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Depression in chronic ketamine users: Sex differences and neural bases

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ABSTRACT

Chronic ketamine use leads to cognitive and affective deficits including depression. Here, we examined sex differences and neural bases of depression in chronic ketamine users. Compared to non-drug using healthy controls (HC), ketamine-using females but not males showed increased depression score as assessed by the Center of Epidemiological Studies Depression Scale (CES-D). We evaluated resting state functional connectivity (rsFC) of the subgenual anterior cingulate cortex (sgACC), a prefrontal structure consistently implicated in the pathogenesis of depression. Compared to HC, ketamine users (KU) did not demonstrate significant changes in sgACC connectivities at a corrected threshold. However, in KU, a linear regression against CES-D score showed less sgACC connectivity to the orbitofrontal cortex (OFC) with increasing depression severity. Examined separately, male and female KU showed higher sgACC connectivity to bilateral superior temporal gyrus and dorsomedial prefrontal cortex (dmPFC), respectively, in correlation with depression. The linear correlation of sgACC-OFC and sgACC-dmPFC connectivity with depression was significantly different in slope between KU and HC. These findings highlighted changes in rsFC of the sgACC as associated with depression and sex differences in these changes in chronic ketamine users.

1. Introduction

First synthesized as a derivative of phencyclidine in 1960s, ketamine has been used as an anesthetic in medicine. Ketamine has powerful psychological effects and recent studies including many clinical trials have focused on its potential as an antidepressant. On the other hand, ketamine elicits euphoria and dissociation ("out-of-body" experiences) and has increasingly become one of the major substances of abuse in many parts of the world, including Asia (Huang et al., 2014; Jia et al., 2015; Liu et al., 2016; Sassano-Higgins et al., 2016; Singh et al., 2013; Tang et al., 2015). In animal studies, ketamine induces self-administration and conditioned place preference (Botanas et al., 2015; De Luca and Badiani, 2011; Guo et al., 2016a; Suzuki et al., 1999; van der Kam et al., 2009; Venniro et al., 2015; Winger et al., 2002; Young and Woods, 1981). The potential of ketamine abuse may have to do with its action on the dopaminergic systems (Hancock and Stamford, 1999; however, see Can et al., 2016). On the other hand, ketamine is an antagonist of N-methyl-D-aspartate receptor, and the neural bases underlying ketamine addiction likely involve more than the dopaminergic circuits.

Drug abuse leads to cognitive and affective dysfunction. Studies in humans have characterized deficits in attention, working memory and executive functions and changes in emotion and affective behavior in substance abusers. In particular, brain imaging has provided an important venue to investigate the neural bases of these cognitive and affective deficits (Li and Sinha, 2008). Resting state functional connectivity (rsFC), which captures the organization of functional brain networks, has been widely used to unravel changes in circuit functions in various neuropsychiatric conditions including addiction. Numerous studies implicated the subgenual anterior cingulate cortex (sgACC, or

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Brodmann area 25) in depression on the bases of functional imaging, lesioning, and electromagnetic stimulation (see Berlim et al., 2014; Dunlop and Mayberg, 2014; Savitz and Drevets, 2009 for a review). For instance, compared to controls, adolescents with depression demonstrated elevated connectivity between the sgACC and insula as well as amygdala, and decreased connectivity between the sgACC and precuneus in association with the severity of depression (Connolly et al., 2013). Compared with controls, unmedicated young adults with remitted depression demonstrated hyperconnectivity of the left sgACC to the right ventromedial prefrontal cortex and left hippocampus (Jacobs et al., 2016). Children at risk in developing major depression exhibited hyperconnectivity between the default mode network (DMN) and sgACC, and the magnitude of connectivity correlated positively with individual depression symptom scores (Chai et al., 2016). In a randomized sham-controlled trial, responders to repetitive transcranial magnetic stimulation treatment of depression showed significantly stronger anti-correlated rsFC between the sgACC and left superior medial prefrontal cortex at baseline (Baeken et al., 2014). Vasopressin, a modulator of mammalian social behavior reduces sgACC activity and its connectivity with the amygdala and other limbic regions implicated in emotional regulation (Zink et al., 2010). Together, these findings highlight sgACC connectivity as a neural marker of depression and response to depression treatment.

Many studies examined the effects of acute ketamine administration on rsFC in healthy volunteers and clinical populations (Abdallah et al., 2016; Li and Vlisides, 2016; Wong et al., 2016) as well as in non-human primates (Gopinath et al., 2016; Lv et al., 2016). In healthy humans, ketamine increased cortical/subcortical-hippocampal connectivity (Grimm et al., 2015; Khalili-Mahani et al., 2015) and thalamic connectivity with the somatosensory and temporal cortex (Hoflich et al., 2015). In contrast, ketamine decreased DMN connectivity with the dorsomedial prefrontal cortex (Scheidegger et al., 2012), fronto-temporal functional connectivity (Kraguljac et al., 2016) and sgACC connectivity with the hippocampus, parahippocampal gyrus, retrosplenial cortex, and thalamus (Wong et al., 2016). Increasing the depth of ketamine sedation suppressed anticorrelated activity between the DMN and other regions in healthy adults (Bonhomme et al., 2016). In rats the strongest ketamine effects were dose- and exposure-dependent increases in functional connectivity within the prefrontal cortex and in connectivities between the posterior hippocampus, retrosplenial cortex, and prefrontal regions (Gass et al., 2014). Task-based imaging studies have also demonstrated the effects of ketamine on regional responses in healthy participants (Kleinloog et al., 2015; Lehmann et al., 2016; Scheidegger et al., 2016; Steffens et al., 2016) and clinical populations (Becerra et al., 2015) in a variety of cognitive and affective paradigms. These findings together characterized a wide range of acute effects of ketamine on cerebral activity.

On the other hand, few studies have examined changes in cerebral structure, activation and connectivity in chronic ketamine users (Hoflich et al., 2016; Liao et al., 2016; Wang et al., 2013), who frequently suffer comorbid depression (Chang et al., 2016). Women are more vulnerable than men to depression (Kessler, 2003). In a survey of over 1600 chronic ketamine users females presented significantly more discontinuation symptoms such as anxiety, dysphoria, and tremors and reported more severe cognitive impairment compared with male users (Chen et al., 2014). Preclinical work also suggested sex differences in the behavioral effects of ketamine. For instance, female Sprague-Dawley rats appeared to be more sensitive to ketamine-induced conditioned place preference than male rats (Guo et al., 2016b). In another study male and female rats were exposed to a single intraperitoneal injection of ketamine of varying dosages and tested 30 min later on forced swim and novelty suppressed feeding (Carrier and Kabbaj, 2013). Compared to male rats, female rats demonstrated greater sensitivity to the antidepressant effects of ketamine, and the effects were contingent on female sex hormones. In a recent study both male and female rats showed depression-like behavior after chronic social isolation as well as synaptic and postsynaptic changes in the medial prefrontal cortex. However, a single ketamine injection reversed these changes in male but not female rats (Sarkar and Kabbaj, 2016). Together, these studies suggest important sex differences in the depression-related behavioral effects of ketamine.

Here, we combined clinical assessments and fMRI to explore changes in rsFC of the sgACC in relation to depression in ketamine users. We broadly hypothesized that female ketamine users will demonstrate more significant depression and altered sgACC connectivity in link with depression, as compared to male users.

2. Methods

2.1. Subjects and clinical assessments

The study was approved by the Research Ethics Committee of the China Medical University Hospital (CMUH103-REC2-052). Candidates were assured at screening that their decision to participate in the study or not would not affect their right to medical care, that all personal information would be kept confidential, and that they could withdraw from the study at any time. Each participant provided a written informed consent prior to data collection.

Ketamine users (KU) and healthy control (HC) participants were recruited through posters at hospitals and online advertisements in the greater area of Taichung City, Taiwan. After consenting to the study, participants completed a clinical interview, questionnaire assessment, behavioral test, and magnetic resonance imaging.

KU met International Statistical Classification of Diseases and Related Health Problems (ICD) criteria for ketamine use disorders and tested positive for ketamine in urine toxicology. A positive test result for other substances including methamphetamine, opioids, ecstasy, or marijuana, was an exclusion criterion. All HC participants denied use of any illicit substances and showed negative urine test results. None of the KU or HC participants had any major medical or neurological illnesses, history of brain concussion that resulted in loss of consciousness, or psychotic disorders. A total of 36 KU and 20 HC participated in

Table 1
Clinical characteristics of the participants.

	KU (M)	KU (W)	HC (M)	HC (W)	ANOVA p value		
					Group	Gender	Interaction
Age	25.2 ± 5.8	27.5 ± 5.7	25.3 ± 4.5	25.1 ± 4.2	0.45	0.50	0.44
CES-D	6.3 ± 4.6	16.5 ± 6.2	6.8 ± 4.8	7.6 ± 4.8	0.005	0.0004	0.002
Ketamine use duration (months)	59.4 ± 37.0	59.0 ± 40.0	NA	NA		0.98*	
Cigarette in 30 days (day)	24.5 ± 11.1	30.0 ± 0.0	1.5 ± 2.5	0.0 ± 0.0	3.6×10^{-16}	0.39	0.13
Cigarette in life (years)	8.4 ± 4.7	12.1 ± 7.7	2.5 ± 3.5	0.0 ± 0.0	4.2×10^{-8}	0.66	0.03
Alcohol in 30 days (day)	4.8 ± 8.5	9.0 ± 11.1	3.0 ± 3.8	0.4 ± 0.7	0.02	0.72	0.14
Alcohol in life (years)	4.3 ± 4.3	6.7 ± 6.2	5.2 ± 6.2	1.9 ± 3.4	0.18	0.76	0.05

All values are mean ± SD; KU: ketamine users; HC: healthy controls; CES-D: Center of Epidemiological Study-Depression score; M: men; W: women; *two sample *t*-test.