

Brain Imaging of Ketamine Abusers



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Abstract In this chapter, we highlight the role of brain imaging techniques (e.g., magnetic resonance imaging [MRI]) in studying ketamine abuse. In the past two to three decades, brain imaging studies demonstrated deficits in brain circuits related to drug addiction and drug abuse. This chapter begins with a brief introduction of structural and functional brain imaging techniques such as computed tomography (CT) and electroencephalogram (EEG). Then, we give a brief introduction of ketamine abuse in mainland China before introducing structural MRI and functional MRI and reviewing the application of structural MRI study for ketamine abusers (including reduction of gray matter volume and disruption of white matter integrity) and functional MRI study for ketamine abusers (including alternation of regional homogeneity (ReHo) of resting-state brain activity, functional connectivity by resting-state fMRI, task-based fMRI). Finally, we discuss the implication for medical use of ketamine by brain imaging study, especially its rapid-acting glutamatergic antidepressant effects and the “ketamine model” of psychosis.

Keywords Brain imaging · Magnetic resonance imaging · Structural MRI · Functional MRI · Chronic ketamine use · Ketamine abusers

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1 Brain Imaging Techniques

Brain imaging or neuroimaging techniques, by either directly or indirectly imaging the structure or function of the brain, have offered us a window to view noninvasively the human brain activity underlying complex affect, behavior, and cognition (Casey et al. 2005). Within the past two or three decades, by uncovering the inner workings of the human brain or revealing the neurological changes that result from brain diseases, these technological advances have accelerated the translation of basic neuroscience discoveries into precision medicine and targeted therapy in clinical management of brain diseases, which have made huge advances in cognitive and behavioral neuroscience.

Conceptually, brain imaging techniques can be classified into two broad categories: structural imaging and functional imaging (Hirsch et al. 2015). Structural imaging is used to reveal the anatomical properties of the brain, detect brain damage and abnormalities, and diagnose the gross intracranial disease and injury. Functional imaging is used to diagnose metabolic diseases and lesions on a finer scale or for neurological and cognitive psychology researches to identify brain areas and underlying brain processes that are linked to a particular cognitive or a behavioral task.

Here, we introduce some commonly used structural and functional brain imaging tools.

Structural brain imaging techniques:

1. Computed tomography (CT) or computed axial tomography (CAT) is a widely used approach that is typically used for viewing gross brain abnormalities, cerebral vascular accidents, and bone structure. However, it requires exposure to differential absorption of X-rays and has relatively low spatial resolution.
2. Magnetic resonance imaging (MRI) is a relatively accessible approach to visualize the soft tissues of brain such as gray matter and white matter with good spatial resolution. But it cannot be used in patients with metallic implants such as certain cardiac pacemakers or implantable cardioverter defibrillators.
3. Diffusion-based MRI (e.g., diffusion tensor imaging (DTI)) is an approach that is used for detecting detailed information of white matter integrity or microstructure and delineating white matter pathways that connect different regions of the brain. However, it requires complex image analyses and is sensitive to patient movement.

Functional brain imaging techniques:

1. Functional MRI (fMRI) and arterial spin labeling (ASL) can localize the brain activity associated with performing a cognitive task and/or behavior. It relies on the paramagnetic properties of oxygenated and deoxygenated hemoglobin to view images of blood flow changes associated with the regional activation of neurons during cognitive or behavioral tasks. The main drawback is its limited temporal resolution ability.

2. Positron emission tomography (PET) is an approach that is used to monitor the brain activity as well as the metabolism associated with performing a cognitive task and/or behavior by measuring emissions from radioactively labeled, metabolically active chemicals (e.g., fludeoxyglucose F 18) that have been injected into the bloodstream. However, it requires the injection of radioactive tracers, which is a main drawback.
3. Electroencephalogram (EEG) and evoked related potentials (ERP) can directly record the underlying electrical brain activity that is associated with a cognitive task and/or behavior with good temporal resolution. However, these techniques have poor spatial resolution compared with fMRI and require a complicated analysis of the acquired data.

Many other brain imaging techniques are also available, such as the functional near-infrared spectroscopy (fNIRS) and magnetoencephalogram (MEG). In this chapter, we focus on MRI (structural and functional) techniques because these are most widely used techniques in drug abuse and addiction (Parvaz et al. 2011). This chapter mainly focuses on structural and functional brain imaging of ketamine abusers. We briefly introduce ketamine abuse in mainland China before reviewing neuroimaging studies of ketamine addiction and abuse.

2 Nonmedical Use of Ketamine in Mainland China

During the last three or four decades, drug abuse spread quickly following its reemergence as a national problem in China (Liu et al. 2016). The number of registered drug abusers increased from 70,000 in 1990 to more than one million by the end of 2005 (Michels et al. 2007). According to China drug situation report 2018, the number of registered drug abusers doubled in the next decade to more than two million by the end of 2018, and the number of abusers of “new” types of drugs including methamphetamine (accounting for 56.1%) and ketamine (accounting for 2.6%) exceeded the number of abusers of opioids (www.nccc626.com). Illicit drug trafficking and production have swept in mainland China, particularly in southern China, which have caused many problems (such as the spread of HIV) for both abusers and the community (Fang et al. 2006).

In mainland China, ketamine was rescheduled from Schedule II in 2001 to Schedule I in 2007 (Liao et al. 2017). It is commonly abused through snorting. Figure 1 shows a typical way of making and snorting ketamine powder. Long-term ketamine abuse often results in bladder dysfunction (Tsai et al. 2009), sleeping disturbances (Tang et al. 2015a), cognitive impairment (Chan et al. 2013; Morgan et al. 2004a, b; Tang et al. 2013), depression (Li et al. 2017a; Tang et al. 2013), and even schizophrenia-like symptoms (Liao et al. 2016a; Tang et al. 2015b). Furthermore, a line of study reported brain structural and functional alterations in ketamine abusers (Liao et al. 2010, 2011, 2012, 2016b, 2018; Wang et al. 2013). This chapter reviews



Fig. 1 Typical way of preparing (left) and snorting (right) ketamine powder

the available structural and functional neuroimaging (mainly MRI) studies of ketamine abusers in detail.

3 Brain Imaging of Ketamine Abusers

Magnetic resonance imaging (MRI) is one of the most commonly used techniques to examine the brain activity in healthy brain and brain with disease, such as addiction or other mental illness. It is often divided into structural MRI and functional MRI (fMRI) (Symms et al. 2004). The field strength of the magnet is measured in tesla (T), and the magnetic strength for most clinical or research MRI scanners is 1.5 or 3 T. Most studies indicate that 3.0-T MRI scanner performs as good as or better than 1.5-T MRI scanner (Wood et al. 2012).

3.1 Magnetic Resonance Imaging

In the magnetic field, the nuclear spins of certain atoms within an object are oriented either parallel or antiparallel to the main magnetic field and produce a secondary spin or wobble (precession) of nuclei around the main or static magnetic field with a certain frequency called the Larmor frequency (named after the Irish physicist and mathematician Joseph Larmor, 1857–1942). The Larmor or precessional frequency in MRI is related to the strength of the magnetic field (the B_0 field). Magnetic resonance occurs when a radio frequency (RF) pulse produced at the (tissue specific) Larmor frequency, exciting and then raising the nuclear spin orientation of hydrogen atoms from lower to higher energy states. By rotating the magnetization, the RF field is switched off and the magnetization once again freely precesses around the direction of the original magnetization. This exchange of energy between spin states is called resonance, and a computer displays the different resonance characteristics of various tissue types as an image. This time-dependent precession produces a current in the receiver RF coil, and the exponentially decaying resultant current (the

free induction decay) constitutes the MR signal. The amount of the signal that is used to compose an image is proportional to the magnetic field strength of the scanner. (Signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), spatial resolution, and temporal resolution are commonly used technical terms to describe MRI image quality.) During the energy transition period, magnetization returns to its original equilibrium state (relaxation), characterized by T1 and T2 time constants, which depend on physical and chemical characteristics unique to the tissue type. The T1 and T2 differences between different tissue types (e.g., gray matter and white matter) produce a high-contrast MR image (Lauterbur 1973; Mansfield and Maudsley 1977).

3.1.1 Structural MRI

Structural MRI is a noninvasive technique that is used for examining the anatomy and pathology of the brain (as opposed to fMRI). It produces images that can be used for clinical radiological reporting as well as for diagnosis or research with detailed analysis. Structural MRI includes high-resolution imaging, T2 relaxation measurement, T2-weighted imaging, T1 relaxation measurement, magnetization transfer imaging, and diffusion imaging (Symms et al. 2004). Some MRI scan sequences are volumetric, and the volumes of regional gray matter and white matter often change considerably in individuals with brain diseases.

3.1.2 Functional MRI

Since its inception in 1990, functional MRI (fMRI) has been used to map human brain function noninvasively and rapidly with full brain coverage, and with relatively high spatial and temporal resolution. John Belliveau, Bruce Rosen et al. introduced it by using gadolinium as a contrast agent (Belliveau et al. 1990; Rosen et al. 1990). This was then immediately followed by a series of fMRI studies using the “blood oxygen level dependent” (BOLD) signal (Hoge et al. 1999; Kwong et al. 1992; Ogawa et al. 1990), which is the best known oxygen sensitive contrast agent. BOLD contrast results from a change in the magnetic field surrounding the red blood cells depending on the oxygen state of the protein hemoglobin, which is used for the indirect measurement of the brain activity.

In the past three decades, with extraordinary features (e.g., widespread availability, noninvasive nature, relatively low cost, and good spatial resolution), fMRI was applied in an exceptionally large number of studies in the cognitive neurosciences, clinical psychiatry/psychology, and presurgical planning to find biomarkers for disease (Bush et al. 1999; Fleisher et al. 2009), to monitor therapy (Stoeckel et al. 2014), or to study pharmacological efficacy (Honey and Bullmore 2004). The use of fMRI at rest has also enabled researchers to investigate resting functional connectivity of the human brain (Biswal et al. 1995). Measures of resting functional connectivity have been shown to be sensitive to brain diseases including drug and nondrug

addiction (Fedota and Stein 2015; Hong et al. 2013; Sutherland et al. 2012). The limitations of fMRI include high susceptibility of the BOLD response to several nonneural and imaging artifacts, especially due to its low SNR and low temporal resolution.

By comparing brain structure, function, and metabolism between drug-abusing and non-abusing individuals, brain imaging techniques enable researchers to observe the disruption of ketamine or other drug abusers' brain activity and allows us to better understand the mechanisms of addiction (Volkow et al. 2014).

3.2 *Structural MRI Study of Ketamine Abusers*

In the past two decades, there was considerable evidence that many psychiatric disorders (e.g., schizophrenia (Canu et al. 2015; Van Erp et al. 2018), bipolar disorder (Hibar et al. 2016; Strakowski et al. 1999), major depressive disorder (Schmaal et al. 2017), autism spectrum disorder (Sparks et al. 2002), obsessive-compulsive disorder (Fouche et al. 2017; Jenike et al. 1996), and attention-deficit/hyperactivity disorder (Seidman et al. 2005)) are associated with either increased or decreased regional brain volumes compared with gender- and age-matched healthy subjects. These brain structural abnormalities were also reported among ketamine abusers. Until now, only a few clinical structural MRI findings, however, have reported that the long-term effects of ketamine abuse is associated with the reduction of gray matter volume and the disruption of white matter integrity.

to assess regional gray matter volume reduction in ketamine abusers, voxel-based morphometry in conjunction with statistical parametric mapping on the structural magnetic resonance images of 41 ketamine abusers and 44 drug-naive control individuals in mainland China was used. This study found reduction of dorsal prefrontal gray matter after long-term repeated ketamine abuse. In particular, this study revealed significant reduction in gray matter volume in left superior frontal gyrus and right middle frontal gyrus of ketamine abusers in comparison with age-matched healthy volunteers (see Fig. 2). Furthermore, the duration of ketamine abuse was negatively correlated with the reduction of gray matter volume in bilateral frontal cortex, whereas the estimated total lifetime ketamine consumption was negatively correlated with the reduction of gray matter volume in left superior frontal gyrus. The association between frontal gray matter loss and the duration of ketamine use or cumulative doses of ketamine may suggest a dose-dependent effect of long-term abuse of the drug (Liao et al. 2011). Neuroimaging studies in other drug addictive users have also identified dysfunction of the prefrontal cortex, which suggests the involvement of this brain region in drug addiction (Goldstein and Volkow 2011).

Several studies, mainly in China and the UK, uncovered the disruption of white matter in chronic ketamine abusers. A study with the same Chinese sample (41 ketamine-dependent subjects and 44 drug-free healthy volunteers), using in vivo diffusion tensor magnetic resonance imaging data, measured white matter volumes. This study also found bilateral frontal and left temporoparietal white matter

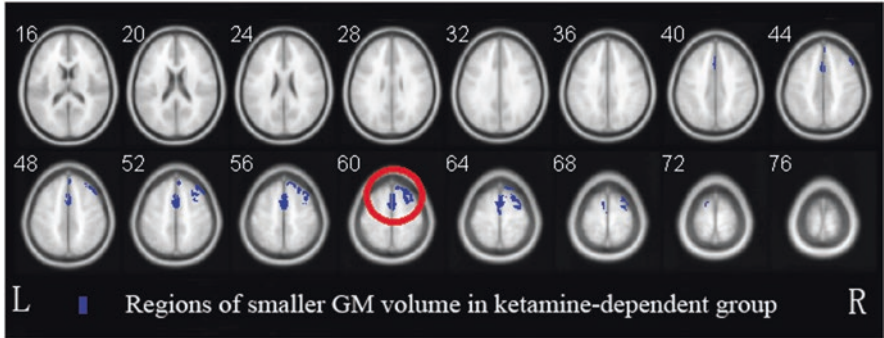


Fig. 2 Dorsal prefrontal gray matter reduction in ketamine abuses compared with healthy controls

alterations associated with long-term ketamine abuse (see Fig. 3). Furthermore, frontal white matter fractional anisotropy (FA is a scalar value between 0 and 1 that describes the degree of anisotropy of a diffusion process.) correlated with the severity of drug use (as measured by estimating totally abused ketamine). This study provided first evidence for dose-dependent abnormalities of white matter in bilateral frontal and left temporoparietal regions following long-term ketamine abuse. These findings further suggest a microstructural basis for the changes in cognition and experience observed with chronic ketamine abuse (Liao et al. 2010).

Another study in the UK measured indices of white matter microstructural integrity and connectivity in 16 ketamine abusers and 16 poly-drug-using controls. The study used probabilistic tractography to quantify alterations in corticosubcortical connectivity associated with repeated ketamine abuse. This study found a decrease in the axial diffusivity profile of white matter in the right hemisphere network of white matter regions in ketamine abusers compared with poly-drug abusers. For ketamine abusers, this study found that the frequency of dissociative experiences reported by chronic ketamine users associated positively with the changes of connectivity in the caudate nucleus and the lateral prefrontal cortex. These findings

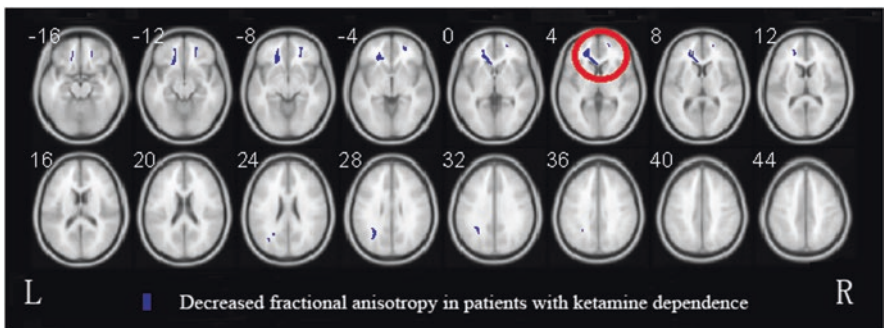


Fig. 3 Frontal white matter alterations in ketamine abuses compared with healthy controls

further confirmed that ketamine abuse may be associated with widespread alternation of white matter integrity. It also suggests that white matter pathways between subcortical and prefrontal cortical regions may in part predict individual differences in the frequency of dissociative experiences due to ketamine abuse (Roberts et al. 2014).

By employing MRI, a study from the south of China illustrated the possible disrupted brain regions due to ketamine abuse by comparing 21 ketamine addicts with three age-matched healthy controls. This study revealed the lesions in many regions (e.g., prefrontal, parietal, occipital, limbic, brainstem, and corpus striatum) of the brain of ketamine abusers (Wang et al. 2013).

Several animal studies using monkeys or rats (Li et al. 2017b; Sun et al. 2014; Yeung et al. 2010; Zou et al. 2009) have also shown that brain structural, especially frontal cortex, disruption is associated with long-term exposure to ketamine.

3.3 Functional MRI Study of Ketamine Abusers

Only a few studies measured the long-term effects of ketamine abuse on brain functional alternations. One resting-state fMRI demonstrated the alterations in regional homogeneity (ReHo) of resting-state brain activity in long-term ketamine abusers. This study examined such effects on spontaneous brain dynamics between 41 patients with ketamine dependence and 44 healthy control subjects by resting-state fMRI. The results showed that compared with healthy controls, ketamine abusers displayed decreased ReHo in the right anterior cingulate cortex and increased ReHo in left precentral frontal gyrus. This study also showed negative correlations between increased ReHo in precentral frontal gyrus and estimated totally abused ketamine in their lifetime and levels of ketamine craving. The findings from this study indicate that ketamine abuse might be associated with alterations in the functional connectivity of medial and lateral prefrontal cortices (Liao et al. 2012).

Decreased thalamocortical connectivity also has been observed in chronic ketamine abusers, which may suggest its role in the mechanistic “switch” from recreational abuse to dysregulated ketamine addiction. In this study, 41 ketamine abusers and 89 healthy control subjects were enrolled to measure the functional connectivity within the cerebral cortex by resting-state fMRI. This study found that ketamine abusers showed significantly decreased (but not increased) connectivity between the thalamic nuclear groups and the cortical regions of interest (ROI), including the prefrontal cortex, the motor cortex/supplementary motor area, and the posterior parietal cortex (see Fig. 4). This finding provided the first evidence of abnormal thalamocortical connectivity of resting state brain activity in long-term ketamine abusers (Liao et al. 2016b).

Ketamine abuse-related cues may induce craving in ketamine-dependent patients. A study measured regional brain activation to ketamine, cigarette smoking, and sexual activity. This functional MRI study recruited 40 smokers with ketamine abuse, 45 smokers without ketamine abuse, and 44 non-ketamine abuse noncigarette

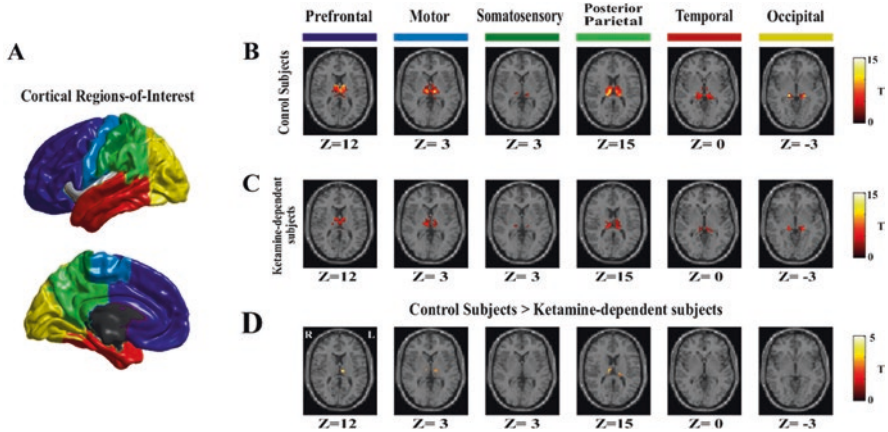


Fig. 4 The diffusively decreased thalamocortical connectivity in ketamine-dependent subjects. (a) The six cortical regions of interest. (b) Thalamocortical connectivity of the drug-free control subjects. (c) Thalamocortical connectivity of the ketamine-dependent subjects. (d) Group differences in thalamocortical connectivity for the drug-free control subjects and the ketamine-dependent subjects

smoking healthy controls to view ketamine use-related cigarette smoking and sexual films. This task-based fMRI found that smokers with ketamine abuse showed significant increased activation in regions of anterior cingulate cortex and precuneus in response to ketamine cues. They also showed reduced activation in cerebellum and middle temporal cortex in response to sexual cues. Smokers (both with and without ketamine abuse) showed increased activation in the right precentral frontal cortex in response to smoking cues. Non-ketamine users (both smokers without ketamine abuse and controls) showed increased activation of cerebellum and middle temporal cortex when they were viewing sexual cues (see Fig. 4). These findings indicated the engagement of distinct neural circuitry for ketamine-related stimuli (compared with cigarette smoking stimuli or sexual stimuli) in ketamine abusers. While smokers (for both with and without ketamine abuse) showed overlapping differences in activation for smoking cues (Liao et al. 2018), which may be partly due to the interaction effects of ketamine and nicotine in multiple brain regions. Nicotine substantially ameliorated the effects of ketamine on anterior cingulate regional cerebral blood flow (rCBF), and those effects may link to psychosis, reward, and addictive behaviors (Rowland et al. 2010).

Besides measuring functional MRI, the consequences of ketamine abuse in the human brain function have also been studied using positron emission tomography (PET) in a group of 14 recreational chronic ketamine users and matched healthy subjects. The study found that chronic ketamine abuse exhibited a regionally selective upregulation of D1 receptor availability in the dorsolateral prefrontal cortex (Narendran et al. 2005). Moreover, functional MRI of the brains in adolescent monkeys with chronic exposure to ketamine showed regional brain functional changes, particularly in the prefrontal dopaminergic system – a system critically involved in

working memory and executive function (Yu et al. 2012). Thus, long-term ketamine administration may involve neurodegenerative process similar to that of aging and/or Alzheimer's disease, which was demonstrated in both animal (Yeung et al. 2010) and human (Chan et al. 2013) studies.

Table 1 presents a summary of regional brain structural and functional disruption in ketamine abusers.

4 Implication for Medical Use of Ketamine by Brain Imaging Study

In addition to its abuse potential, ketamine is commonly used for medical purposes (Morgan et al. 2012). Ketamine is a noncompetitive antagonist at the glutamatergic *N*-methyl-*D*-aspartate (NMDA) receptor that is most widely used injectable anesthetic agent in veterinary medicine (Clarke and Hall 1990; Young et al. 1993). It is also used in specialist anesthesia, particularly pediatrics and field medicine for human (Cartwright and Pingel 1984; Green and Johnson 1990). Furthermore, ketamine has a role in pain management in both human and veterinary medicine (Elia and Tramèr 2005). Ketamine, as an *N*-methyl-*D*-aspartate (NMDA) receptor antagonist, has been found to induce schizophrenia-type symptoms in humans. Thus, there

Table 1 Regional brain structural and functional disruption in ketamine abusers

	Sample	Disrupted brain regions
Structural MRI	41 ketamine abusers 44 age-matched healthy controls	Dorsal prefrontal gray matter reduction (Liao et al. 2011)
	41 ketamine abusers 44 age-matched healthy controls	Bilateral frontal and left temporoparietal white matter alterations (Liao et al. 2010)
	16 ketamine abusers 16 poly-drug abusers	Reduction in the axial diffusivity profile of white matter in a right hemisphere network of white matter regions (Roberts et al. 2014)
	21 ketamine addicts 3 age-matched normal subjects	Brain damages in prefrontal, parietal, occipital, limbic, brainstem, and corpus striatum (Wang et al. 2013)
Functional MRI	41 ketamine abusers 44 age-matched healthy controls	Alterations in regional homogeneity of resting-state brain activity in ketamine addicts (Liao et al. 2012)
	41 ketamine abusers 89 healthy control subjects	Decreased thalamocortical connectivity in chronic ketamine users (Liao et al. 2016b)
	40 smokers with ketamine abuse 45 smokers without ketamine abuse 44 healthy controls	Cue-induced brain activation in chronic ketamine-dependent subjects, cigarette smokers, and healthy controls: a task functional magnetic resonance imaging (Liao et al. 2018)

are also a line of experimental studies using brain imaging to explore the “ketamine model” of psychosis (Deakin et al. 2008; Honey et al. 2008). As ketamine can block bursting in the lateral habenula to rapidly relieve depressive symptoms (Yang et al. 2018), it is used today for the treatment of depression, particularly for treatment-resistant depression (Aan Het Rot et al. 2012; Katalinic et al. 2013; Rosenblat et al. 2019). Recently, it was also found to be promising for addiction relapse prevention (e.g., heroin and alcohol addiction) as it reduced symptoms of depression (Ezquerro-Romano et al. 2018).

A series of pharmacological MRI study examined ketamine’s pharmacological effects on brain function, mainly to explore its potent and fast-acting antidepressant effects and uncover the neural mechanisms of psychosis and schizophrenia (as it produces similar symptoms).

4.1 For Depression

The abuse potential and psychotomimetic effects of ketamine may be linked with the dopaminergic system that also associated with antidepressant effects. Traditional antidepressants require several weeks to show their therapeutic effects. A single subanesthetic dose of the *N*-methyl-D-aspartate glutamate receptor antagonist ketamine, however, can produce significant clinical improvement within hours, getting the approval of Food and Drug Administration (FDA) of esketamine nasal spray for patients with treatment-resistant depression. Ketamine as a rapid-acting glutamatergic antidepressant, its novel treatment mechanisms are emerging a line of research (Krystal et al. 2013). The antidepressant properties of (*R,S*)-ketamine have also relevance for the development of next-generation, rapid-acting antidepressants (Zanos et al. 2016).

Subanesthetic doses of ketamine increase dopamine levels in the frontal cortex, in the striatum, and in the nucleus accumbens in rodents (Kokkinou et al. 2017). Applying 1H-MRS to 10 major depressive disorder (MDD) patients, however, did not observe the association between ketamine infusion with changes in occipital amino acid neurotransmitter (AANt) content, which indicates that these changes are not a correlate of ketamine’s antidepressant action (Valentine et al. 2011). A study using resting-state fMRI to investigate the intrinsic brain networks in MDD patients with ketamine treatment showed that ketamine significantly increased global signal regression (GBCr) in the PFC and reduced GBCr in the cerebellum, which may serve as a putative marker for successful treatment and a target for antidepressants’ development (Abdallah et al. 2017). However, it is important to be aware of ketamine abuse and addiction potential, even in MDD patients who received ketamine for antidepressant purposes (Bonnet 2015). In the future, research should explore more details about ketamine’s acute and chronic antidepressant effects on neuropharmacological and cognitive levels.

4.2 For Psychosis and Schizophrenia

On the contrary, several studies indicate that subanesthetic doses of ketamine impair prefrontal cortex (PFC) function in the rat and produce schizophrenia-like symptoms and dissociative states, including impaired performance of frontal lobe-sensitive tests, which is similar to cognitive impairment (Morgan and Curran 2006), persistent dissociative, depressive, and delusional thinking (Sassano-Higgins et al. 2016) by long-term ketamine use. It is suggested that ketamine may disrupt PFC function partly by interacting with dopaminergic neurotransmission in this region. By increasing the release of glutamate, thereby stimulating postsynaptic non-NMDA glutamate receptors, it probably impairs cognitive functions associated with PFC as a result (Moghaddam et al. 1997). Intravenous ketamine (1-min bolus of 0.26 mg/kg) to healthy individuals induced a rapid, focal, and unexpected decrease of the brain activity in ventromedial frontal cortex, including orbitofrontal cortex and subgenual cingulate, which strongly predicted its dissociative effects and increased activity in regions of midposterior cingulate, thalamus, and temporal cortex (Deakin et al. 2008).

Human and animal studies indicate that NMDA receptor hypofunction has been implicated in the pathophysiology of psychosis and schizophrenia and diminishes the inhibitory control of PFC output neurons. The findings of the present study suggest that both chronic ketamine users (Narendran et al. 2005) and schizophrenia patients (Laruelle et al. 2003) display the same endophenotypic trait – upregulated D1 receptor expression in the dorsolateral PFC, which supports the hypothesis that this alteration might be secondary to NMDA dysfunction in schizophrenia. For example, a 4-T 1H proton magnetic resonance spectroscopy (1H-MRS) study with ketamine administration in 10 healthy subjects found increased glutamatergic activity in the anterior cingulate, which may associate with acute hypofunctional NMDA receptor state (Rowland et al. 2005). Animal study also found its NMDA receptor hypofunction. Thus, reducing this effect may be critical for the treatment of psychosis and schizophrenia (Homayoun and Moghaddam 2007).

5 Conclusion

Brain imaging technology has had a tremendous impact on evaluating the neural mechanism associated with acute or chronic administration of ketamine. It provided a basic knowledge of ketamine's medical use- or abuse-related brain circuits and the related cognitive and behavior outcomes. However, a major caveat remains in the uncertainty is its long-term safety, such as how to use ketamine for MDD treatment while limiting its psychotomimetic and dissociative side effects as well as addiction and abuse potential. Novel analytical approaches for brain imaging data should also be developed to facilitate the translation of findings from the research to the clinical setting, promoting the medical benefits of ketamine's medical use while preventing

from its addiction and abuse potential. In the future, the insights provided by neuro-imaging studies of ketamine could contribute to biomarker development for its effective treatment of MDD and even other disorders, and to new approaches to discover better treatment strategies.

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