewarder brain which remains to be invented.

## IS2 - Dopamine circuits in reward and aversion

**Stephan Lammel**

*Department of Molecular and Cell Biology and Helen Wills Neuroscience Institute, University of California, Berkeley*

The mesocorticolimbic dopamine (DA) system, composed of DA neurons in the ventral tegmental area (VTA) projecting to nucleus accumbens and prefrontal cortex, has been intensively studied because of its importance in reward processing and drug addiction. Importantly, while VTA DA neurons were thought to represent a homogeneous cell population, recent research has demonstrated a much greater diversity of DA cell type and function than had been previously supposed. Accordingly, VTA DA neurons encode much more than reward and also contribute to negative affect such as aversion and depression. How DA mediates both reward and aversion is currently unknown and an important goal of my research. In my presentation, I will discuss recent work from the lab that has elucidated the circuit architecture and function of the different mesolimbic DA subcircuits (Yang et al., 2018, Neuron; de Jong et al., 2019; Neuron). Moreover, I will discuss unpublished data on the role of DA release in distinct nucleus accumbens subregions for action selection and inhibition. Altogether, our research suggest that we need to develop a new perspective on the mesocorticolimbic DA system that will guide future treatment strategies for addiction and other neuropsychiatric disorders where dysfunction of the neural systems underlying motivated behaviors have been strongly implicated.

## IS3 - The subthalamic nucleus: an unexpected critical node in the reward circuit

**Christelle Baunez**

*Institut de Neurosciences de la Timone, UMR7289 CNRS & Aix-Marseille Université, Marseille, France*

The subthalamic nucleus has been associated with motor functions for a long time. It has however revealed a critical role in frontal functions such as attention, control of inhibition, motivation and emotions. The presentation will focus on the involvement of STN in reward processes. The effects of STN manipulations (lesions, pharmacological inactivation, deep brain stimulation or optogenetic activation or inhibition) in rats, monkeys or human patients suffering from Parkinson's Disease, Obsessive Compulsive Disorders or addiction will be reviewed, as well as electrophysiological recordings of STN activity during performance of reward-related tasks. All these results will converge to suggest this critical structure as a possible target for the treatment of addiction.

## IS4 - Corticolimbic circuitry in reward learning and pursuit

**Kate Wassum**

*Department of Psychology, UCLA*
*Brain Research Institute, UCLA*

To make adaptive decisions we must cast ourselves into the future and consider the outcomes of our potential choices. This prospective consideration is informed by our memories. I will discuss our lab's recent work investigating the neural circuits responsible for encoding, updating, and retrieving reward memories for use in the considerations underlying decision making. We have taken a multifaceted approach to these investigations, combining recording, circuit dissection, and behavioral tools. Our results are indicating that the orbitofrontal cortex and basolateral amygdala work in a circuit to regulate the encoding and retrieval of reward memories to ensure adaptive reward pursuit. The cognitive symptoms underlying addiction can result from a failure to appropriately learn about and/or anticipate potential future events, making these basic science data relevant to the understanding and potential treatment of addiction to drugs or alcohol.

## IS5 - Model-based predictions for dopamine

**Angela Langdon**

*Department of psychology, Princeton Neuroscience Institute*

Anticipating the timing of rewards is as crucial to adaptive behavior as predicting what those rewards will be. In the brain, reward learning is understood to depend on dopamine signals that convey a prediction error whenever reward predictions do not accord with reality. Neural and behavioral correlates of reward prediction errors indicate that predictions in the brain can be remarkably temporally precise. Prominent temporal-difference reinforcement-learning models suggest learning is 'model-free', and purport to explain how the timing of rewards is learned based on a simplified temporal representation of sequential, momentary, reward predictions that may not be tenable in the biological circuits that support reward learning. This leaves an important question unaddressed: how are temporally precise reward predictions dynamically represented and learned in the brain?

Motivated by recent experimental results that demonstrate a neural dissociation between predictions about the amount and timing of upcoming rewards, I will present a computational framework for reward prediction and learning in which both the value and duration of hidden task states are learned concurrently. This framework proposes a mechanism for learning a representation of hidden task states by tracking the elapsed time between events within a task and suggests that predictions about reward timing act to 'gate' the broadcast of reward prediction errors, providing a testable mechanism for the dynamic influence of temporal predictions on the neural computations necessary for reward prediction and learning.

## IS6 - A computational model to study the dynamics of representations of rewards in the orbital and medial frontal cortex

**Frédéric Alexandre**

*Inria-Labri UMR 5800 Talence*
*IMN - UMR 5293 Bordeaux Neurocampus*

In Machine Learning, value prediction and decision making are implemented in classical models of reinforcement learning evaluating state and action values. Considering limitations of these models, inspiration from neuroscience can be seen as a valuable way to revisit these algorithms. But a thorough study of the literature in neuroscience indicates diverging interpretations about the roles of the main regions of the orbital and medial frontal cortex, collectively reported to play a central role in extracting and representing these values. A reason for these divergences is that reported experiments were not associated to the same kind of behaviors and most of the time in non-ecological conditions. We report here about a large scale model that has been designed to associate different frontal regions (and not to focus on a specific one) and to implement an ecological behavior associating foraging and decision making when an interesting place has been detected. This global model allows to re-interpret several observations and is consistent with a wide series of behavioral experiments. Particularly, it reveals an interesting dynamic between the lateral and medial regions of the orbitofrontal cortex, respectively representing the sensory and the rewarding values of outcomes. This dynamic can be also exploited in a purely Machine Learning perspective to design an artificial agent able to autonomously identify goals and to exploit them in various perspectives.

# IS7 - Exploiting individual differences to inform computational models of dopamine in reinforcement learning

**Mehdi Khamassi**

*Sorbonne Université, CNRS, Institute of Intelligent Systems and Robotics, F-75005 Paris, France.*

The model-free reinforcement learning (MFRL) framework, where agents learn local, cached, implicit action values without trying to estimate a model of their environment, has been successfully applied to Neuroscience in the last two decades. It can account for most dopamine reward prediction error signals (RPEs) in Pavlovian and instrumental tasks. However, it is still not clear why in the Pavlovian autoshaping paradigm RPEs can been recorded in some individuals but not in others. Moreover, the role of dopamine in other functions not related to learning, such as exploration, is still not understood. Here we present a computational model of dopamine-based learning and exploration regulation, and show how it can account for inter-individual differences, termed sign-tracking and goal-tracking, in a Pavlovian lever-autoshaping procedure. The model combines MFRL with a model-based (MBRL) component which estimates an internal model of different actions' consequences in the environment. This model can explain inter-individual differences by a different relative contribution weight of MFRL and MBRL in choice behavior: The behavior of sign-trackers is mostly led by MFRL, displaying dopamine RPEs and pushing them towards reward predicting stimuli; In contrast the behavior of goal-trackers is mostly led by MBRL, where dopamine RPEs are absent, and pushing them towards the outcome of their behavioral responses. Moreover, the model suggests that injection of flupenthixol in goal-trackers impairs the exploration-exploitation trade-off and thus blocks the expression of a covert dopamine-independent MBRL learning process. This model led to a series of novel predictions produced through simulations in variants of the classic autoshaping procedure. Most notably, the model predicts that sign-trackers would be less sensitive to outcome devaluation than goal-trackers, which has recently been confirmed experimentally. The model also predicts that changing the duration of the inter-trial interval should change the relative proportion of sign- and goal-trackers in the population as well as the dopamine RPE profile in these individuals. Recent experimental results collected by the group of Matthew R. Roesch at the University of Maryland, USA, partially confirming these predictions will be presented. Other recent results collected by the group of Etienne Coutureau and Alain Marchand at the CNRS in Bordeaux, also confirm some of the model predictions, namely that dopamine blockage impairs exploration regulation mechanisms in rats. Together these results suggest a variety of mechanisms on which dopamine can impact, which can be progressively better understood through the tight collaboration between experimentation and computational modeling. Moreover, sign- and goal-tracking behavior having been related to different vulnerability degrees to drug seeking, this computational model may have impacts on the understanding of some individuals' transition to addiction.

## IS8 - Peripheral sensory control of brain reward systems

**Ivan E de Araujo**

*Nash Family Department of Neuroscience, Friedman Brain Institute, Diabetes, Obesity and Metabolism Institute, Icahn School of Medicine at Mount Sinai, New York City, NY*

The presentation will describe recent advances linking peripheral sensory organs to the brain circuits that control reward, emotion and motivation. Specifically, neuroanatomical and functional data will be shown to demonstrate that gustatory and gastrointestinal peripheral sensory neurons are connected to reward dopamine neurons via sensory-specific brainstem relays. Via ascending pathways of vagal and facial nerve origin, visceral neurons function as genuine reward neurons by stimulating midbrain dopamine secretion in striatum. More generally, a topographic sensory organization appears to exist throughout the striatum, with gastrointestinal vs. orosensory rewarding signals causing dopamine release into different striatal sectors. The extent to which these findings are confirmed by recent human neuroimaging findings will be also discussed. From a practical standpoint, cranial nerve pathways may thus constitute an accessible target for novel stimulation therapies for affective and eating disorders.

## IS9 - Dopamine neuron activity and the desiderata of learning

**Joshua T Dudman**

*Janelia Research Campus of the Howard Hughes Medical Institute*

Mammalian midbrain dopamine (mDA) neurons exhibit phasic activity in short bursts of <200 ms in response to reward related stimuli and actions, with 50-90% of neurons encoding the most salient incentive events. This phasic activity is thought to underlie the essential ability of animals to pursue rewarding outcomes; however, little was known about the quantitative changes in mDA activity during novel learning. I will describe a series of experiments conducted by our group that using both detailed single cell physiology in multiple mDA populations as well as simultaneously imaged axonal activity in multiple mDA projection targets longitudinally as mice first learned that a cue predicted a sweetened liquid reward. We have also combined these measurements with calibrated exogenous activation of mDA burst activity to test reinforcement learning models. Our physiology, imaging and perturbation data are difficult to reconcile with an error-based signal that directly updates an inferred value function during novel learning. In contrast, we propose that the causal effects of phasic mDA activity are best described as a teaching signal within a policy optimization reinforcement learning algorithm that optimizes the vigorous pursuit of reward.

# IS10 - VTA neuronal diversity and motivated behavior

**Marisela Morales**

*Integrative Neuroscience Research Branch, Neuronal Networks Section, National Institutes of Health, National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD*

The ventral tegmental area (VTA) dopamine neurons are intermixed with GABA and glutamate neurons. In this talk, I will provide an overview on the characterization of VTA neurons that release GABA, glutamate or both. All VTA glutamatergic neurons express the vesicular glutamate transporter type 2 (VGluT2; Yamaguchi et al.,2007). The VTA VGluT2 neurons establish local synapses as well as synapses outside the VTA. Within the VTA, some VGluT2 neurons establish excitatory synapses on mesoaccumbens dopamine neurons, and the local glutamate release from VTA VGluT2 neurons drives the firing of mesoaccumbens dopamine neurons, the release of dopamine in nucleus accumbens, and drives place preference. These findings indicate that contrary to the idea that all glutamatergic inputs to VTA are from neuronal outside the VTA, and determined that glutamatergic neurons (expressing VGluT2) within the VTA through their local connections play a role in reward. We had also found that the VTA has a subset of VGluT2 neurons that co-expresses the enzyme for the synthesis of GABA (glutamic acid decarboxylase, GAD) and for its vesicular transporter (VGaT; Root, Mejias-Alponte, Zhang et al., 2014). Single axon terminals from these VTA VGluT2+GAD+VGaT+ neurons establish independent glutamate- and GABA-releasing synapses on the lateral habenula neurons. Although both glutamate and GABA may be present within the same axon terminal, they are released from different pools of vesicles. By cell-specific mapping, we had determined the VTA distribution of neurons that co-express VGluT2 and VGAT (VGluT2+ VGaT+ neurons), neurons that express VGluT2 without VGAT (VGluT2+ VGaT- neurons) and neurons that express VGaT without VGluT2 (VGluT2- VGaT+ neurons). By cell specific targeting, we had determined distinct signaling among VTA VGluT2+ VGaT+, VGluT2+ VGaT- and VGluT2- VGaT+ neurons in motivated behaviors.

# IS11 - Functional and molecular heterogeneity of D2R-expressing neurons along dorsal ventral axis in the striatum

**Emmanuel Valjent**

*IGF, CNRS, INSERM, Université Montpellier, Montpellier, France*

Control of motor actions is a key brain function that determines the survival of animals in their environments. In the striatum, dopamine D2 receptors (D2Rs) play an essential role in regulating movement since D2R ablation induces similar motor deficits as those observed after dopamine depletion. However, D2Rs' precise contribution to motor control remains unclear, especially in light of increasing evidence that D2Rs are expressed in many distinct cell types throughout the striatum. Here, we addressed this issue by evaluating multiple behavioral tasks after the temporally-controlled deletion of D2R selectively from a striatal subpopulation expressing the Wfs1 gene. Conditional D2R knockout mice displayed discrete behavioral impairments. RNAseq and histological analyses identified hundreds of novel region-specific molecular markers, which may serve as tools to target and manipulate other striatal D2R-subcircuits. Moreover, our translatome analysis revealed specific cellular and functional signatures of D2R-expressing subpopulations for intercellular communication, metabolism, imprinting, and translation, indicating an unforeseen heterogeneity in striatal D2R neurons. Altogether, our results provide anatomo-functional evidence of multiple region-specific genetically-defined D2R cell populations and, by manipulating one of these subpopulations, we revealed a specific role of D2R in digging, an innate motor behavior whose neurobiological substrate was previously unknown.

# IS12 - Modulation and functions of dopamine and glutamate receptor heteromers in cocaine-evoked adaptations

**Peter Vanhoutte**

*INSERM, UMR-S 1130, Neuroscience Paris Seine, Institute of Biology Paris Seine, F-75005, Paris, France*
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Drug addiction is defined as a compulsive pattern of drug seeking- and taking- behavior, with recurrent episodes of abstinence and relapse, and a loss of control despite negative consequences. Addictive drugs promote reinforcement by increasing dopamine (DA) in the mesocorticolimbic system, which alters excitatory glutamate transmission within the reward circuitry and hijacks reward processing. The striatum is a key target structure of drugs of abuse since it is at the crossroad of converging glutamate inputs from limbic, thalamic and cortical regions, encoding components of drug-associated stimuli and environment, along with DA that mediates reward prediction error and incentive values. This integration of DA and glutamate inputs is achieved by striatal projection neurons (SPN) that are mainly segregated populations: the “direct pathway” (dSPN), expressing DA D1 receptors (D1R) and the “indirect pathway” (iSPN) that express DA D2 receptors (D2R), which play distinct roles in drug-mediated reinforcement. We identified heteromers formed by the D1R with glutamate NMDA (NMDAR) receptors as molecular bridges by which DA facilitate glutamate-dependent synaptic transmission and in dSPN. Conversely, other groups found that the D2R/NMDAR interaction mediates the inhibitory effect of DA on NMDAR-signaling in iSPN. However, the modulation and function of these heteromers in responses to cocaine are yet unknown. To address this question, we developed approaches to detect endogenous receptor heteromers in the mouse brain and showed that repeated exposures to cocaine favor the formation D1R/NMDAR heteromers in both ventral and dorsal parts of the striatum, while D2R/NMDAR heteromerization is restricted to the ventral striatum. We also detected DAR/NMDAR complexes from human-post mortem caudate-putamen samples and describe their modulations in subjects with a history of dependence to psychostimulants. To study the functions of these receptor heteromers in the different phases of cocaine-mediated adaptations, we designed a viral-based approach to disrupt DAR/NMDAR heteromers in a time-controlled manner. We established that D1R/NMDAR interaction control cocaine-induced ERK activation and dendritic spine growth in dSPN, as well as the development of psychomotor sensitization and conditioned place preference. By contrast, D2R/NMDAR interaction appeared critical for the maintenance of the sensitizing and rewarding effects of cocaine. These observations posit DAR/NMDAR heteromers as molecular targets with a potential therapeutic interest, not only in addiction, but also for the numerous psychiatric disorders associated with an imbalance of DA and glutamate transmission.

## IS13 - Ventral striatal D2 receptors and motivation

**Christoph Kellendonk**

*Department of Psychiatry, Department of Pharmacology, Columbia University, New York*
*New York State Psychiatric Institute*

Impaired motivation has been a long recognized negative symptom of schizophrenia, as well as a common feature of non-psychotic psychiatric disorders. It is responsible for a significant share of functional burden, also because treatment options are limited. Pharmacological studies have demonstrated an important role of dopamine D2 receptors in the ventral striatum in regulating motivated behaviors. However, D2 receptors are expressed in different neuronal cell types within the striatum including indirect pathway projection neurons, cholinergic interneurons and terminals from cortical and dopaminergic neurons. Expression in these different cell types complicates the interpretation of pharmacological manipulations. To dissect the function of D2 receptors in distinct striatal cell types we used genetic tools in the mouse and selectively overexpressed D2 receptors in either indirect pathway projection neurons or cholinergic interneurons of the Nucleus accumbens core.

During my presentation I will show evidence that D2Rs in both cell types of the ventral striatum regulate distinct motivated behaviors via different neuronal mechanisms. Understanding the mechanisms that regulate motivated behavior should in the long-term enable the development of new treatment strategies towards treating deficits in motivation.

## IS14 - Neurobiological bases of the rewarding value of exercise

**Francis Chaouloff**

*Neurocentre Magendie INSERM U1215, Bordeaux Neurocampus, University of Bordeaux*

Rodent studies, using conditioned place preference protocols, cue- or drug priming-induced reinstatement of reward seeking, and withdrawal severity tests, have suggested that exercise practice might be a useful tool in the treatment of drug relapse. To date, a review of clinical studies examining the influence of exercise on withdrawal symptoms and craving for several drugs of abuse (e.g. nicotine, alcohol, cannabis, cocaine) strengthens the above hypothesis. Taken with growing evidence that exercise also bears addictive properties in susceptible individuals, these data suggest that exercise and the aforementioned drugs of abuse share common pathways, one of these being the mesocorticolimbic dopaminergic system. Although there is indirect preclinical support for this system being a target of exercise, the model used, i.e. home cage wheel-running, impedes an analysis of the neurobiology underlying exercise motivation, including in drug-dependent animals. The presentation will focus on our development of a mouse operant conditioning task which has helped to uncover the unique role of ventral tegmental area cannabinoid type-1 receptors in running motivation. More recent data linking craving for exercise with synaptic plasticity in mesolimbic dopaminergic systems will also be presented.

# IS15 - Imaging and treatment development for substance use disorders

**Diana Martinez**

*Columbia University Irving Medical Center*
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While treatment options exist for some substance use disorders (SUD), there has been a lack of novel therapies despite the clinical need. Human brain using Positron Emission Tomography (PET) has the potential to identify the neurotransmitter systems involved in relapse and treatment retention. Many of these studies have focused on striatal dopamine transmission and show that addiction is associated with a decrease in dopamine D2/3 receptors and blunted pre-synaptic dopamine release. Additionally, these imaging studies also show that low striatal dopamine signaling is associated with compulsive drug use.

Although dopamine is thought to drive much of the positive reinforcement in substance use, the kappa opioid receptor (KOR)/dynorphin system plays a significant role in modulating the negative aspects of addiction. Activation of this receptor system exacerbates stress induced reinstatement in animal models of SUD, while blocking the receptor reduces it. We recently completed a PET imaging study of KOR in cocaine use disorder that investigates stress induced cocaine seeking behavior. The results suggest that this receptor serves as a target for medication development in this disorder.

Despite these findings, there has been little advancement in medication development for SUD. As a result, our current focus is on developing transcranial magnetic stimulation (TMS) as a potential treatment for alcohol use disorder and chronic pain with opioid misuse. The rationale and early results from these studies will be presented.

# IS16 - Probing alcohol induced mechanisms of altered threat response

**Thomas Kash**

*Department of Pharmacology, University of North California, Chapel Hill, USA*

Alcohol use disorders have a high comorbidity with a range of psychiatric conditions, with anxiety disorders being the most common affliction. One of the challenges in clinical studies is determining the causality of the comorbidity, that is, does heightened anxiety drive increased alcohol abuse, or does alcohol abuse alter anxiety-like behavior. This is a question that is readily addressed using preclinical animal models. Our goal was to explore how a history of high level alcohol consumption could lead to persistent changes in a range of threat related behaviors. After six weeks of intermittent access to 20% ethanol, C57BL/6J mice show altered behavior in the forced swim assay, a visual threat assay, and to predator odor compared to water drinking mice. We found that KOR antagonist norBNI could restore stress coping in the repeated forced swim and responses to predator odor. To next determine which DYN/KOR populations may drive these altered stress reactions, whole-brain c-Fos mapping in a transgenic DYN reporter line was conducted to reveal the dorsal bed nucleus of the stria terminalis (dBNST) contained the highest c-Fos interaction between alcohol history and stress. Based on this finding, we locally blocked KOR signaling in the BNST and found that this reversed alcohol drinking-induced deficits in responses to predator odor. We next examined synaptic transmission using whole cell patch clamp recordings of dBNST DYN neurons. IA robustly silenced synaptic drive on to BNST DYN neurons while the combination of IA and stress significantly increased glutamatergic activity. This increased glutamatergic drive was blocked by in vivo antagonism of KOR, and in slice activation of KOR lead to increases in excitatory drive in alcohol-drinking mice. Using an optogenetic approach, we identified the mPFC as a potential source of this increased glutamatergic tone in the BNST. Altogether, this research shows a behavioral representation of an allostatic shift of stress coping after long-term alcohol. The imbalance of stress neuropeptide signaling may ultimately underlie this complex relationship between alcohol and stress.

## IS17 - Cortico-striatal glutamatergic underpinnings of inflammation-induced reward dysfunction in depression

**Ebrahim Haroon**

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Reward functions can be conceptualized as a neural balancing act, where positively- (hedonic) and negatively- (aversive) valenced feeling states triggered by environmental stimuli are compared to guide ongoing behavior. The convergence of top-down glutamatergic inputs from the frontal/prefrontal regions with bottom-up dopaminergic inputs from the brainstem nuclei occurring at the level of the striatum may be a significant aspect of this neural balancing act. By supplying sensory information matched to context and valence to the striatal processing hubs, frontostriatal glutamatergic projections guide and shape reward behavior. For instance, water can be more rewarding than sucrose in the context of thirst. Inflammatory activation is an influential contextual variable that reorients reward systems to prioritize healing and survival. Thus, inflammatory stimulation can shift motivational priorities of an organism from a hedonic/activity-oriented state to a withdrawing/inactive-state known as "sickness behavior" - till healing can be ensured. However, chronic, unresolved inflammatory stimulation can lead to enduring reward processing deficits by promoting persisting neurotransmitter dysfunction, functional dysconnectivity, and network rewiring. Accordingly reward processing deficits manifested by clinical symptoms such as anhedonia, apathy, and amotivation are commonly seen states with high chronic inflammation such as chronic medical ill-health, obesity, and some subjects with major depression. In this presentation, we will focus on the link between striatal glutamate (reflecting exaggerated and possibly anti-hedonic inputs from fronto-striatal systems) and reward network pathology in a group of medically-ill and medically healthy depressed subjects with high inflammation. By combining multi-modal neuroimaging data with machine learning algorithms, we will demonstrate that inflammation-associated glutamate dysregulation leads to dysconnectivity of functional networks both within the striatal hub and its connections with the more extensive reward processing network. Therapeutic targeting of inflammation-glutamate associated network pathology and resetting the resulting excitatory/inhibitory striatal inputs using inflammatory- and glutamate-modulating agents will be discussed.

# IS18 - Reward dysfunction in Parkinson's disease: trying to disentangle the contributions of neurodegeneration, drugs and individual vulnerability using animal models

**Pierre-Olivier Fernagut**

*Université de Poitiers, INSERM, U-1084, Laboratoire de Neurosciences Expérimentales et Cliniques, Poitiers, France*

Altered reward processing is a prominent feature of Parkinson's disease that can manifest over a wide spectrum of behavioural dysfunctions, being either linked to the disease process and/or to dopamine replacement therapy. With regards to the degenerative process, dopaminergic as well as non-dopaminergic neurodegeneration (e.g. serotonergic and noradrenergic) can trigger apathy, anhedonia and depression that will negatively affect the patients' ability to process rewards through distinct mechanisms (lack of interest and/or motivation, decreased reactivity to pleasurable stimuli, decreased reward value). On the other hand, ifdopamine replacement therapy can reverse some of the reward dysfunctions linked to dopaminergic loss, it can push the patients over the edge and trigger several types of addictive behaviours. Patients treated with dopamine D3/D2 agonists may develop impulse control disorders, which are behavioural addictions such as binge eating, hypersexualtity, compulsive gambling/shopping or punding (a complex form of repetitive and stereotyped behaviours). Those treated with levodopa or short-acting dopamine agonists may also develop a dopamine dysregulation syndrome characterized by compulsive intake of dopamine replacement therapy, drug seeking and hoarding, strongly resembling features of psychostimulant addiction. Importantly, these behavioural side effects of dopamine replacement therapy only affect a subset of patients, suggesting a critical role for individual vulnerability factors. In this presentation, I will discuss how nigrostriatal dopaminergic loss can modify the rewarding properties of several types of dopamine replacement therapy as a gateway for the development of a dopamine deregulation syndrome. I will also discuss how the loss of nigrostriatal dopaminergic neurons leads to various outcomes depending on baseline individual differences in inhibitory control and behavioural flexibility. Finally, I will show how D3/D2 agonists differentially affect impulse control and behavioural flexibility depending on baseline individual differences and dopaminergic loss, thereby highlighting multiple interactions between dopaminergic drugs and individual traits in a dopamine lesioned brain. Understanding how dopamine modulates inter-individual differences in cognitive processes relevant to impulse control disorders is now the next step to decipher the pathophysiology of these devastating side-effects of dopamine replacement therapy in Parkinson's disease.

## IS19 - Dopaminergic treatment and excessive behaviours: impulse control disorders in Parkinson disease

**Ignacio Obeso**

*CINAC - HM Puerta del Sur, Madrid, Spain*
*San Pablo-CEU University, Madrid, Spain*

Patients with Parkinson´s disease (PD) may develop impulse control disorders (ICDs) under dopaminergic treatments and result in excessive behaviours. The non-motor unwanted side effects only occur in a subset of patients exposed to dopamine agonists (about 14%) or on Levodopa (7.2%), suggesting an underlying vulnerability. The wide spectrum of excessive approach tendencies towards appetitive items include primary and secondary rewards such as binge eating, hypersexuality, pathological gambling or compulsive shopping. The neurocognitive profile of ICD is marked by preference of immediate gratification and lack of adaptation to negative outcomes paralleled by enhanced signalling of the mesocortical valuation system. To date, the precise behavioural and neural changes involved in ICD are unclear. More precisely, is unclear whether ICD is a deficit of impulsive choice or impulsive actions that cannot override excessive desire of appetitive items. In my presentation, I will discuss our results that put forward the field on one specific ICD (i.e. hypersexuality) in choice behaviour (Girard, Obeso et al., 2019, Brain) and present unpublished evidence on action impulsivity (using fMRI and computational modelling). Ultimately, preliminary findings may support a transfer towards clinical consequences that will impact ICD with neuromodulation techniques. Our findings give rise to a new neurocognitive and imaging profile on one ICD subtype to open new research avenues and bridge our findings into clinical contexts.

## IS20 - Too much sugar at adolescence: brain reward deficits at adulthood

**Martine Cador**

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The way rewarding stimuli is perceived evolves across life-time. Adolescence is a period of high sensitivity to rewarding stimuli leading to overconsumption of sugary foods or drinks easily accessible. Adolescence, a transition to adulthood, is also a critical developmental period characterized by major behavioral and neurobiological changes. Interestingly, the dopamine (DA) system, which plays a central role in reward-related processes, presents a delayed maturation during adolescence and may therefore be vulnerable to protracted impact of sugary reward overconsumption. I will present data in rats showing that sucrose overconsumption during the 15 days of the rat adolescent period induces remote behavioral and neurobiological deficits, signing a preclinical "depressive"-like phenotype. I will discuss the hypothesis that an overstimulation of the reward system such as the dopamine one, during critical periods of development might lead to decreased reward brain processing and to hedonic imbalance and might play a role in the etiology of reward-related disorders such as depression.

# IS21 - Sex differences in the reward-related effects of opioids in rats

**Elena Chartoff**

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Initial opioid misuse is thought to arise either from a drug's euphoric effects (i.e. positive reinforcement) or from its ability to mitigate pre-existing negative affective states (i.e. negative reinforcement). There is clinical evidence suggesting that these initiating factors are, in part, gender-dependent. The goal of the studies presented here was to rigorously assess effects of acute and prolonged opioid exposure on reward-related function in adult male and female Sprague Dawley rats in order to determine which opioid actions on reward are through positive or negative reinforcement. We used a variety of behavioral methods including intracranial self-stimulation (ICSS), place conditioning, and intravenous self-administration (IVSA) to assess how the mu opioid receptor (MOR) agonist oxycodone and the kappa opioid receptor (KOR) agonist U50,488 modulate different aspects of reward function. We found that oxycodone produces similar levels of conditioned place preferences in male and female rats under our conditions, whereas it produced greater suppression of ICSS behavior and is initially less reinforcing in the IVSA paradigm in females compared to males. Interestingly, microdialysis sampling of the nucleus accumbens shell showed greater oxycodone-induced dopamine levels in females compared to males—despite identical brain levels of oxycodone. Overall, females were less sensitive to the aversive effects of U50,488: KOR activation resulted in a decreased right-ward shift in ICSS thresholds (indicating less anhedonic-like effects in females) and a less robust conditioned place aversion. This reduced sensitivity to the depressive-like effects of KOR activation in females correlated with a reduced ability of U50,488 to suppress stimulated dopamine release in the nucleus accumbens. Finally, we tested the hypothesis that the reward-related effects of oxycodone depend on prior opioid exposure and withdrawal in males, but not females, suggesting that these manipulations impacted MOR-mediated intracellular signaling and sensitivity to oxycodone to a greater extent in males. Taken together, there is no one-size-fits-all answer to sex differences in opioid effects on reward function. Rather, the complexity that emerges calls for further and more mechanistic studies, as future treatments for Opioid Use Disorder and mood disorders will best be served by sex-dependent targets.

## IS22 - The reward circuitry in adolescence is still under construction

**Cecilia Flores**

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*Douglas Mental Health University Institute, Montreal, Quebec, Canada*

Reward processing differs substantially between adolescents and adults, but the cellular and molecular mechanisms mediating this difference remain largely unknown. Understanding the developmental processes that are ongoing in reward-relevant circuitries during adolescence and how these events are impacted by experience, including drugs of abuse and stressors, may shed light on this question. This talk focuses on the adolescent maturation of mesocorticolimbic dopamine neurons and on the emerging role of the Netrin-1 guidance cue system and its microRNA regulators in the gradual unfolding of dopamine connectivity during this age, including dopamine axon tagging and pathfinding. I also discuss (i) how drugs of abuse and chronic social stress in adolescence alter these developmental events, inducing susceptibility or resilience later on in life and (ii) how sex, dose, and specific age within adolescence modify these effects.

Interestingly, the Netrin-1 system continues to be expressed in the adult brain and is also involved in the plasticity of the adult mesocorticolimbic dopamine circuitry induced by drugs of abuse or chronic stressors. However, the direction, magnitude, and enduring consequences of these adult effects are opposite from those observed in adolescence. We propose that the developmental cellular and molecular processes that are ongoing in reward-relevant circuitries in adolescence could explain the reward processing differences in adolescents versus adults and to be intimately connected with the immediate and enduring effects of experiences on reward sensitivity.

## IS23 - $CRH^{PVN}$ neurons decode stress controllability and modify defensive behaviour

**Jaideep Bains**

*Hotchkiss Brain Institute, University of Calgary*

The perception of control during stressful events has lasting behavioural consequences that are apparent even in situations that are distinct from the stress context. How the brain links prior stressful experience to subsequent behaviours remains poorly understood. Here we show that hypothalamic CRH neuron activity in response to a cue prior to a potential threat, predicts the innate defensive behaviour to that threat. This cue-induced activity can be modified by prior instrumental training. Specifically, exposure to stress with high outcome control increases cue-induced CRHactivity while stress with no outcome control decreases this activity. These specific changes in cue-induced activity are enduring and predictive of subsequent defensive behaviours in unrelated tasks. Collectively, our observations demonstrate that CRH decode stress controllability and contribute to shifts between active and passive innate defensive strategies.

## IS24 - Individual traits and nicotine addiction

**Philippe Faure**

*Neuroscience Paris-Seine – IBPS, Sorbonne Université*

Consistent individual differences in behaviours represents a ubiquitous feature in animal populations. These behavioural differences among individuals define personality and have been linked to the susceptibility to addiction. Indeed, the susceptibility to develop drug addiction differs substantially between individuals and some traits that characterize an individual, such as impulsivity, exploration or novelty seeking, have been shown to represent a predictive factor for the addictive properties of drugs. The presentation will explore how nicotine, through its action on DA cells, modifies different traits of an individual, such as the exploration / exploitation balance but also how social factor, by their action on VTA DA cells could impact specific traits and vulnerability to drug.

## IS25 - Neural mechanisms underlying social motivation

**Camilla Bellone**

*Dept Basic Neuroscience, University of Geneva Switzerland*

Social behavior is the interaction of two or more individual of the same species and encompass a robust behavioral continuum that includes both affiliative and antagonistic contacts between conspecifics. Sensory inputs, internal states and environmental contexts are factors that strongly regulate social behavioural decisions, but how the brain processes this diverse information and makes these choices is unknown. Using state-of-the-art techniques, I will discuss the role of the mesolimbic dopamine system in social motivation using mice as animal model. Collectively, the data present here will provide a deeper insight into the neurocircuitry guiding specific aspects of social behavior, which are not only important to understanding the neural basis of complex behavior but also highlight potential dysfunctions underlying neuropsychiatric diseases such Autism Spectrum Disorders.

# Oral presentations

## Selected talks

ST1 **Giulia FOIS**

*Cocaine use the circuit of novelty to trigger plasticity in dopamine neurons*

ST2 **Marcello SOLINAS**

*Environmental enrichment reverses the neuroadaptations produced by escalated cocaine intake*

ST3 **Enrica MONTALBAN**

*Implication of Ankk1 in the regulation of food reward-based behaviors*

ST4 **Maria Flavia BARBANO**

*Modulation of cocaine seeking-behavior by VTA glutamatergic neurons*

ST5 **Claire ESCHBACH**

*Multilevel recurrent architecture for adaptive regulation of learning in the insect brain*

ST6 **Frederic AMBROGGI**

*Orexin in the posterior paraventricular thalamus mediates hunger-related signals in the nucleus accumbens core*

ST7 **Léa TOCHON**

*Lack of α5 nicotinic receptors increases alcohol self-administration at high dose and reverses the pattern of alcohol-induced neuronal activity in VTA and IPN*

## ST1 - Cocaine use the circuit of novelty to trigger plasticity in dopamine neurons

**Fois GR[1]**, Bosque-Cordero KY[2], Vazquez-Torres R[3], Miliano C[4], Chauquet S[1], Nogues X[5], Jimenez-Rivera CA[3], Caillé S[6], Georges F[1]

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A key feature of human and animal brain is to handle novelty. Anything that is new, different or unusual exerts an attractive power, catches our attention and triggers exploration. Exploring a novel context (environmental novelty) is essential for the species survival, and has been proposed to increase motivation, facilitate reward processing, and potentiate cocaine consumption. Different brain circuits are activated by novelty, but three specific brain regions seem critical for this environmental novelty detection network: the noradrenergic neurons originating from the locus Coeruleus (LC), the dopaminergic neurons from the ventral tegmental area (VTA) and the hippocampus. However, how environmental novelty can interfere with the reward system and control cocaine impact on VTA dopamine neuron plasticity and associated-behavior is not well understood yet. Here we investigate: 1) how novelty induced by a switch of context trigger changes in electrophysiological properties of VTA dopamine neurons and 2) the role of novel environment to trigger cocaine-evoked plasticity in dopamine neurons. We combined in vitro and in vivo electrophysiological approaches to uncover the early cellular targets of cocaine in the mesolimbic dopamine system and the consequent adaptations at the circuit and behavioral level. We found that the novelty exposure is necessary for cocaine-induced effects on VTA dopaminergic neurons activity and that this effect is due to the exploration of a novel environment and is not supported by a stress-effect during novelty exposure. Our data also reveal the key role of LC to the cocaine-induced effects on VTA dopamine neurons during exposition in a new context.

## ST2 - Environmental enrichment reverses the neuroadaptations produced by escalated cocaine intake

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Escalation of cocaine taking is associated with loss of control, excessive motivation and compulsive seeking and taking of the drug. Cocaine escalation produces neuroadaptations in a network of brain areas involved in motivation, salience attribution, memory, stress, and inhibitory control, which may persist after long periods of abstinence and may underlie the persistent risks of relapse. A promising strategy to help recovery from addiction and reduce relapse is to provide “addicted” rats with environmental enrichment (EE) during abstinence. However, little is known on the neurobiological mechanisms underlying the anti-craving effects of EE affects. Here, we combined escalation of cocaine self-administration and brain-imaging approaches using fluoro-deoxyglucose microPET in rats to investigate whether EE counteracts cocaine-induced changes in brain metabolic activity. Consistent with our previous findings, escalation of cocaine, followed by a month of abstinence, led to decreased activity in the anterior cingulate and insular cortex and the dorsal striatum (DSt) and increased activity in the amygdala, the dorsal hippocampus and the mesencephalon of rats housed in standard environments (SE) compared to naïve controls. In contrast, rats housed in EE after escalation of cocaine, showed complete recovery of brain metabolic activity. Direct comparison of EE and SE rats indicates that increased activity of DSt is a selective marker of the anti-craving effects of EE. Altogether these results demonstrate that the positive effects of EE on relapse are associated with a widespread recovery of normal metabolic activity in the brain. Moreover, these results suggest that manipulating the activity of the DSt may be a strategy to help recovery from addiction.

## ST3 - Implication of Ankk1 in the regulation of food reward-based behaviors

**Montalban E**, Gangarossa G, Luquet S

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The motivational control of feeding exhibits a reward-based regulation and largely relies on dopamine (DA) transmission within the mesocorticolimbic system. Similarly to drugs of abuse that hijack the reward system resulting in loss of control over drug consumption, exposure to highly palatable food can disrupt normal regulation of feeding and induce the development of compulsive-like behavior leading to obesity. The A1 allele of the ANKK1-TaqIA gene has been associated with addictive disorders, inflexibility, and obesity. This polymorphism leads to a decrease of up to 30 % of the DA-D2 receptor and is the most-studied genetic variant related to DA signaling and obesity. The TaqIA polymorphism induces a mutation producing a single amino acid change within the substrate-binding domain of the ankyrin repeat and kinase domain containing 1 (Ankk1) protein, which function is still unknown. Herein, we aimed at unraveling the implication of Ankk1 in the regulation of reward-based behaviors. First, we demonstrated that Ankk1 is enriched in the striatum and unraveled its modulation downstream of dopaminergic receptors stimulation. Next, we developed a unique mouse model that allows viral-mediated time- and region-restricted KO of Ankk1. Thanks to this model we showed that ablation of Ankk1 in the dorsal striatum alters flexibility and impairs performance in an operant conditioning paradigm. Ablation of Ankk1 in the lateral hypothalamus affects motivation, as well as locomotors response to cocaine and haloperidol. Moreover, this manipulation impacts the metabolic state of the animals as well as food intake in a binge-eating paradigm. Our study provides a first evidence of the implication of Ankk1 in the motivational and homeostatic components of feeding behavior.

## ST4 - Modulation of cocaine seeking-behavior by VTA glutamatergic neurons

**Barbano MF**, Qi J, Morales M

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Converging evidence indicates that both dopamine and glutamate neurotransmission within the nucleus accumbens (nAcc) play a role in the neurobiology of drug addiction. Increases of nAcc dopamine release from ventral tegmental area (VTA) inputs have been shown to play a role in the rewarding effects of drugs of abuse. In contrast, nAcc glutamate release from prefrontal cortex inputs synapsing on medium spiny neurons (MSNs) have been shown to play a role in cocaine reinstatement. Recent findings have demonstrated that, in addition to dopamine neurons, VTA glutamate neurons also target the nAcc and establish excitatory synapses on parvalbumin GABAergic interneurons. Here, we determined whether this recently identified mesoaccumbens glutamatergic pathway plays a role in the neurobiology of cocaine reinforcement. By using a conditioned place preference (CPP) procedure, we optogenetically activated VTA glutamatergic inputs to nAcc during the acquisition, expression or reinstatement phases of cocaine-induced CPP. We found that photostimulation of the VTA-nAcc glutamatergic pathway does not alter CPP acquisition but inhibits both CPP expression and reinstatement behaviors. These findings indicate that VTA neighboring dopamine and glutamate neurons innervating the nAcc play different roles in the neurobiology of cocaine reward, and that glutamatergic inputs depending on their nAcc targets (MSNs vs parvalbumine neurons) differentially modulate cocaine-seeking behavior.

## ST5 - Multilevel recurrent architecture for adaptive regulation of learning in the insect brain

**Eschbach C**[1], Fushiki A[1,2], Winding M[1], Schneider-Mizell CM[1,3], Shao M[1], Arruda R[1], Eichler K[1,4], Valdes-Aleman J[1], Ohyama T[1,5], Thum AS[6], Gerber B[7], Fetter RD[1,8], Truman JW[1,9], Ashok Litwin-Kumar[2,10], Albert Cardona[1,11], Marta Zlatic[1,12]

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Populations of dopaminergic neurons (DANs) in the Insect brain respond to externally applied reward or punishment signals and are involved in the formation of appetitive or aversive associative memory.
Yet the responses to these reinforcing stimuli show variability and adaptability. Also, the same types of DANs have been shown to encode other type of signals such as odor or movement. These findings suggest DANs in Insect integrate many internal and external inputs over time.
To determine the role and properties of such integration, we reconstructed all neurons forming synapses onto the DANs in the brain of Drosophila larva. We counted that more than 50% of the total synaptic inputs they receive are indirect feedback from the neurons reading out the associative memory and subject to dopamine-driven plasticity. Interestingly, this newly described layer of feedback neurons (FBNs) shows marked interconnection and inhibition.
Anatomical and experimental characterization suggest that FBNs 1. can encode valence of external and/or memory-based signals, 2. process competing signals from different memory compartments, 3. play a direct role in memory formation or update. Furthermore, neural network simulations suggest that FBNs can improve performances in complex reinforcement learning tasks, such as extinction or second-order conditioning. This work in a (not so) simple model organism details aspects of the organization of a reinforcement system, and provides tools to investigate mechanism of memory- and reward-based decision at the circuit and neuron level.

## ST6 - Orexin in the posterior paraventricular thalamus mediates hunger-related signals in the nucleus accumbens core

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Animals use exteroceptive stimuli that have acquired, through learning, the ability to predict available resources allowing them to engage in adaptive behaviors. Meanwhile, peripheral signals related to internal state (e.g. hunger) provide information about current needs, modulating the ability of exteroceptive stimuli to drive food-seeking behavior (Dickinson and Balleine, 1994; Holland and Petrovich, 2005). The nucleus accumbens core (NAcC) is essential for encoding the value of reward-predictive cues and controlling the level of behavioral responding (Ambroggi et al., 2008, 2011; Roesch et al., 2009; Floresco, 2015; Nicola, 2016). However, the way in which interoceptive information related to physiological needs is integrated in the NAcC remains to be clarified. Located in the lateral and perifornical hypothalamic regions, orexin neurons (Peyron et al., 1998; Sakurai et al., 1998) are implicated in a wide range of functions, including arousal, feeding and reward-seeking (Adamantidis and de Lecea, 2009; Choi et al., 2012; Mahler et al., 2014; Sakurai, 2014; Baimel et al., 2015; Castro et al., 2015; Gao and Horvath, 2016). Paraventricular thalamus (PVT) neurons receive a strong orexinergic projection (Kirouac et al., 2005) and are excited by orexins (Ishibashi et al., 2005; Huang et al., 2006; Kolaj et al., 2007). Hence, Kelley et al. (2005) proposed that the PVT serves as an integrative relay, conveying hypothalamic energy-balance information to the NAc through its glutamatergic projection. Here, we test whether NAcC encoding of reward-predictive cues is modulated by the integration of posterior PVT (pPVT) orexin-mediated hunger-related signals. Using freely-moving electrophysiology in rats performing a cue-driven reward-seeking task, we show that satiety decreases cue responses in NAcC and pPVT neurons. Blockade of pPVT orexin-2 receptors reduces responding in hungry rats. Activation of pPVT neurons either with local infusion of orexin-A or via optogenetics, positively controls NAcC cue responses and restores behavioral responding in sated rats, highlighting a circuit that integrates reward-predictive cues perceived in the environment with the current metabolic state of the animal.

# ST7 - Lack of α5 nicotinic receptors increases alcohol self-administration at high dose and reverses the pattern of alcohol-induced neuronal activity in VTA and IPN

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Recent human genetic studies have implicated gene variants in the α5 nicotinic acetylcholine receptor (nAChRs) subunit as high risk factors for developing both tobacco and alcohol addictions in humans[1,2]. The strongest association was found with a missense mutation (the single nucleotid polymorphism rs16969968) of the CHRNA5 gene, for which the frequency in populations of Europeans is around 40%[3]. Yet, mechanisms through which α5*nAChRs may influence drinking behavior remain unkown. Strong expression of α5 is found in ventral tegmental area (VTA) dopaminergic (DA) neurons and in interpeduncular nucleus (IPN) GABAergic neurons[4]. Thus, the aim of the current study was to evaluate the role of α5*nAChRs in ethanol's addictive properties in male and female α5 knock-out (KO) mice, which did not express α5*nAChRs, and wild-type (WT) mice. Using an intra-VTA self-administration paradigm based on the animal's choice in a Y-maze, we assessed rewarding and aversive effects of several doses of alcohol. Concurrently, we analyzed the effects of alcohol on the activity of VTA-DAergic neurons and GABAergic neurons in the IPN using in vitro electrophysiological recordings in VTA/IPN slices.

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# Posters

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## P1 - Impact of chronic alcohol consumption and withdrawal on learning strategies, hippocampal and striatal

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The hippocampus and striatum have dissociable roles in memory: while the former is necessary for spatial/declarative forms of learning, the latter is required to process procedural learning. An emerging hypothesis suggest that drug addiction could lead to a functional cognitive imbalance, which would maintain addictive behavior and support the risk of relapse by promoting habit learning while disrupting spatial memory. Here we examined, in C57BL/6J male mice, whether chronic alcohol consumption or withdrawal might modulate the use of spatial memory vs cued memory, related to hippocampal and striatal functional synaptic plasticity respectively. Mice were subjected to a 5-month chronic alcohol consumption (CAC; 12%v/v); at the end of this period, half of subjects were kept on an alcohol diet whereas the other half went through progressive withdrawal for 2 weeks. Memory was assessed using a competition protocol in the Barnes maze assessing the respective use of hippocampus vs striatum-dependent learning strategies. Concurrently, we performed in vivo electrophysiological studies in freely-moving mice to assess learning-induced synaptic plasticity in the dorsal hippocampus (CA1) and dorsolateral striatum (DLS). Our results first show that withdrawn animals, but not animals which are still consuming alcohol, are severely impaired in the retention phase of the task. Moreover, alcohol withdrawal, and also to a lesser extent CAC, promote a shift from the selection of spatial hippocampal-dependent strategy to a preferential use of non-flexible striatal-dependent cued strategies. Concurrently, we found that task-induced synaptic plasticity activity was reduced in the CA1 and increased in the DLS of withdrawn mice, and to a lesser extent, alcohol mice as compared with controls. Besides, the capacity to induce LTP was impaired in both withdrawn and CAC-treated mice. We conclude that early alcohol withdrawal and, to a lesser extent, CAC, have disrupting effects on spatial memory processes and on synaptic plasticity in the dorsal CA1 of the hippocampus, leading to the compensatory use of non-spatial, striatum-dependent learning strategies.

# P2 - Cortically-projecting hypocretin/orexin neurons of the lateral hypothalamus as a neural substrate for arousal-dependent emotion regulation

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Background

Neurons in the lateral hypothalamus (LH) expressing the neuropeptide hypocretin (Hcrt; also known as orexin) are critical for maintaining and stabilizing wakefulness and arousal states. Loss of Hcrt neurons in the LH is associated with the sleep disorder Narcolepsy-Cataplexy (NC), in which patients display episodes of normal wakefulness that are interrupted by sleep. Interestingly, NC patients opt for choices with higher immediate emotional valence (regardless of future punishment). This suggests that loss of Hcrt-LH neurons alters arousal-dependent regulation of emotions, leading individuals to compensate for reduced reactivity to emotional stimuli (Bayard et al., 2011).

The Yerkes Dodson law (YD-Law) posits that performance increases with arousal levels up to an optimum point, decreasing in hypoarousal and hyperarousal conditions (Yerkes and Dodson, 1908). However, proof of the Y-D law in the process of Emotion Regulation (ER) is missing. ER influences which emotions we have, when we have them, and how we experience and express them (Gross, 1998b). ER aims to decrease the probability of states that have negative value, or increase the probability of states that have positive value. Among the brain regions that modulate ER, the ventromedial prefrontal cortex (vmPFC) supports the valuation of a stimulus in current context, and modulates higher cognitive-behavioral functions such as Decision-Making.

Hypothesis and Objective

Here we investigated the hypothesis that arousal promoting Hcrt neurons project to the ventromedial prefrontal cortex. We sought to establish anatomical and morphological evidence of the connectivity between arousal-promoting Hcrt system on the cognition-related vmPFC system.

Materials and Methods

We used viral vectors for retrograde tracing (vmPFC AAV2retro-EF1a-DIO-mCherry) to dissect Hcrt → vmPFC circuits in Hcrt-Cre mice, mapping Hcrt synaptically-connected networks on the vmPFC.

Results and Conclusions

Hcrt-Cre mice receiving the Cre-dependent AAV2retro-mCherry virus in the vmPFC displayed mCherry+ cells throughout the LH. We used Hcrt immunostaining to identify double-labeled cells and confirm the existence of a subpopulation of vmPFC-projecting Hcrt+ neurons that comprised approximately 30-40% of the total population of Hcrt-LH neurons.

According to these findings, the HCRT system could play a role in maintaining the excitability of vmPFC neurons, supporting the high efficiency of cognitive functions.

# P3 - A bed nucleus of the stria terminalis to medial preoptic area pathway gates pup retrieval

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Elaborate maternal care is a defining characteristic of mammalian species and is underscored by highly conserved neural circuits. A prototypical maternal response in rodents is pup retrieval, whereby displaced pups are rapidly retrieved by dams back to the nest. The medial preoptic area (MPO) in the hypothalamus orchestrates diverse aspects of the maternal repertoire, and projections from the MPO to the ventral tegmental area (VTA) are necessary for enactment of maternal behaviors and maternal reward. Recent work has begun to address the neurochemical mediators within the MPOïƒ VTA pathway that drive maternal responses, but the major inputs that regulate this circuit remain undefined. Here, we demonstrate that a population of neurons in the bed nucleus of the stria terminalis (BNST) that express relaxin family peptide receptor 3 (RXFP3), the cognate receptor for the neuropeptide relaxin-3, project densely to the MPO and provide putative synaptic input onto MPOïƒ VTA projections. Further, anatomical tracing studies indicated that BNSTRXFP3 neurons are the primary RXFP3-expressing afferents to the MPO. To examine whether BNSTRXFP3ïƒ MPO projections are functionally involved in maternal responses, we injected an inhibitory retrograde Designer Receptor Exclusively Activated by Designer Drug (DREADD) (retrograde AAV-DIO-hM4Di-mCherry) (n=6) or control virus (n=6) bilaterally into the MPO of female RXFP3-Cre mice (7-8 weeks of age) to enable chemogenetic manipulation of Cre-expressing inputs to the MPO. On postnatal days 4-7, primiparous dams were tested for pup retrieval after brief separation from pups. Dams were injected with either saline or clozapine-N-oxide (CNO; 10 mg/kg, i.p.), and all pups but one were removed from the home cage. After 20 minutes of separation, five pups were placed in the corner most distant to the nest. Latency to retrieve pups and total time taken to retrieve all pups were quantified. Compared to saline injections, CNO injections significantly increased the total time taken to successfully retrieve all pups back to the nest in hM4Di-injected dams but not control virus-injected dams. Collectively, our findings highlight a neurochemically discrete BNSTïƒ MPO pathway that forms part of maternally relevant circuits and modulates pup retrieval in primiparous dams.

## P4 - Dopamine D2 Receptors modulate hippocampal theta rhythm by modifying the intrinsic excitability of interneurons in mice

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Inhibitory interneurons entrain excitatory principal neurons to orchestrate information processing in the hippocampus and are instrumental in generating hippocampal oscillations. Spikes of different interneurons were found to lock to different phases of particular band oscillation to exert distinct and coordinated functions. Recent evidence suggest that dopamine facilitates the encoding of novel spatial memories by the hippocampus. By acting through D2 receptors (D2R), dopamine modulates the power of theta hippocampal oscillations (6-14Hz) by impairing the onset of rapid-eye-movement (REM) sleep which is important for mnemonic processes. However, the identity of the hippocampal D2R neurons through which dopamine acts on, to alter hippocampal rhythms, remains unknown. In this work, we used fluorescent in situ hybridization (RNAscope) to build a map of D2R-expressing hippocampal neurons. Our preliminary data indicated that in addition of hilar mossy cells, Drd2 mRNAs were preferentially found both PV- and SOM-positive neurons located in the stratum oriens of the CA3/CA1 subfields of the dorsal hippocampus. Using electrophysiological recordings of CA3 pyramidal cells in organotypic slices, we observed that the application of D2R agonist quinpirole (10 min, 10µM) in presence of methacholine (muscarinic agonist, 50 nM) increases the number of oscillation periods. To go further in the mechanism of how D2Rs alter hippocampal theta rhythms, we next examined the intrinsic excitability of D2R-expressing cells in CA3 hippocampal slices. Our first data suggest that pharmacological D2R activation alters the excitability of specific types of hippocampal interneurons, by increasing the frequency of action potential firing of regular-spiking interneurons (<30Hz) and decreasing the action potential firing of fast-spiking interneurons (>30Hz). The precise identification of these two populations of interneurons is critical to better understand the cellular mechanisms by which dopamine acts on the hippocampal circuitry to enable information processing.

## P5 - Cannabinoid type-1 receptors on GABAergic neurons are necessary and sufficient for running motivation

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The lack of intrinsic motivation to engage in, and adhere to, physical exercise has major health consequences. However, the neurobiological bases of exercise motivation are still unknown. Using wheel-running as an animal model of voluntary exercise, we have proposed that the latter is under tonic control by the endocannabinoid system (Dubreucq et al., Biol. Psychiatry 2013). However, because the analysis of wheel-running performance is by no means an index of motivation for running, we have developed an operant conditioning paradigm wherein mice have to nose poke to unlock temporarily a running wheel, doing so under fixed ratio (FR) and progressive ratio (PR) reinforcement schedules. Using pharmacological tools for the main cannabinoid receptor in the brain, namely the cannabinoid type-1 (CB1) receptor, we show that the acute blockade of CB1 receptors decreases running motivation, as assessed during PR sessions. This observation extended to mice bearing either a global deletion of CB1 receptors or a selective deletion of CB1 receptors from GABAergic neurons. Conversely, the inhibitory impacts of these deletions on PR performances were not associated with intrinsic wheel-running performances, as indicated by the ratio of the time spent running per rewarded running sequence. As opposed to the tonic role exerted by CB1 receptors on GABAergic neurons on running motivation, the deletion of CB1 receptors from cortical glutamatergic neurons proved inefficient on running motivation but increased the running duration per rewarded sequence. In keeping with the aforementioned evidence for CB1 receptors on GABAergic neurons playing a necessary role on running motivation, we next explored whether such a receptor subpopulation also plays a sufficient role. We thus used mutant mice in which CB1 receptors were silenced throughout and compared these animals to mice in which we specifically reexpressed these receptors in GABAergic neurons. The inhibitory impact of CB1 receptor silencing on running motivation was prevented by the reexpression of CB1 receptors in GABAergic neurons, hence indicating that this receptor population plays a necessary and sufficient role on running motivation (Muguruza et al., J. Clin. Invest. Insight, 2019).

## P6 - Modulation and roles of dopamine and glutamate receptor heteromers in cocaine-evoked adaptations

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Drugs of abuse hijack the natural reward by increasing dopamine (DA) in the mesolimbic system, especially in the striatum, where it shapes the efficacy of glutamatergic synapses and contributes to long-lasting behavioral alterations. This integration of DA and Glutamate (Glu) inputs is achieved by striatal projection neurons (SPN), which form two mainly segregated populations: the “direct pathway” SPN (dSPN), expressing DA D1 receptors (D1R) that promotes reward, and the “indirect pathway” SPN (iSPN) that express DA D2 receptors (D2R) that inhibits reinforcement. We identified heteromers formed by the D1R with Glu NMDA (NMDAR) receptors as molecular bridges by which DA facilitate Glu-dependent synaptic transmission in dSPN. Conversely, others found that the D2R/NMDAR interaction mediates the inhibitory effect of DA on NMDAR-signaling in iSPN. However, the modulation and function of these heteromers in responses to cocaine are yet unknown. Using Proximity Ligation Assay, we found that cocaine-induced locomotor sensitization was associated with the formation D1R/NMDAR heteromers in the Nucleus Accumbens (NAcc) and the Dorsal Striatum, while D2R/GluN2B heteromerization was restricted to the NAcc. We also detected DAR/NMDAR complexes from human-post mortem caudate-putamen samples and describe their modulations in subjects with a history of dependence to psychostimulants. To identify the roles of DAR/NMDAR in the different phases of cocaine-mediated molecular, morphological and behavioral responses in vivo, we designed a viral-based approach to disrupt DAR/NMDAR heteromers in a time-controlled manner owing to a doxycycline-dependent promoter. We found that the disruption of the D1R/NMDAR interaction in the NAc blocks cocaine-induced ERK activation and abrogates the development of both psychomotor sensitization and cocaine conditioned place preference (CPP), whereas the blockade of D2R/NMDAR interaction interferes with the maintenance of psychomotor sensitization and cocaine CPP. This work identifies DAR/NMDAR heteromers as molecular targets with a therapeutic potential not only in addiction abut also for the numerous psychiatric disorders associated with an imbalance of DA and Glu transmission.

## P7 - Respective roles of the distinct populations of Medium Spiny Neurons of the Nucleus Accumbens in reward processing

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The nucleus accumbens (NAc) is a major structure that plays a key role in action selection and execution as well as reward processing and reward-dependent learning. It is largely composed of GABAergic Medium Spiny Neurons (MSN) that are divided into two distinct subpopulations, those expressing the dopamine D1 receptor (D1R; dMSNs), and those expressing the D2 receptor (D2R; iMSNs). Based on the model of the dorsal striatum, it has been proposed that dMSNs and iMSNs of the NAc play antagonistic effects on reward processing, but their respective roles are still largely debated (Carvalho Poyraz et al. 2016; Soares-Cunha et al. 2016). Herein, we aimed at deeper exploring the implication of these two populations of MSNs of the NAc core on various components of reward processing. Using operant conditioning tasks and pharmacogenetic approaches we show that activation of iMSNs decreases motivation to obtain a food reward but increases food consumption, while inhibition had the opposite effect, with no impact on hedonic reactivity. Interestingly, in vivo electrophysiology experiments in anesthetized animals revealed that the increased iMSN excitability boosts the activity of dopaminergic VTA neurons. Surprisingly, we observed that both inhibition and activation of dMSNs led to a decrease in performance in motivational tasks, likely related to a strong modulation of consummatory processes. Our data shed light on the complex function of dMSNs and iMSNs of the NAc core in reward processing and highlight differential effects on consummatory vs. motivational processes.

## P8 - Structural plasticity of glutamatergic synapses and dopaminergic boutons in the Nucleus Accumbens upon cocaine administration

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Neural correlates of reward-driven learning and addiction include functional and structural synaptic plasticity. So far, studies of structural plasticity in medium spiny neurons have restricted their analysis to the increase of dendritic spine density. We have developed techniques for imaging of both dendritic spines and glutamatergic and dopaminergic boutons, as well as methods for 3D automated analysis of spatial organization of spines and boutons. This allowed us to describe the patterns and rules of glutamatergic synaptogenesis and to reveal changes in dopaminergic boutons density upon cocaine administration. Furthermore, we demonstrate structural meta-plasticity occurs in D1-expressing medium spiny neurons. Finally, we have unraveled distinct signaling events for spine growth and stabilization in D1DR-expressing neurons. We have shown in time-lapse imaging that spine growth is controlled by ERK independently of transcription and translation, while stabilization of the new spines is controlled by ERK-induced MNK-1 and protein synthesis in a transcription-independent manner.

# P9 - The involvement of the insular cortex on frustration stress-induced binge eating in female mice

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Overeating of highly palatable food is a major contributing factor to obesity and related health complications. For women in particular, stress, frustration, and anxiety, have been shown to strongly influence eating behavior and bingeing episodes. Despite this knowledge, there is a paucity of research investigating the neurobiology underlying emotional and stress related bingeing, particularly in female subjects. The aim of this study was to investigate the involvement of the insular cortex in binge eating behavior, in a model of frustration stress-induced bingeing. Female vGlut2-Cre positive mice (n=16) underwent a frustration stress-induced bingeing protocol which consisted in 16 days in total, divided by two cycles of 8 days each. Half animals were subjected to frustration stress (n=8) and the other half were not (n=8). All mice were given intermittent access, on days 4 and 5 of cycle 1 (days 1-8) and 14 and 15 on cycle 2 (days 9-16) (2h per day) to a highly palatable food reward. The stress group was subjected to a frustration stress on the last day of each cycle where the mouse could smell and see the highly palatable food but could not consume it for 15 minutes. After 15 minutes the food was made available and animals were allowed to consume it. 90 minutes after the stress, animals were perfused for Fos protein immunohistochemistry. A 2nd cohort of female Vglut2-Cre animals received stereotaxic injections of a calcium indicator (AAV9.Syn.Flex.GCaMP6m.WPRE.SV40, n=3) and fibre optic implant into the insular cortex for fiber photometry calcium imaging. After sufficient time to allow for viral expression (21 days), all mice were submitted to the same frustration stress protocol described above. Stressed mice ate significantly more palatable food when compared to control mice during the first 15 minutes following stress ($p<0.005$). Fos immunohistochemistry results showed a high percentage of double labelling of Vglut2-Cre+ and Fos+ neurons, suggesting the involvement of this neuronal population in this type of bingeing behavior. Furthermore, to support Fos protein results, fiber photometry recordings demonstrated high levels of activity in the insula cortex during the frustration stress, and bingeing behavior. Collectively these data provide insight into the involvement of the insular cortex in bingeing behavior after a frustration stress.

## P10 - Natural modulations of decision-making: dopamine beyond reward effects within the basal ganglia

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Midbrain dopamine (mDA) is often viewed as a brain signal for informing prediction error. This reward-based evaluation however only takes into account phasic variations in mDA, leaving behind any functional effect from basal or tonic mDA neural activity. Phasic mDA variations determine the magnitude and direction of plasticity in corticostriatal synapses through positive reinforcement processes. This reinforcement changes lead to competitive interactions at cortico-basal ganglia circuits, compounding an essential process that shapes action-selection to maximize expected rewards. As reinforcement learning (RL) in artificial intelligence has a well-described mathematical framework, functional descriptions of mDA neurons are usually modeled as artificial prediction error following an RL architecture, which then modifies corticostriatal synaptic connections. These models have proven capable of producing stimulus-action, action-reward, and stimulus-reward associations, in coherence with reports showing that DA effects on corticostriatal connections are necessary for these associations. Concerning the tonic activity in mDA neurons, recent works have associated its level with the exploration/exploitation ratio of a performing agent (i.e., how much the animal selects an option known as worst, evaluating changes in contingency).
How tonic mDA can regulate the exploration/exploitation ratio in a decision-making task when the contingency between actions and their reward outcome vary? What is the interplay between tonic and phasic mDA in the striatum and how do these two components of DA delivery contribute locally to neuronal dynamics? These open questions are crucial both for understanding the physiological mechanisms underlying reward-driven learning and for improving artificial agent performing complex decision making tasks. To answer these questions, we propose a single theoretical framework describing how mDA neurons affect striatal and BG dynamics through both tonic and phasic delivery, and how tonic dopamine can drive significant changes in the exploration ratio.
By taking known neurophysiological effects mDA neuronal activity in the corticostriatal connections, this work comprises a mathematical description of mDA neurons following a firing rate model. The proposal is an extension of a well-described model with four parallel cortico-basal ganglia circuits, integrating the direct and hyper-direct loop in each circuit, executing two (cognitive and motor) decisions. The model combines in a single neural dopaminergic population with tonic and phasic effects, generating long-term depression, long-term potentiation, and online variations in corticostriatal connections,. We show that changes in tonic mDA is sufficient to regulate the exploration/exploitation ratio when confronted to a reversal in the reinforcement contingencies of the task.

## P11 - Implication of nuclear calcium signaling in cocaine-evoked adaptations

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Addiction is a form of pathological memory in which mechanisms engaged in normal learning and memory processes are “highjacked” by exposure to drugs of abuse. These pathologic memories are robust, long-lasting and require changes in gene expression in specific neuronal populations. Drugs of abuse modify the reward system by increasing dopamine (DA) in the mesolimbic system, especially in the striatum, resulting in alterations of glutamate (Glu) transmission-dependent plasticity. The integration of DA and Glu inputs in the striatum is achieved by striatal projection neurons (SPN), which comprise two distinct populations: the “direct pathway” (dSPN), expressing DA D1 receptors (D1R) and promoting reward processes, and the “indirect pathway” (iSPN) that express DA D2 receptors (D2R) and inhibits reinforcement. The team showed that the interaction of D1R with Glu NMDA receptors (NMDAR) controls some cocaine-evoked alterations. We showed that the disruption of D1R/NMDAR heteromers, which alters cocaine-induced long-term behavioral responses, also impacts on calcium influx towards the nucleus. Nuclear calcium (nucl-Ca2+) signaling is a key route linking neuronal activity to gene transcription in multiple models of long-lasting neuroadaptation, but its role in addiction is unknown. This project aims at unravelling the dynamics and functions of nucl-Ca2+ signaling in dSPN and iSPN in cocaine-mediated molecular, cellular and behavioral adaptations. By using an ex-vivo model of cocaine exposure, nucl-Ca2+ dynamics was studied by two-photon imaging on acute striatal slices owing to viruses expressing the Ca2+ indicator GCaMP3 fused to a nuclear localization signal either in dSPN or iSPN. To study the roles of nucl-Ca2+ signaling in dSPN and iSPN, we used a viral-based approach to achieve a cell type-specific expression of nucl-Ca2+ blockers. This will allow us characterize the specific implication of nucl-Ca2+ signaling in dSPN and iSPN on cocaine-evoked transcriptional, morphological and behavioral alterations.

# P12 - Reinforcing values of exercise and feeding examined in stressed adolescent male and female mice

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Anorexia nervosa (AN), mostly observed in female adolescents, is the most fatal mental illness. Its core is a motivational imbalance between exercise and feeding in favor of the former. The most privileged animal model of AN is the activity-based anorexia (ABA) model wherein partly starved rodents housed with running wheels exercise at the expense of feeding. However, the ABA model bears face and construct validity limits, including its inability to specifically assess running motivation and feeding motivation. As infant/adolescent trauma is a precipitating factor in AN, this study first analyzed post-weaning isolation rearing (PWIR) impacts on body weights and wheel-running performances in female mice exposed to an ABA protocol. Next, we studied through operant conditioning protocols i) whether food restriction affects in a sex-dependent manner running motivation before ii) investigating how PWIR and sex affect running and feeding drives under ad libitum fed conditions and food restriction. Besides amplifying ABA-elicited body weight reductions, PWIR stimulated wheel-running activities in anticipation of feeding in female mice, suggesting increased running motivation. To confirm this hypothesis, we used a cued-reward motivated instrumental task wherein wheel-running was conditioned by prior nose poke responses. It was first observed that food restriction increased running motivation in male, but not female, mice. When fed grouped and PWIR mice were tested for their running and palatable feeding drives, all mice, excepted PWIR males, displayed increased nose poke responses for running over feeding. This was true when rewards were proposed alone or within a concurrent test. The increased preference for running over feeding in fed females did not extend to running performances (time, distance) during each rewarded sequence, confirming that motivation for, and performance during, running are independent entities. With food restriction, mice displayed a sex-independent increase in their preference for feeding over running in both group-housed and PWIR conditions. This study shows that the ABA model does not specifically capture running and feeding drives, i.e. components known to be affected in AN.

**References**

Hurel I, Redon B, Scocard A, Malezieux M, Marsicano G and Chaouloff F (2019) Beyond the Activity-Based Anorexia Model: Reinforcing Values of Exercise and Feeding Examined in Stressed Adolescent Male and Female Mice.Front. Pharmacol.

# P13 - Control of nicotine consumption by β4-containing nicotinic receptors of the interpeduncular nucleus neurons

**Mondoloni S**, Nguyen C, Durand-de Cuttoli E, Torquet N, Marti F, Faure P, Mourot A

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Nicotine, the main active component of tobacco, mediates both rewarding and aversive effects in mammalian brains. Nicotine binds to nicotinic acetylcholine receptors (nAChRs) which are ligand-gated cation channels. In the brain, different α (α2-10) and β (β2-4) nicotinic subunits co-assemble into pentameters of various combinations, resulting in a high diversity of neuronal nAChRs with variable localization and function. Dopamine neurons of the ventral tegmental area are enriched with β2-containing (β2*) nAChRs and are implicated in nicotine reinforcement (1,2), whereas neurons of the habenulo-interpeduncular (MHb-IPN) tract instead express β4* nAChRs at high levels, and this pathway has been implicated in the aversive effects of nicotine (3). The dichotomy between reinforcement and aversion is often ascribed to the dose of nicotine, with low and high doses mediating rewarding and aversive effects respectively. However, how acute and chronic nicotine affects neuronal activity in the IPN, and how this translates to aversion (and thereby control of consumption) is not known.

We first assessed how WT and transgenic β4-/- mice consume nicotine in a two-bottle drinking task, in which nicotine concentration gradually increases from 10 to 200 ug/ml. We found that WT mice titer their consumption to reach on average a daily dose of 10mg/kg. Interestingly, we observed significant inter-individual differences in how WT mice consumed nicotine, with some individuals actively drinking nicotine and others avoiding it. In contrast, β4-/- mice consumed much higher levels of nicotine, especially for high nicotine concentrations, and showed much fewer inter-individual differences. To implicate β4* nAChRs of the IPN in this difference in behavior, we then re-expressed β4 selectively in the IPN using a lentiviral strategy. Preliminary experiments show that these mice consume nicotine at WT level, strongly pointing toward a role of β4* nAChRs of the IPN in regulating nicotine consumption. To get molecular insight into this behavioral difference, we then recorded the amplitude of nicotine-evoked currents (Inic) in IPN neurons in these mice. We found that on average Inic was much larger in WT than in β4-/- mice. In addition, we observed an inverted correlation between nicotine consumption and Inic in WT animals: mice that consumed high levels of nicotine had smaller responses in the IPN. Our results suggest that β4* nAChRs of the IPN could play a role in mediating the aversive properties of nicotine, and thereby in the control of nicotine consumption. We then used passive nicotine treatment with implanted minipumps to assess how chronic nicotine affects the expression level of nAChRs in the IPN. We found that chronic nicotine induces a decrease of functional β4*nAChR in IPN neurons in WT animals. Together, our results suggest that chronic nicotine consumption alters the expression of β4*nAChRs in the IPN, diminishing the response of these neurons to nicotine, and possibly weakening the aversive effects of the drug. Overall, our results indicate β4*nAChR in IPN neurons are important drug targets for smoking cessation therapies.

**References**

Maskos et al., Nature. 2005 ;436(7047):103-7.
Durand-de Cuttoli et al., Elife. 2018 ;7. pii: e37487.
Antolin-Fontes Neuropharmacology. 2015;96(Pt B):213-22.

## P14 - Impact of n-3 PUFA deficiency on executive control: likely implication of cortical dopaminoceptive signal

**Contini A**, Arrondeau C, Walle R, De Smedt-Peyrusse V, Coutureau E, Ferreira G, Ducrocq F, Trifilieff P

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In the last decades, a series of clinical studies have highlighted a link between a deficit in the levels of n-3 long chain polyunsaturated fatty acids and some psychiatric conditions such as schizophrenia and bipolar disorder. However, preclinical studies providing mechanistic evidence on the origin of this link are lacking, and whether or not n-3 PUFA deficiency is directly implicated in the symptomatology of these disorders is at present still unknown.
Among the main symptoms that characterize the aforementioned disorders, cognitive dysfunctions are the most predictive of relapse and therapy discontinuation, and are often associated to lower functional outcome. From a neurobiological point of view, a reduced tone of dopaminergic signal in cortical regions is thought to be a critical determinant for the maturation of these symptoms.
In order to evaluate whether a reduced accrual of n-3 PUFAs could be involved in the etiology of psychiatric endophenotypes, we employed a developmental mouse model of n-3 PUFA deficiency and assessed the effect on various neurochemical and behavioral parameters. We found that decreasing n-3 PUFA biostatus across development leads to reduced dopamine release capacity in the medial prefrontal cortex that correlates with a perturbation in the ability of mice to display goal-directed actions, which is indicative of maladaptive behavior and poor executive control.
In order to further investigate the role of cortical dopaminergic transmission in executive functions, we employed a chemogenetic approach to selectively manipulate the activity of the two main populations of cortical dopaminoceptive neurons during a sensory-specific outcome devaluation task. We found that lowering the activity of either dopamine D1 or D2 receptor-expressing neurons impairs the ability of mice to emit goal-directed actions.
Altogether these findings suggest that n-3 PUFA deficiency could lead to impaired executive functions through a perturbation of dopamine transmission in the prefrontal cortex and support its causal implication in the symptomatology of psychiatric symptoms.

## P15 - Dynamics of the midbrain dopaminergic activity during early et protracted abstinence from cocaine self-administration

**Salin A**, Lardeux V, Solinas M, Belujon P

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The chronic relapsing nature of cocaine addiction suggests that chronic cocaine exposure produces persistent neuroadaptations in several brain areas, notably the dopaminergic system, a main actor in motivated behaviors and relapse to addiction. The dynamic neuroadaptations that occur during abstinence are associated with changes in behavior and emotional state. For example, early cocaine abstinence is characterized by a negative emotional state whereas with extended abstinence, the sensibility to drug-associated cues increases (incubation of craving). A recent PET-imaging study by our group (Nicolas et al., 2017) has shown that, during abstinence, the metabolic activity changes dynamically in dopaminergic target structures, with the nucleus accumbens showing changes after one week and the dorsal striatum after one month of abstinence. However, because of the low spatial resolution of PET, distinguishing specific metabolic changes in origin of these dopaminergic projections, the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc), was not possible. Thus, here we used in vivo electrophysiological extracellular recordings to investigate the time- and region-specific changes in the activity of VTA and SNc dopaminergic neurons after short and long-time abstinence.

Sprague Dawley male rats had either an extended access to cocaine (Long-Access group (LgA); 6h/session) or a recreational cocaine use (Short-Access group (ShA); 1h/session) for 25 sessions. We then recorded spontaneously active VTA and SNc DA neurons during early (D7) and late (D30) abstinence, in isoflurane anesthetized rats.

No change in DA neuron population activity was found in ShA rats in the midbrain (VTA or SNc) at any time of abstinence. In contrast, a significant decrease in the number of spontaneously active VTA DA neurons of LgA rats was found after 7 days and 28 days of abstinence. After 7 days of abstinence we also found a significant decrease in the bursting activity of VTA DA neurons of LgA but this effect did not persist after 28 days. In the SNc of LgA rats, we found a significant increase in the firing rate of DA neurons during early abstinence but no significant change was found in all three parameters of DA activity during late abstinence. These results demonstrate that dopaminergic activity state is altered only in rats with excessive cocaine self-administration. These alterations were time- and region-specific. During early abstinence, a negative state could be mediated by both a decrease in VTA DA activity and possibly a decreased signal-to-noise ratio in SNc DA neurons target structures. Interestingly, we found no change in SNc activity after prolonged abstinence, but a persistent decrease in VTA activity suggesting that alterations in the activity of this region may play a role in the persistence of cocaine craving.

# P16 - Differences in nucleus accumbens transcriptome are associated with high motivation for palatable reward in mice exposed to early-life stress

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Background
Early life adversity exerts long-lasting effects on physiological functions and vulnerability to psychiatric diseases in particular depression and anxiety disorders. Recent studies also suggest higher vulnerability to eating disorders in subjects exposed to childhood adversity. Maternal separation in rodents leads to an exaggerated hypothalamic-pituitary-adrenal axis response to stress and impairs emotional behaviors in adult offspring. In contrast, the impact of early-life stress (ELS) on food motivation in rodent remains poorly characterized.

Methods
C3H/HeN pups were submitted to ELS procedure consisting in chronic maternal separation (3h per day, from PND2 to PND14) combined with chronic unpredictable stress in dams during separation. Body weight growth was assessed during development and motivation for palatable food was investigated using operant conditioning paradigm at adulthood. Brain changes associated with ELS were studied by transcriptomic analysis (Agilent Sureprint G3 Mouse microarrays) followed by Opossum and Ingenuity Pathway Analysis (IPA) in the hypothalamus, the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC), three brain areas involved in stress and reward processes.

Results
ELS reduced body weight in dams and offspring until adulthood. ELS increased basal plasma corticosterone levels at the beginning of the dark phase. In the operant task, ELS did not affect training performances in the fixed-ratio 1, but the number of lever presses was significantly higher in ELS mice when the effort to obtain the palatable reward was increased in variable ratio 20. The number of lever presses was also increased in ELS mice in comparison to controls during the progressive ratio procedure. Microarrays study revealed that ELS drastically modifies the transcriptional profile specifically in the NAc (375 genes), without significant impact in the mPFC or the hypothalamus. Opossum analysis showed that transcription factors regulated by ELS in NAc are associated with stress, inflammation, and metabolism. IPA revealed GABA receptor signaling and Corticotropin releasing Hormone signaling as top canonical pathways.

Conclusion
ELS in mice exacerbates motivation for palatable food and alters gene expression into the NAc which is one of the main structure involved in reward processes. Further studies are needed to determine the role of these transcriptional changes on behavioral alterations reported after ELS.

## P17 - Opposite effects of nicotine on distinct dopamine neurons: a specific role for VTA-amygdala pathway

**Nguyen C**, Mondoloni S, Centeno Lemaire I, Tolu S, Durand-de Cuttoli R, Dalkara D, Pons S, Maskos U, Mourot A, Faure P, Marti F

*Neuroscience Paris Seine – IBPS, Paris, France*

The ventral tegmental area (VTA), in the core of the mesocorticolimbic system, is involved in many functions such as motivation, decision-making, motor control and reinforcement. Dysfunction at the level of this system have been link to many diseases such as schizophrenia, ADHD, hyperactivity and typically addiction. Drugs like nicotine acts accessing the same mechanism as reinforcement learning, that leads to an overvaluation of the drug reward at the expense of other natural rewards.
Nicotine, the main psychoactive compound of tobacco, binds nicotinic acetylcholine receptors (nAChR) that are cation permeable ligand-gated ions channels composed of five subunits organized in homopentameres Î± or heteropentameres Î±/Î². When nicotine binds Î²2 containing nAChRs on VTA dopaminergic neurons, it increases their firing rate which triggers a higher release of dopamine in the targeted structures, promoting rewarding effect and nicotine reinforcement (Tolu et al. 2013).
Beside reward properties, nicotine has also been reported to produce aversive or anxiogenic effect. Contrasting with the classical view that DA neurons are all activated by addictive drugs, we reported here that a large population of dopaminergic (DA) neurons located in the medial part of the VTA are inhibited by nicotine. Combining in vivo recordings with retrograde tracers (retrobeads), we investigated the projection-dependent activation/inhibition profiles of DA cells in response to nicotine. We demonstrate that NAc-projecting neurons are exclusively activated by nicotine, that AMg-projecting neurons are mostly inhibited neurons. To understand the functions of those two DA pathways in reinforcement, we used optogenetic tools in the elevated O-maze and a real time place preference paradigm to demonstrate that inhibition of AMg-projecting DA neurons mediate both aversive and anxiogenic effects similar to those observed with nicotine. Finally we used targeted Î²2 nAChRs re-expression determine if the inhibition of DA cell promote the anxiogenic effect of nicotine.

# Name index

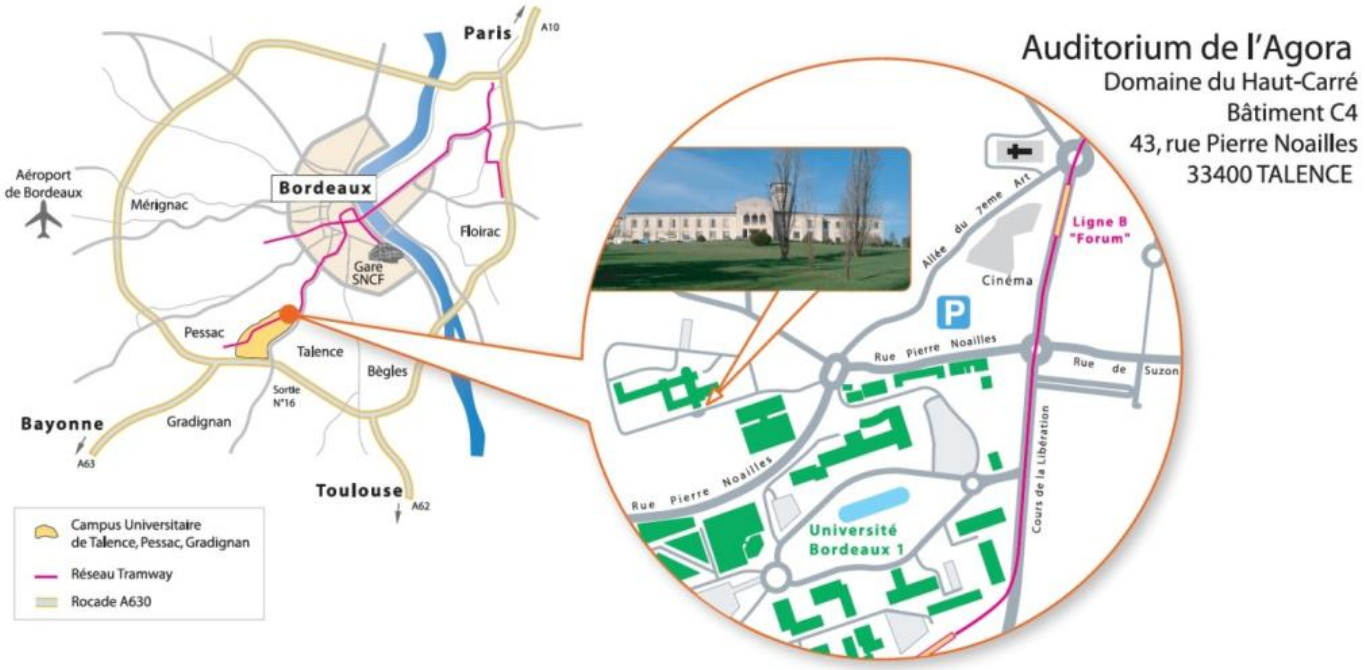
# Practical information

## Where and when

The conference will take place
**from 2 to 4 October 2019**

**Venue:**
Espace AGORA - Domaine du **Haut Carré**
Campus de l'Université de Bordeaux
43 rue Pierre Noailles, TALENCE

Agora du Haut-Carré is an unusual setting, being housed in a former convent built in the 1950's. It is located in the southwest of the city on the Bordeaux University campus, it has a direct access to Bordeaux city center by the tramway in less than 20 minutes.




**Tramway station : « Forum » (line B)**

**GPS:** 44.810012 / -0.59645

**Location on Google map:** https://goo.gl/maps/82hP19V8fLnBctbW7

# Registration

We will be waiting for you at the Haut-Carré from 8:30.

# Luggage

VIGIPIRATE safety instructions strongly recommend to the participants to avoid to come with their luggage. Exceptionally, the bags could be left at the front desk after being screened.

# Wi-Fi

Wi-Fi will be available at the Haut-Carré. Instructions will be given during the event.
Access through Eduroam will be possible.

# Presentations

A laptop will be available for your presentation, with PDF and PPT software.

For safety, you can send us your presentation by email.

You can come with your own laptop. HDMI and VGA connections will be available.

Several type of connection devices will be available.

# Coffee and lunch

A welcome coffee will be served between 8:30 and 9:00 every morning.

Coffee, tea and refreshments will be available during morning and afternoon breaks.

Lunches will be taken at the conference venue.

A lunch box will be given on Friday.

# Gala dinner

**Thursday, October 3rd / 7:30PM - 11PM**

only for participants registered to the gala dinner

**Château Luchey-Halde** is located in the heart of Bordeaux, in the prestigious Pessac-Léognan appellation, and benefits from an exceptional terroir.

It is constituted of several ridges which contain gravel, pebbles and fine soil deposited by the Garonne River and its tributaries between the end of the Tertiary and the beginning of the Quaternary periods. It is a poor but well-drained soil perfectly adapted to winegrowing in the oceanic climate of Bordeaux.

The gala dinner includes a visit of the cellar.

www.luchey-halde.com

## How to get there?

**A shuttle will be arranged from hotels to gala dinner.**

**If you want to go by yourself:**

**- By tram:** line A – Stop: "Fontaine d'Arlac" stop (10 min by walking)

**- By taxi:** address is "7 avenue du Maréchal Joffre – Mérignac»

# Organization

## Scientific committee

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