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EDITORIAL

Neuroscience and addiction research: current advances and perspectives

Emmanuel Darcq[1] · **Brigitte L. Kieffer**[1]

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Addiction, or substance use disorder, is a complex relapsing disorder that affect millions of individuals worldwide (United Nations Office on Drugs and Crime. 2023; SAMHSA 2022). The disease stems from recreational use of euphorigenic substances as diverse as psychostimulants (cocaine, amphetamine), narcotics (morphine, oxycodone, fentanyl), cannabinoids, alcohol or more recent synthetic drugs of abuse (Gilpin 2023; Kaye et al. 2023). In some cases (Maldonado et al. 2021), occasional use switches to a compulsive drug taking with loss-of-control over drug use. Vulnerable individuals then enter a vicious cycle where intoxication episodes are followed by a highly aversive withdrawal state, leading to a craving phase with increasing desire for the drug, which typically causes the next intoxication episode (Koob and Volkow 2010; Stewart et al. 2019). As the brain adapts to repeated exposure to the drug, negative affect gradually overrides the positive subjective of the drug (Koob 2020), and maintaining abstinence represents a major defy for affected individuals (Beaulieu et al. 2021; Parvaz et al. 2022). Molecular determinants and the neurocircuitry of addiction are intensively investigated since decades, and have addressed all stages of the vicious cycle (Darcq and Kieffer 2018; Koob and Volkow 2016; Volkow and Blanco 2021; Nestler and Luscher 2019), however prevention, diagnostic and treatment still remain insufficient. The recent opioid epidemics, originally triggered by opioid over prescription for pain treatment (Marshall et al. 2019; Volkow and Blanco 2021; Volkow et al. 2019), has even more increased the need for innovative and personalized approaches to diagnostic and treatment, using the most advanced tools in neuroscience and mental health research.

This special issue of *Journal of Neural Transmission* is dedicated to addiction research. The fourteen articles together expose some of the significant recent advances in the field, highlight growing areas of investigation, and offer ideas and opinions on perspectives for both basic and clinical investigations.

In a first short overview, Valentina, Nair and Volkow describe the multiple challenges of addiction research, and stress the need for basic research to exploit the current surge of novel methodologies in neuroscience, as well as data science. The article describes representative examples, including for instance innovative imaging studies from molecules and cells to whole brain, or cell-specific technologies revealing the importance of non-neuronal cells. The report also underlines the importance of integrating the neurobiology with social and environmental aspects of the disorder. The following articles touch a number of these points and are organized in two main areas, i.e. neurobiology and therapy.

In basic research, the development of animal models is a prerequisite to investigate addiction-related behaviors. A plethora of rodent models have been developed since the early 20th century, evolving from forced administration to voluntary drug taking (Venniro et al. 2020), then including DSM-based behavioral criteria to test addiction vulnerability (Piazza and Deroche-Gamonet 2013), or more specifically focused on craving and relapse after voluntary abstinence, most relevant on the path to recovery (Fredriksson et al. 2021; Venniro et al. 2020). The commentary by Ahmed discusses novel experimental designs, including giving laboratory animals the choice between drug and nondrug alternatives (food, social interactions) that has provided surprising findings, and the interesting question of whether self-remission could be modeled in the laboratory setting. In addition to behavioral models, the advent of genetic manipulations in rodents has provided unique

✉ Brigitte L. Kieffer
brigitte.kieffer@unistra.fr

Emmanuel Darcq
edarcq@unistra.fr

[1] Strasbourg Translational Neuroscience and Psychiatry, Université de Strasbourg (UNISTRA), INSERM UMR-S 1329, Centre de Recherche en Biomédecine de Strasbourg, Strasbourg, France

tools to causally link gene function and behavior in addition research (Charbogne et al. 2014; Darcq and Kieffer 2018; Jordan and Xi 2021; Neasta et al. 2020). Recently, conditional gene mutagenesis strategies have identified cellular phenotypes and brain circuits where those genes operate. Here, Avila-Zozaya and Zachariou overview genetic models for opioid receptors and their signaling effectors, in neuronal, glial and immune cells, illustrating how genetic models have advanced our understanding of molecular mechanisms underpinning opioid use disorders.

In the cell, molecular mechanisms underlying drug-induced brain plasticity range from adaptations of receptor response to the drug at the cell surface, to modifications of a plethora of intracellular signaling effectors that ultimately alter gene expression in the nucleus. The latter effect, in turn, durably modifies cell physiology, neuron function and ultimately brain network connectivity within the addiction circuitry, with impactful effects on behavior. Nuclear events include notably epigenetic remodeling of gene expression, which has been causally related to addiction-related behaviors (Browne et al. 2020; Muenstermann and Clemens 2024) and has become druggable (epidrugs) (Koijam et al. 2024). In the context of alcohol use disorder, Hilal, Ben Hamida and colleagues review preclinical evidence supporting the therapeutic potential of epidrugs, in connection with another emerging treatment approach, i.e. the use psychedelics that attracts increasing interest in addiction therapies, and more generally in psychiatric research (Reiff et al. 2020; Rucker et al. 2018). Another recently discovered mechanism tightly associated to gene transcription and epigenetic regulation is alternative mRNA splicing, and here Martins de Cavalho and Lasek discuss emerging data showing the contribution of alternative splicing in the risk of developing substance abuse, and in particular alcohol use disorder.

Molecular responses to drugs of abuse are detected throughout all cell types of the brain, including neurons and glial cells. Conditional gene knockout approaches, and the more recent single-cell transcriptome studies have revigorated interest for non-neuronal cells in drug-induced adaptions, and the regulation of drug-seeking behaviorsVilca et al. 2023; Wang et al. 2022; Li et al. 2024). Holt and Nestler extensively review the implication of astrocytes, the most abundant glial cell type in the brain, in the development of addiction. These cells surround both pre- and post-synaptic elements of the synapse and regulate the many aspects of neuronal activity. Cocaine, alcohol and opioids influence astrocyte biology, including glutamate neurotransmission, transcription and epigenetic regulation in a region-specific manner. Evidence for causal effects on behavior is emerging for cocaine and, while less information is available for cannabis and nicotine today, this field is expanding rapidly.

On another front, the well-described immunomodulatory effects of chronic exposure to drugs of abuse (Gipson et al. 2021) have drawn attention to microglial cells, the resident macrophages of the brain. Here, Soares and Picciotto overview nicotine effects on neuroimmune signaling and discuss microglial engagement in nicotine addiction, involving in particular the alpha7 nicotinic acetylcholine receptor. Reducing pro-inflammatory effects of microglial activation is proposed to be a viable therapeutic target for nicotine dependence, an emerging concept that also applies to alcohol, stimulants and opiate use disorder (Agarwal et al. 2022; Loftis and Huckans 2013).

Finally, circuit neuroscience has become a most intensive research field in the past decade, and addiction research is largely part of the game (Luscher and Janak 2021; Nestler and Luscher 2019). In this issue two articles address specific aspects considered key for on-going and future research. Avramescu, Hernandez and Flores address the negative impact of drug use on development, in particular during adolescence, a period of major vulnerability to develop mental disorders including addiction (Crews et al. 2007). In their focus is the potential miswiring of dopamine neurons projecting to the prefrontal cortex, and leading to disrupted impulse control. Senol and Mohammad, on the other hand, discuss circuits underlying compulsivity in food consumption, touching on the growing area of non-pharmacological addictions (food, sex, gambling, video games or internet; (Grant et al. 2010). Findings of common alterations in circuits of reward and emotions, or decision-making, for both drug and food addiction opens the way to novel views to treat some eating disorders, generated notably by excessive consumption of energy-dense food (Koban et al. 2023; Val-Laillet et al. 2015).

Moving to human research, a first article by Harp, Wager and Kober stresses the need to develop brain-based biomarkers (neuromarkers) for substance use disorder. Consistent with animal data, human neuroimaging MRI studies have clearly demonstrated alterations of brain functioning across the addiction circuitry (Stewart et al. 2019) however translating this information into measurable and stable neuromarkers is complex and, for addiction research, progress has been slow compared to other fields in psychiatric research. Today, combining computational methods (machine learning and artificial intelligence) with neuroimaging data represents a most promising path to develop the several needed biomarkers (susceptibility, diagnostic, prognostic, response and prediction), and the authors discuss the great potential of a neurobiological craving signature, addressing a key diagnostic criterion of the disease.

Development of opioid use disorder have been associated with self-medication to face mood and anxiety disorders (Turner et al. 2018), mental distress and psychological

trauma (Cruden and Karmali 2021) or chronic pain (Han et al. 2018). In this issue, Dagher, Cahill and colleagues summarize clinical and epidemiological evidence to support that chronic pain is a risk factor for developing opioid or cannabis use disorder. Further, the review describes the overlap between neurobiological mechanisms underlying substance use disorder and those contributing to pain and negative affective states, as indicated by preclinical investigations. The authors indicate that normalization of dopamine transmission by neuroinflammatory modulators or kappa opioid receptor antagonists may help for the treatment of chronic pain and substance use disorder.

For individuals with substance use disorder, medication is an important part of the treatment strategy, but it is well established that medication should be used in combination with other non-pharmacological therapies in the course of care (Douaihy et al. 2013). Recent advances on non-pharmacological therapies are important and include both psychotherapies and brain stimulation methods (Rosenthal et al. 2022). In this issue, Durpoix, Lalanne and colleagues highlight the crucial need of psychotherapies to treat opioid use disorder and to prevent suicide and overdoses. The review describes several strategies including counselling, motivational interviewing, contingency management, cognitive behavioral therapy as well as dialectical behavior therapy and their benefits for adults and adolescents according to opioid use disorder severity. In conclusion, the authors suggest a new stepped-care model for psychosocial interventions in both adults and adolescents with or without pharmacological therapies.

Brain stimulation has gained tremendous interest in recent years. The approach aims at restoring abnormal circuit network activities by modifying plasticity of brain regions involved in substance use disorder (Brown 2023). Two approaches exist, i.e. deep brain stimulation, an invasive method that permits interventions into subcortical areas (Mahoney et al. 2020), and transcranial magnetic stimulation, a non-invasive approach that allows targeting cortical areas (Ross et al. 2023). Swinford-Jackson and Pierce survey preclinical and clinical studies addressing the potential of deep brain stimulation in the nucleus accumbens to treat cocaine and methamphetamine use disorder. Deep brain stimulation is already approved by the U.S.A. Food and Drug administration for the treatment of essential tremor, Parkinson's disease, dystonia, obsessive and compulsive disorder and for treatment-resistant depression. Madeo and Bonci, on the other hand, describe the use of transcranial magnetic stimulation of the medial prefrontal cortex to restore the imbalance between salience and reward networks. At present, transcranial magnetic stimulation is approved by U.S.A. and European regulatory agencies to treat resistant major depressive disorder, obsessive-compulsive disorder and tobacco use disorder (Johnson et al. 2013). Authors conclude that it is necessary to combine transcranial magnetic stimulation with more classical pharmacotherapies and psychotherapies, as individuals with substance use disorder often manifest co-morbidities. Both Swinford-Jackson and Pierce and Madeo and Bonci agree that more pre-clinical studies are necessary to understand the neuroadaptation induced by these stimulations, and also more clinical studies are necessary to assess individual variabilities and sex differences.

In conclusion, this special issue on addiction research overviews current highlights from animal and human neuroscience research. Recent advances will undoubtedly boost translational approaches that bridge the gap between basic findings and clinical needs, and advance addiction research in the era of personalized psychiatry.

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