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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.

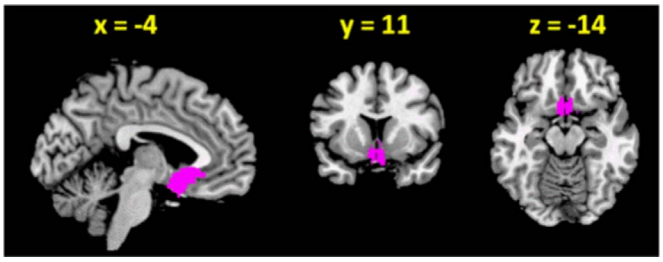

Fig. 1. Seed region: subgenual anterior cingulate cortex (sgACC).

this study. Table 1 summarizes the key clinical characteristics of the participants.

2.2. Magnetic resonance imaging: procedures and parameters

Participants underwent an MRI scan, consisting of 6- to10-minute resting-state fMRI and high-resolution structural imaging. MR image data were acquired using a 3-Tesla scanner (Signa HDx, GE, Milwaukee, USA) at the Department of Radiology, China Medical University Hospital, Taichung, Taiwan. The high-resolution structural images were acquired in transverse plane along the AC-PC line. A three-dimensional spoiled gradient-recalled protocol with inversion recovery pulse prepared (3D-SPGR-IrP) sequence was used (parameters: TE = minimal; prep time = 450 ms; flip angle = 12 degree; image matrix = 224 × 224; FOV = 224 mm × 224 mm; slice thickness = 1 mm; NEX = 1). The resting-state fMRI data were acquired using a gradient echo single-shot echo planar imaging sequence (parameters: TE = 35 ms; TR = 2000 ms; slice thickness = 4.4 mm; slice number = 32; image matrix = 64 × 64; FOV = 240 mm; total scan time = 10 min). Four dummy scans acquired at the beginning of EPI were discarded.

2.3. Imaging data pre-processing

Brain imaging data were preprocessed using Statistical Parametric Mapping (SPM 8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). We followed standard procedures in image preprocessing, as in our recent work (Kann et al., 2016; Kline et al., 2016; Zhang et al., 2016a, 2016b). Images of each individual subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were co-registered with the high resolution structural image and then segmented for normalization with affine registration followed by non-linear transformation (Ashburner and Friston, 1999; Friston et al., 1995). The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum.

Additional preprocessing was applied to reduce spurious BOLD variances that were unlikely to reflect neuronal activity (Fair et al., 2007; Fox and Raichle, 2007; Fox et al., 2005; Rombouts et al., 2003). The sources of spurious variance were removed through linear regression by including the signal from the ventricular system, white matter, and whole brain, in addition to the six parameters obtained by rigid body head motion correction. First-order derivatives of the whole brain, ventricular and white matter signals were also included in the regression.

Cordes and colleagues suggested that BOLD fluctuations below a frequency of 0.1 Hz contribute to regionally specific BOLD correlations (Cordes et al., 2001). Thus, we applied a temporal band-pass filter ($0.009 < f < 0.08$ Hz) to the time course in order to obtain low-frequency fluctuations, as in previous studies (Fair et al., 2007; Fox and Raichle, 2007; Fox et al., 2005; Lowe et al., 1998).

As extensively investigated in Van Dijk et al., 2012, micro head motion (> 0.1 mm) is an important source of spurious correlations in rsFC analysis (Van Dijk et al., 2012). Therefore, we applied a "scrubbing" method proposed by Power et al. (2012) and successfully applied in previous studies (Power et al., 2012; Smyser et al., 2010; Tomasi and Volkow, 2014) to remove time points affected by head motions. Briefly, for every time point t, we computed the framewise displacement given by $FD(t) = |\Delta d_x(t)| + |\Delta d_y(t)| + |\Delta d_z(t)| + r|\alpha(t)| + r|\beta(t)| + r|\gamma(t)|$, where (d_x, d_y, d_z) and (α, β, γ) are the translational and rotational movements, respectively, and r (= 50 mm) is a constant that approximates the mean distance between center of MNI space and the cortex and transform rotations into displacements (Power et al., 2012). The second head movement metric was the root mean square variance (DVARS) of the differences in % BOLD intensity I(t) between consecutive time points across brain voxels, computed as follows: $DVARS(t) = \sqrt{\langle |I(t) - I(t-1)|^2 \rangle}$, where the brackets indicate the mean across brain voxels. Finally, to compute each subject's correlation map, we removed every time point that exceeded the head motion limit FD (t) > 0.5 mm or DVARS(t) > 0.5% (Power et al., 2012; Tomasi and Volkow, 2014). On average, 1% of the time points were removed across subjects.

2.4. Seed based correlation and group analyses

Seed region of the sgACC (Brodmann area 25) was derived from a connectivity-based parcellation atlas (Neubert et al., 2015, Fig. 1).

The BOLD time courses were averaged spatially across voxels over the sgACC seed. For individual subjects, we computed the correlation coefficient between the averaged time course of seed region and the time courses of all other brain voxels. To assess and compare rsFC, we converted these image maps, which were not normally distributed, to z score maps by Fisher's z transform (Berry and Mielke, 2000; Jenkins and Watts, 1968): $z = 0.5 \log_e[(1 + r)/(1 - r)]$. The Z maps were used in group, random effect analyses. We performed a two-sample *t*-test to compare the Z maps of HC and KU and one-sample *t*-test on the Z maps of sgACC for HC and KU combined. We also performed analysis of variance with group and sex as two factors as well as covariance analysis to include variables of nicotine and alcohol use as covariates. Additionally, we performed whole brain simple regression analyses with CES-D as a regressor for KU. All results were examined with a voxel $p < 0.05$, corrected for family-wise error (FWE) of multiple comparisons or a combination of uncorrected voxel $p < 0.001$ and cluster $p < 0.05$, FWE corrected, on the basis of Gaussian random field theory, in SPM, following current reporting standards (Eklund et al., 2016). Effect sizes of regions of interest were derived with MarsBar (http://marsbar.sourceforge.net/) for additional analyses.

3. Results

3.1. Clinical assessments

For all clinical measures, we conducted an analysis of variance (ANOVA) with group (KU vs. HC) and sex (men vs. women) as factors. The p values for main and interaction effects are shown in Table 1. Compared to HC, KU showed higher CES-D score ($p = 0.005$); women also showed higher CES-D score as compared to men ($p = 0.0004$). Further, there was an interaction effect ($p = 0.002$), with female KU showing a significantly higher CES-D score than female HC (16.5 ± 6.2 vs.7.6 ± 4.8, $p = 0.003$, two-sample *t*-test) but no difference in men (6.3 ± 4.6 vs. 6.8 ± 4.8, $p = 0.77$). KU also showed significantly higher cigarette and alcohol use than HC (Table 1).

3.2. Resting state functional connectivity of the subgenual anterior cingulate cortex

In a two-sample *t*-test we observed that KU and HC did not show differences in rsFC at a corrected threshold. Thus, we combined KU and

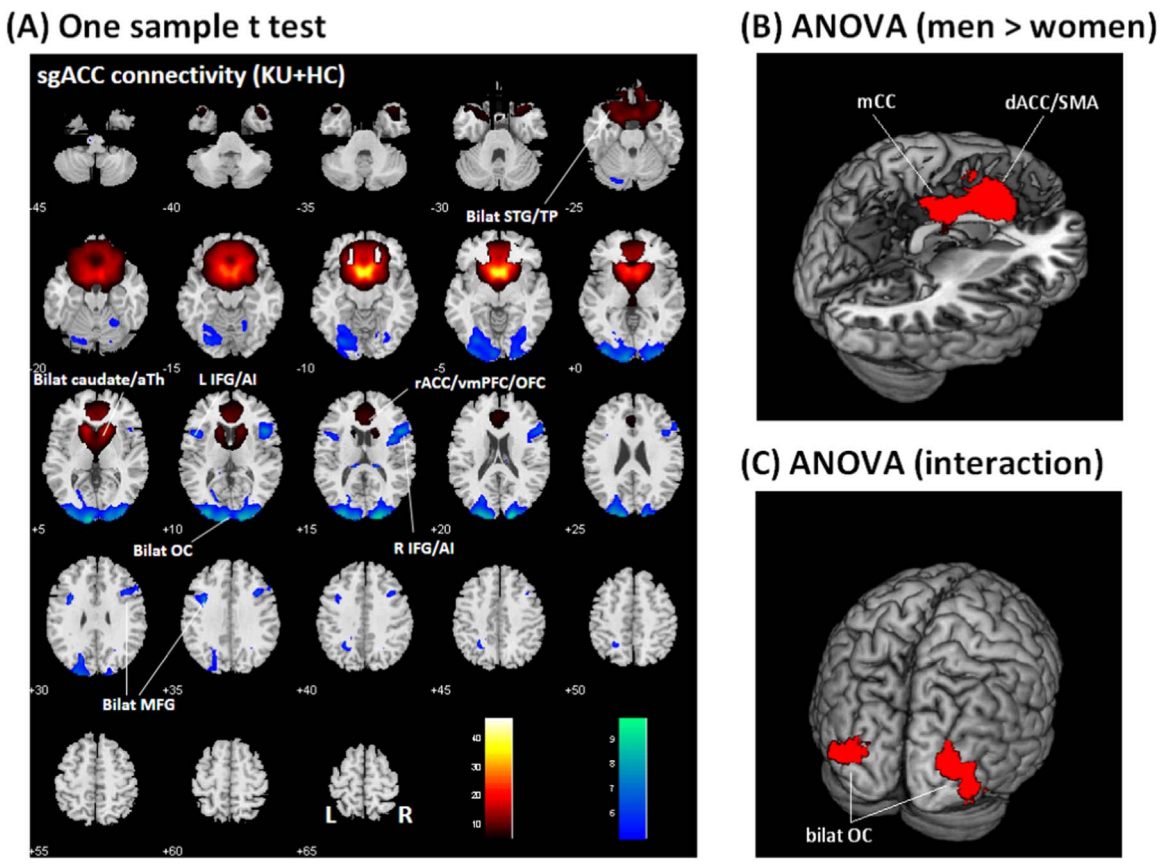

Fig. 2. (A) One-sample *t*-test of whole brain functional connectivity of the subgenual anterior cingulate cortex (sgACC), $p < 0.05$ FWE, in all subjects. Positive and negative connectivities are shown each in warm and cool color. Scale represents voxel T value. Neurological orientation: R = right. ACC: anterior cingulate cortex; aTh: anterior thalamus; Bilat: bilateral; IFG/AI: inferior frontal gyrus/anterior insula; L: left; MFG: middle frontal gyrus; OC: occipital cortex; OFC: orbitofrontal cortex; R: right; STG: superior temporal gyrus; TP: temporal polar cortex; vmPFC: ventromedial prefrontal cortex. ANOVA showed (B) greater activation in the dorsal anterior cingulate cortex and supplementary motor area (dACC/SMA) and mid-cingulate cortex (mCC) in men, as compared to women; and (C) an interaction effect, with men showing greater connectivity than women in HC, as compared to KU, in bilateral occipital cortex (OC). Results of ANOVA were examined at a threshold of $p < 0.001$ uncorrected, combined with cluster $p < 0.05$, FWE corrected.

HC in a one-sample *t*-test of whole-brain connectivities of the subgenual anterior cingulate cortex (sgACC, Fig. 2A). The sgACC showed positive connectivity to the rostral ACC/medial prefrontal cortex/medial orbitofrontal cortex, bilateral temporal poles/superior temporal gyri, bilateral caudate head/ventral striatum/anterior thalamus, and negative connectivity to bilateral occipital cortex, bilateral inferior frontal cortex/anterior insula (rIFC/AI), bilateral middle frontal gyrus and left angular gyrus.

In an ANOVA of the z maps, we included group and sex as two factors. At a corrected threshold, KU and HC did not differ in sgACC connectivity, consistent with the results of two-sample *t*-test. However, compared to women, men showed greater sgACC connectivity to the dorsal ACC/supplementary motor area (dACC/SMA, $x = -6$, $y = 20$, $z = 31$, voxel $Z = 4.97$) and mid-cingulate cortex (mCC, $x = 6$, $y = -13$, $z = 34$, voxel $Z = 4.96$) with a total volume of 21,411 mm^3 (Fig. 2B). Further, an interaction effect with KU (men – women) < HC (men – women) was observed in bilateral occipital cortices ($x = -30$, $y = -88$, $z = 7$, voxel $Z = 4.46$, 8127 mm^3 and $x = 36$, $y = -73$, $z = -8$, voxel $Z = 4.21$, 9288 mm^3), with men showing greater connectivity than women in HC, as compared to KU (Fig. 2C).

3.3. Depression and sgACC connectivity

We performed whole brain simple regression of sgACC connectivity maps on CES-D scores in KU. At a combined threshold of uncorrected voxel $p < 0.001$ and FWE-corrected cluster $p < 0.05$, CES-D score negatively correlated with the sgACC connectivity to the right lateral orbitofrontal cortex (OFC, $x = 36$, $y = 20$, $z = -14$, voxel $Z = 4.97$; 3618 mm^3) and bilateral medial OFC ($x = 3$, $y = 50$, $z = -11$, voxel $Z = 3.63$; 6156 mm^3) for all KU. We also performed the analyses separately for men and women. At the same threshold, CES-D score positively correlated with sgACC connectivity to bilateral superior temporal gyrus (STG, $x = 66$, $y = -37$, $z = 19$, voxel $Z = 3.97$; 3834 mm^3; and $x = -60$, $y = -61$, $z = 4$, voxel $Z = 3.68$; 2916 mm^3) in male KU. CES-D score positively correlated with sgACC connectivity to dorsomedial prefrontal cortex (dmPFC, $x = -6$, $y = 29$, $z = 52$, voxel $Z = 4.87$; 3267 mm^3) in female KU.

We derived the effect sizes of connectivity of these three regions and tested for differences between KU and HC in the correlation with CES-D score (Fig. 3). The results showed that, with men and women combined, sgACC connectivity to the OFC was negatively and significantly correlated with the CES-D ($p = 0.00001$, $r = -0.66$) in KU, but not in HC ($p = 0.58$, $r = 0.13$). Further, KU and HC significantly differed in the slope of the regressions ($p = 0.001$). For men, sgACC connectivity to the STG showed positive correlation with the CES-D both in KU ($p = 0.00002$, $r = 0.74$; $n = 26$ KU men) and in HC ($p = 0.009$, $r = 0.74$; $n = 11$ HC men). There was no difference between KU and HC in the slope of the regressions ($p = 0.13$). For women, sgACC connectivity to the dmPFC showed positive correlation with the CES-D in KU ($p = 0.00003$, $r = 0.97$) but not in HC ($p = 0.69$, $r = -0.16$); and the two groups differed significantly in the slope of the regressions ($p = 0.03$).

3.4. sgACC connectivity: cigarette and alcohol use as potential confounds

KU and HC differed in the extent of cigarette and alcohol use (Table 1). We examined whether the findings described above were

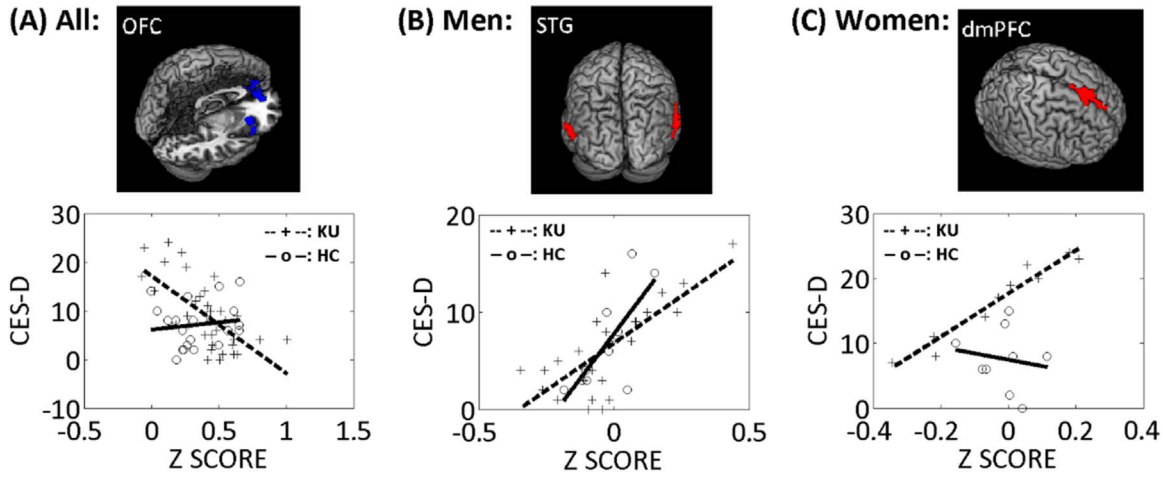

Fig. 3. sgACC connectivity in relation to depression. (A) sgACC connectivity with the orbitofrontal cortex (OFC) was negatively correlated with CES-D score in male and female KU combined (blue clusters). (B) sgACC connectivity with bilateral superior temporal gyrus (STG) was positively correlated with CES-D score in male KU (red clusters). (C) sgACC connectivity with dorsomedial prefrontal cortex (dmPFC) was positively correlated with CES-D score in female KU (red cluster). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

related to cigarette and alcohol use. We correlated the effect size of sgACC connectivity of the OFC, STG, and dmPFC with days of cigarette use in the past month, years of cigarette use in life, days of alcohol use in the past month, and years of alcohol use in life. The results showed that there were no significant correlations (all p's > 0.14) except for a trend-level negative correlation between the effect size of STG and days of cigarette use in the prior month ($p = 0.05$, $r = -0.39$) as well as years of smoking ($p = 0.07$, $r = -0.36$) in men. None of these correlations were significant when examined at a corrected threshold (of $p < 0.05/12 = 0.0042$).

We also conducted analysis of covariance for whole brain sgACC connectivity with group and sex as two factors and alcohol and nicotine use variables as covariates. The results were nearly identical (Section 3.2). There were sex main effect and group by sex interaction effect. Compared to women, men showed greater sgACC connectivity with the dACC/SMA ($x = -6$, $y = 23$, $z = 31$, voxel $Z = 4.91$) and mid-cingulate cortex (mCC, $x = 6$, $y = -13$, $z = 34$, voxel $Z = 4.83$) with a total volume of 19,980 mm^3. There was an interaction effect in bilateral occipital cortices ($x = -30$, $y = -88$, $z = 7$, voxel $Z = 4.24$, 4617 mm^3; and $x = 36$, $y = -73$, $z = -8$, voxel $Z = 3.98$, 7263 mm^3).

4. Discussion

Compared to non-drug using controls (HC), ketamine users (KU) did not demonstrate significant changes in sgACC connectivity at a corrected threshold. However, in KU, a linear regression of sgACC connectivity against CES-D demonstrated less connectivity with the right lateral orbitofrontal cortex (lOFC) and bilateral medial OFC (mOFC) in association with depression severity. Examined separately, male and female KU showed higher sgACC connectivity with bilateral superior temporal gyrus (STG) and dorsomedial prefrontal cortex (dmPFC), respectively, in correlation with depression. The sgACC connectivity to the OFC and dmPFC in relation to depression significantly differed between KU and HC. These findings are discussed in the below.

4.1. sgACC connectivity and depression in ketamine users

In KU the severity of depression is associated with decreased sgACC connectivity with lateral and medial OFC in men and women combined. The lOFC is involved in affective regulation and emotional experience. For instance, ratings of subjective emotion were correlated with activation in the right lOFC during viewing of negative versus neutral emotional images (Garrett and Maddock, 2006). The lOFC appeared to be specifically involved in reappraisal of negative emotions (Golkar et al., 2012). Higher neuroticism and introversion was associated with activation in the lOFC during losses in a card choice task to maximize profits (Fujiwara et al., 2008). Individual differences in negative urgency (impulsive behavior under negative emotional states) was associated with lOFC activation during exposure to negative as compared to neural emotional images (Cyders et al., 2015). The mOFC plays an important role in determining the affective tone of unconstrained thoughts (Tusche et al., 2014) and processing stimuli of positive affective value and those learned to be associated with stimuli of positive affective value (Shenhav et al., 2013). Being in a congruent emotional state, irrespective of the valence of emotion, activates the mOFC (Kuhn et al., 2011). The medial and lateral OFC were each related to counterfactual thinking and regret in economic decisions (Sommer et al., 2009). Thus, lOFC and mOFC appears to respond to distinct emotional states. The finding of altered sgACC connectivity to both lOFC and mOFC suggest the possibility of dysregulation of both positive and negative emotions in chronic ketamine users.

4.2. Sex differences in sgACC connectivity in KU

Increased sgACC connectivity with the dorsomedial prefrontal cortex (dmPFC) was associated with higher CES-D score in women but not in men. Previous studies have shown increased sgACC connectivity with the dmPFC in patients with major depressive disorder (Davey et al., 2012; Hamilton et al., 2011; Sheline et al., 2010). Increased sgACC connectivity with the dmPFC may be related to depression symptoms such as self-reproach and guilty rumination (Davey et al., 2012), in relation to the role of the dmPFC in autobiographical recall and self-referential analyses (Bado et al., 2014). Importantly, guilty rumination figured more prominently in women than in men with depression (Nolen-Hoeksema, 2012; Shors et al., 2017). A study combining fMRI and magnetic resonance spectroscopy revealed a significant negative correlation between GABA concentration in the dmPFC and BOLD signals in sgACC during exposure to sad face in contrast to control images (Stan et al., 2014). In individuals with treatment-refractory depression undergoing a 4-week course of repetitive transcranial magnetic stimulation of the dmPFC, higher baseline sgACC to dmPFC connectivity was associated with better treatment outcomes (Salomons et al., 2014). The latter finding support the importance of sgACC-dmPFC connectivity as a clinical biomarker of depression. However, as suggested by the current findings of sex

difference, more work is warranted to elucidate whether and how sgACC-dmPFC connectivity influences cognitive and affective functions differently in men and women with depression.

The superior temporal gyrus (STG) along with the dmPFC is involved in evaluating emotional facial and vocal expressions (Dricu and Fruhholz, 2016). Adults with childhood maltreatment exhibited increased STG activity during emotional processing (Hein and Monk, 2016). A meta-analysis associated an inter-connected network of brain regions including the STG during experiences of guilt (Gifuni et al., 2016). Individuals with social anxiety disorder demonstrated increased activation in the STG, insula, and medial frontal cortex during exposure to facial emotions (Binelli et al., 2014). An earlier study reported changes in sgACC activity and connectivity to a swath of cortical and subcortical structures including the STG and dmPFC during facial emotional processing in individuals exposed to mood deterioration induced by typhoid vaccination (Harrison et al., 2009). Algorithm of machine learning showed that sgACC connectivity with the STG may represent a diagnostic marker of major depression (Zeng et al., 2014). However, as with work on the dmPFC, none of these studies described how men and women differed in STG responses or sgACC-STG connectivity during emotional processing. As men and women showed differences in sgACC connectivity with a wide limbic circuit that supports nociception (Wang et al., 2014) and with the saliency network in association with shyness (Yang et al., 2015), it is important to examine sex differences in sgACC activity and connectivity in association with emotion regulation and depression.

4.3. Limitations of the study and conclusions

A number of limitations are worth considering. First, we did not include a group of non-substance abusing individuals with depression for comparison, so it remained unclear whether the current findings were specific to chronic ketamine users or related broadly to depression. Second, although regression analyses largely ruled out an effect of alcohol and cigarette use on the current findings, it remained unclear how these comorbidities may influence sgACC connectivity, particularly in terms of the interacting effects with sex differences. That is, while the analyses did not reveal a significant relationship between imaging findings and smoking/drinking variables, we could not conclude that the current findings are specific to ketamine misuse. Third, we did not assess history of childhood trauma, which can dispose individuals to depression, and this issue may be most relevant in the context of sex differences. Fourth, a few subjects underwent resting state fMRI for only 6 min; a longer scan duration would be needed to minimize within-subject variability in connectivity metrics (Tomasi et al., 2016). Finally, we targeted the sgACC in the current study, but other regions of the limbic circuit need to be investigated in future work for their role in the pathogenesis of depression in chronic ketamine users (Downey et al., 2016). In conclusion, we demonstrated altered sgACC connectivity in association with depression and sex differences in the altered patterns of connectivity in chronic ketamine users. These findings add to a growing literature of the addiction neuroscience of ketamine misuse.

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