

## **Title of the special issue: “Addiction: a neurobiological and cognitive brain disorder”**

### **Editorial**

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Addiction is now recognized as a chronic neurobiological and cognitive brain disorder and is generally viewed as a switch from recreational to compulsive substance use despite aversive effects. However, addiction also emerges following misuse and/or abuse of prescription drugs after an initial therapeutic use or in patients that self-medicate. The latter aspect is at the root of the current opioid crisis that strikes North America but is also observed worldwide.

One of the major issues associated with addiction is the high prevalence of relapse that may persist for a lifetime. Several factors contribute to both the development of this brain disease and the susceptibility to relapse. They include sociocultural, psychological, genetic and neurobiological aspects, the balance of which varies depending on the substance of abuse. In the recent years, efforts have been made to develop a translational approach in which preclinical research on rodent models would benefit to human prophylaxis and therapy. Also, the concept of addiction has been enlarged to encompass addiction to behavioural patterns such as gambling or food.

A meeting entitled « **Addiction: a neurobiological and cognitive brain disorder** » has been organized in Europe, within the scope and with the financial support of the international Neurex network, the most important European network in the field of neuroscience (<http://www.neurex.org>) (Strasbourg, March 28-29, 2017). During two days,

scientists from United Kingdom, France, Italy, Belgium, and Germany gathered at the Forum de la Faculté de Médecine de Strasbourg to propose a translational perspective from molecular determinants to integrated aspects of addiction that included both preclinical and clinical data. The topics highlighted the alterations taking place during the development of addictive behaviours, their persistence in the abstinent state and their contribution to relapse.

This special issue of *Neuroscience & Biobehavioral Reviews* entitled “Addiction: a neurobiological and cognitive brain disorder” elaborates on the various aspects covered during the meeting but is also enriched with contributions of highly renowned specialists from North America. A large part of its content is devoted to brain plasticity and neurobiological substrates critically involved in addictive behaviours through a translational perspective. Several contributions detail the effect of drugs of abuse on neuronal plasticity, at the molecular or cellular level, in preclinical studies. Among critical players, this issue focuses on three main actors: the dopaminergic, opioid and endocannabinoid systems. All three are direct molecular targets of substance of abuse namely cocaine and psychostimulants for the dopaminergic system, cannabis and derivatives for the endocannabinoid system and opiates for the opioid system. The latter also constitutes a molecular gateway for most other drugs of abuse including alcohol, THC or nicotine. In addition, the dopaminergic system is central to the anticipation process common to all types of reward. More recently, opioid and endocannabinoid systems have both attracted renewed attention as they get activated by natural rewards such as food, sex or physical exercise that lead to endogenous opioid peptides or endocannabinoids release. *Hansson et al* illustrate a highly dynamic regulation of the reward system (dopaminergic and opioid) during alcohol abstinence using positron emission tomography (PET) and binding assays in preclinical studies and extend their review on human data. *Chaouloff et al* address the role of the endocannabinoid system in motivational behaviour, with a focus on running motivation. *Marie et al* focus on adaptations to opioid and psychostimulant treatments and point to critical pharmacodynamic issues in rodent models. *Karila et al* present an analysis of new synthetic opiates found on the market and the lack of knowledge on their mode of action having large consequences on health issues. *Comer & Cahill* centre their review on a new illicitly manufactured powerful opiate, Fentanyl, highlight the addictive power of such compounds and discuss whether any current treatment is efficient for fighting such effects. Moreover, beside neurotransmitter cross-talks at system and cellular levels, novel concepts are emerging that propose additional interactions at molecular level through direct physical interaction between receptors. *Derouiche & Massotte* review our

current understanding of the functional impact resulting from such novel molecular entity. In addition, modulations at the chromatin level appear as strong actors of plastic changes occurring in addiction. Two contributions address such epigenetic adaptations in rodent models following treatments with all drugs of abuse (*De Sa Nogueira et al*) and in alcohol-related animal research and human alcohol addicts (*Pucci et al*). The latter contribution specifically concentrated on stress effects because this environmental factor strongly impacts all three stages of the addiction cycle (intoxication/withdrawal/craving), exposing the animal to an emotional state as specifically discussed by *Koob & Schulkin*.

Cognitive factors such as impulsivity, or loss of inhibitory controls, have recently been recognized as major key players in the vulnerability to addictive behaviours and susceptibility to relapse. This important aspect is addressed by *Paasche et al* within the context of time and is also examined on the emotional point of view by *Hermann & Duka*, with a focus on alcohol consumption. Among other factors, circadian rhythms recently attracted strong interest as illustrated by the discussion from *Mendoza* concerning its impact on addictive-like eating behaviours. Alteration of the habenular activity has also been proposed as a major factor contributing to the loss of control over the use of drugs of abuse and the emergence of compulsive drug seeking behaviors and the specific role of this hub brain structure involved in reward and aversion behaviors is reviewed by *Mathis & Kenny*.

As stated earlier, in-depth knowledge of the changes underlying the different stages of addiction, and in particular cognitive deficits that may arise, is pivotal for developing novel prophylactic and therapeutic strategies. Three contributions propose reviews on therapeutic approaches with a cognitive focus. *Campanella et al* concentrate on new research avenues to implement event-related potentials (ERPs) in the management of alcohol disorders in humans, where the main problem for clinicians lies with the prevention of relapse. *Luquiens et al* discuss the matter of associating, in humans, cognitive training, identified as self-control network training, with other strategies, particularly those enhancing self-control. Finally, *Sampedro-Piquero et al* include a comprehensive perspective on recent studies at the pre-clinical and clinical levels, and propose cognitive stimulation, either by formal cognitive training or non-drug related environmental experiences, as a therapeutic perspective in drug addiction.

Finally, appropriate preclinical models are instrumental to study addiction. Three contributions are addressing this fundamental aspect by examining the development of animal models of binge drinking by *Jeanblanc et al*, discussing the importance of adopting a

dimensional framework based on domains of function by *Lamontagne & Olmstead*, and proposing the retina as a relevant site to investigate brain neurotransmission anomalies in cannabis users by *Schwitzer et al.*

As a whole, this special issue highlights our current view on cognitive and pharmacological clinical strategies and integrates the translational value of the knowledge gathered from preclinical models that directly shapes therapeutic approaches.

As guest-editors of the current issue, we would like to warmly thank all authors who made this adventure possible. We would also like to thank Dr Laviola for supporting this idea and more specifically the reviewers who participated in a great improvement of the final reviews proposed in this issue. Also, our deep greetings go to Ms Pascale Piguet and Stephanie Klipfel from Neurex who were incomparable in providing support and logistic for our meeting.

## **Contributors**

- Hansson AC et al. Dopamine and opioid systems adaptation in alcoholism revisited: Convergent evidence from PET and post-mortem studies.
- Chaouloff F et al. Exercise motivation: the key role for the endocannabinoid system
- Marie N et al. Role of pharmacokinetic and pharmacodynamic parameters in neuroadaptations induced by drugs of abuse with a focus on opioids and psychostimulants.
- Karila K et al. New Synthetic Opioids: Part of a new addiction landscape
- Comer S & Cahill C. Fentanyl and Structurally Related Compounds: Preclinical and Clinical Pharmacology?
- Derouiche L & Massotte D. G protein-coupled receptor heteromers are key players in substance use disorder
- De Sa Nogueira D et al. Neuroepigenetic and addictive behaviors: where do we stand?
- Pucci M et al. Environmental stressors and alcoholism development: focus on molecular targets and their epigenetic regulation
- Koob GF & Schulkin J. Addiction and stress: An allostatic view
- Mendoza J. Food intake and addictive-like eating behaviors: Time to think about the circadian clock(s)"
- Mathis V & Kenny P. From controlled to compulsive drug-taking: the role of the habenula in addiction

- Paasche C et al. Impulsivity and time perception: which relationship in addictive disorders
- Herman AM & Duka T. Facets of impulsivity and alcohol use: what role do emotion play.
- Jeanblanc J et al. Binge drinking, better definition required in humans to improve animal models
- Lamontagne SJ & Olmstead MC. Animal Models in Addiction Research: a dimensional approach
- Schwitzer T et al. Is the retina a relevant site of investigation for brain neurotransmission abnormalities in cannabis users ? Current knowledge and perspectives.
- Campanella S et al Why cognitive event-related potentials (ERPs) should have a role in the management of alcohol disorders
- Luquiens A et al. Cognitive training: a new avenue in gambling management?
- Sampedro-Piquero P et al. Neuroplastic and cognitive impairment in substance use disorders: a therapeutic potential of cognitive stimulation.