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EDITORIAL

Special Topic on Mental Health and Addiction

Lin Lu[1,2] · **Wenhua Zhou**[3]

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We are delighted to have been invited to edit this Special Topic on Mental Health and Addiction. Mental disorders like drug addiction, mood disorders, and schizophrenia affect a sizeable proportion of the human population, severely compromise the quality of life, and constitute a large global burden of disease. The evolution of molecular, cellular, and neurophysiological studies of rodents and the technical advances in human imaging and assessment have gradually extended our understanding of the molecular and neural mechanisms underlying these disorders. It is becoming possible to investigate the role of neuronal circuits, microRNAs, signaling pathways, and gene polymorphisms in the pathogenesis and treatment of mental disorders.

Advances in neuroscience have identified addiction as a chronic relapsing brain disease with strong genetic, neurodevelopmental, and sociocultural components. Addictive drugs modulate the expression of genes involved in neuroplasticity, ultimately disturbing intracellular signaling cascades and the neuronal circuits implicated in the long-lasting changes associated with addiction [1]. Dopaminergic neurons located in the ventral tegmental area and projecting to the nucleus accumbens (NAc) play a key role in the rewarding response to drugs. Besides, the NAc is also involved in the aversive emotional state linked to drug withdrawal, which induces continued and compulsive drug use. Inputs from the prefrontal cortex, ventral hippocampus, and basolateral amygdala to the NAc have been implicated in the rewarding effects of addictive drugs, while input from the paraventricular nucleus of the thalamus to the NAc mediates the physical changes and aversive memory induced by opiate withdrawal [2, 3]. In addition, Wang *et al*. [4] showed that both intraperitoneal injection of the D1 receptor antagonist, SCH23390, and intra-NAc injection of the MEK inhibitor, U0126, attenuate the propofol self-administration and diminish the expression of phosphorylated extracellular signal-regulated kinase (ERK) in the NAc. These results suggest that ERK signaling coupled with D1 receptors in the NAc may be involved in the maintenance of propofol self-administration and its rewarding effects.

Alterations in gene regulation caused by exposure to drugs of abuse lead to long-term changes in brain structure and function, and consequently induce drug-seeking behaviors. The transcriptional and epigenetic mechanisms of drug action on gene expression are well established, including alterations in transcription factors, histone tail modification, DNA methylation, and microRNAs. These changes contribute substantially to the neuronal adaptions that result from chronic drug exposure [5]. Jia *et al*. [6] showed that miR-137 and miR-149 negatively regulate dopamine transporter (DAT) expression and dopamine transport at the post-transcriptional level in neural cells.

Lin Lu and Wenhua Zhou are the Guest Editors of the Special Topic.

✉ Lin Lu
linlu@bjmu.edu.cn

✉ Wenhua Zhou
whzhou@vip.163.com

[1] Institute of Mental Health, National Clinical Research Center for Mental Disorders, Key Laboratory of Mental Health and Sixth Affiliated Hospital of Peking University, Beijing 100191, China

[2] Peking-Tsinghua Center for Life Sciences and PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China

[3] Laboratory of Behavioral Neuroscience, Ningbo Addiction Research and Treatment Center, Medical School of Ningbo University, Ningbo 315010, China

Moreover, the miR-491 seed region is located on the variable-number tandem repeat (*VNTR*) sequence in the 3'-untranslated region of the DAT, and the regulatory effect of miR-491 on the DAT is dependent on the *VNTR* copy-number. Interventions targeting miR-137 and miR-149 may be considered a practical therapeutic strategy for diseases associated with DAT dysfunction, including drug addiction.

Drug exposure directly or indirectly triggers pathological changes in glutamatergic neuroplasticity in the circuitry underlying drug dependence [7]. Agmatine is endogenously synthesized by the decarboxylation of L-arginine in mammals, and is a putative neurotransmitter and/or neuromodulator. Wang *et al*. [8] showed that agmatine treatment reverses the increase in the hippocampal extracellular glutamate level induced by naloxone precipitation. In rats chronically administered with morphine, agmatine reverses the decrease in release and increase in uptake of glutamate in synaptosomes. Agmatine also reverses the decrease in expression of the hippocampal NR2B subunit induced by chronic morphine administration. Prevention of adaptation of the glutamatergic system in the hippocampus by agmatine may underlie its attenuation of opioid addiction.

Drug addiction has a high prevalence worldwide, but clinically effective treatment is still not available. Methadone maintenance treatment (MMT) is an opioid replacement therapy that is widely used to treat heroin dependence. Studies have shown it to be effective in decreasing illicit opioid use, criminal activity, and mortality rates among patients with opioid use disorder. Furthermore, its efficacy is superior to other non-pharmacological approaches (such as detoxification, offer of drug-free rehabilitation, placebo medication, and wait-list controls) [9]. Inconsistent with the results of studies in the west, Jiang *et al*. [10] found that the blood level of methadone is not correlated with the clinical outcome of MMT in Chinese patients. The discrepancy may be caused by the relatively low doses of methadone in the Chinese population, which may be attributed to social and political factors. The retention rate of patients with a high free peak-to-trough ratio was significantly lower than those with a low ratio. Thus, when the compliance rate with MMT is already very high or when the methadone dose is no longer the dominant factor in determining the clinical outcome, monitoring plasma methadone levels is unlikely to be effective for making dosing decisions.

In nicotine addiction, nicotine replacement therapy and bupropion or varenicline are the most used alternatives for smoking cessation. Wang *et al*. [11] found that two single-nucleotide polymorphisms of microsomal epoxide hydrolase (rs1051740 and rs2234922) are involved in the processes of nicotine metabolism and abstinence. In addition, both polymorphisms are associated with the effectiveness of nicotine replacement therapy in a Chinese population. Mi *et al*. [12] found that the haplotype T-C carrier (rs2235048-rs1045642) in the *ABCB1* gene (encoding p-glycoprotein) is associated with a better response to risperidone or paliperidone treatment in Chinese schizophrenic patients. Moreover, *ABCB1* gene polymorphisms also influence the incidence rate of extrapyramidal symptoms and the blood prolactin level.

Non-invasive brain stimulation (NIBS), including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), is emerging as a promising method for the treatment of a wide range of neurological and neuropsychiatric disorders [13]. Yang *et al*. [14] review the potential and challenges of using NIBS to treat nicotine addiction. Although there is interesting potential for decreasing craving and reducing smoking-related behaviors by both TMS and tDCS, several important factors need to be addressed in future work to improve clinical assessment and the effects of NIBS, such as brain stimulation devices and paradigms, brain states and participants' characteristics, and cultural differences [14]. Importantly, the different forms of NIBS affect brain activity in distinct ways, which have important ramifications for clinical efficacy. Understanding the brain's response to NIBS by combining behavioral and neuroimaging measures is a critical first step toward the efficient restoration of networks altered by disease. In addition, optimizing NIBS protocols using brain connectomics, the development of individualized NIBS protocols, and cross-cultural studies on its effects are directions for future research.

Depression is a common devastating psychiatric disorder that is associated with enormous personal suffering and societal economic burden. More than 20 different antidepressant medications targeting the monoaminergic system are currently available. However, their efficacy is limited, including a delayed response onset of weeks to months, high rates of partial responsiveness or non-responsiveness, and limited duration of efficacy. Ketamine has attracted much attention in recent years due to its rapid antidepressant effects (within hours of administration) in treatment-resistant depressed patients. This finding has also been replicated in several controlled clinical studies, and its neurobiological mechanisms have been extensively studied in animal models of depression. However, the off-label use of ketamine as an antidepressant remains under debate, and further investigations are needed to verify its safety and tolerability. Zhu *et al*. [15] review ketamine-related adverse effects occurring with high doses or prolonged treatment, such as neurotoxicity, cognitive dysfunction, adverse events associated with mental status, psychotomimetic effects, cardiovascular events, and uropathic effects. These effects certainly limit the use of ketamine to

treat depression and should be carefully considered in clinical settings.

Ketamine is stereo-selectively and region-specifically hydroxylated into a broad array of metabolites, such as norketamine, hydroxyketamine, dehydronorketamine, and hydroxynorketamine (HNK). Recent studies have shown that (2*R*,6*R*)-HNK has rapid and sustained antidepressant effects without ketamine-like side-effects [16, 17]. Compared with (*S*)-ketamine, the (*R*)-ketamine enantiomer has greater and longer-lasting antidepressant efficacy in several animal models of depression, such as the forced swim test, learned helplessness, and chronic social defeat stress. However, because of inconsistencies with previous studies and controversy regarding the antidepressant actions of ketamine metabolites independent of NMDA receptor inhibition, this conclusion should be treated with caution, and it needs further investigation and verification [18].

This special issue covers a wide range of topics from the neuronal mechanisms underlying addiction and depression, to the association between gene polymorphism and treatment responses. Treatment options are also addressed, including the use of NIBS and pharmacological replacement therapies for drug addiction. This special issue attempts to offer insights into the challenges faced by researchers in the field of mental health and addiction.

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