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Research paper

Persistent antidepressant effect of low-dose ketamine and activation in the supplementary motor area and anterior cingulate cortex in treatment-resistant depression: A randomized control study

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ABSTRACT

Background: A single low-dose ketamine infusion exhibited a rapid antidepressant effect within 1 h. Despite its short biological half-life (approximately 3 h), the antidepressant effect of ketamine has been demonstrated to persist for several days. However, changes in brain function responsible for the persistent antidepressant effect of a single low-dose ketamine infusion remain unclear

Methods: Twenty-four patients with treatment-resistant depression (TRD) were randomized into three groups according to the treatment received: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, and normal saline infusion. Standardized uptake values (SUVs) of glucose metabolism measured through ^{18}F-FDG positron-emission-tomography before infusion and 1 day after a 40-min ketamine or normal saline infusion were used for subsequent whole-brain voxel-wise analysis and were correlated with depressive symptoms, as defined using the Hamilton Depression Rating Scale-17 (HDRS-17) score

Results: The voxel-wise analysis revealed that patients with TRD receiving the 0.5 mg/kg ketamine infusion had significantly higher SUVs (corrected for family-wise errors, $P = 0.014$) in the supplementary motor area (SMA) and dorsal anterior cingulate cortex (dACC) than did those receiving the 0.2 mg/kg ketamine infusion. The increase in the SUV in the dACC was negatively correlated with depressive symptoms at 1 day after ketamine infusion

Discussion: The persistent antidepressant effect of a 0.5 mg/kg ketamine infusion may be mediated by increased activation in the SMA and dACC. The higher increase in dACC activation was related to the reduction in depressive symptoms after ketamine infusion. A 0.5 mg/kg ketamine infusion facilitated the glutamatergic neurotransmission in the SMA and dACC, which may be responsible for the persistent antidepressant effect of ketamine much beyond its half-life.

1. Introduction

Major depressive disorder (MDD) has been increasingly recognized as a chronic and deteriorating mental illness over recent decades (Krishnan, 2003). Without adequate and optimal treatment, the residual symptoms of major depression can lead to worsening clinical outcomes such as high relapse rates, suicidality, and diminished quality of life and psychosocial functioning (Roose et al., 2001; KrishnanKrishnan, 2003; Kennedy and PaykelPaykel, 2004; Kennard et al., 2006). In fact, up to 50% of patients with major depression exhibited poor or partial responses to traditional antidepressant medication treatments (Trivedi et al., 2006; MollerMoller, 2008), and those who were resistant to antidepressant treatment accounted for most of the overall disease burden caused by depression (Roose et al., 2001; KrishnanKrishnan, 2003; Kennedy and PaykelPaykel, 2004; Kennard et al., 2006). Antidepressant-resistant depression has been associated with poor clinical and psychosocial outcomes (DignamDignam, 2009; Fekadu et al., 2009; LittleLittle, 2009).

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been approved to be an anesthetic agent by the U.S. Food and Drug

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Administration in 1970 and is widely used in anesthesia, particularly in pediatric surgery. The half-life values of ketamine and its active metabolites, norketamine and dehydronorketamine, are approximately 3, 5, and 7 h, respectively (Hijazi et al., 2003). A growing body of evidence suggests that a 0.5 mg/kg ketamine infusion has a rapid antidepressant effect for treatment-resistant patients (i.e., onset of the antidepressant effect occurs within hours following injection), which may be related to the rapid synaptogenesis and brain-derived neurotrophic factor release (Zunszain et al., 2013; Abdallah et al., 2016; Lener et al., 2016). The results from several recent ^{18}F-FDG positron-emission-tomography (PET) studies investigating changes in brain function before and immediately after a 0.5 mg/kg ketamine infusion in patients with treatment-resistant depression (TRD) may explain the mechanisms underlying the rapid improvement in the clinical symptomatology of depression (Carlson et al., 2013; Lally et al., 2015; Li et al., 2016). For example, Carlson et al. conducted an open-labeled study and measured glucose metabolism through ^{18}F-FDG PET at the baseline and 2 h post-ketamine infusion. They reported that improvement in depression symptoms was correlated directly with changes in metabolism in the right superior and middle temporal gyri (Carlson et al., 2013). In another open-labeled study, Lally et al. reported that reduced anhedonia, a core symptom of depression, was significantly correlated with increased glucose metabolism in the hippocampus and dorsal anterior cingulate cortex (dACC), as measured through PET at the baseline and 2 h post-ketamine infusion (Lally et al., 2015).

Our previous study assessed changes in brain function measured through ^{18}F-FDG PET at the baseline and immediately after a 40-min infusion of low-dose ketamine (0.5 or 0.2 mg/kg) or normal saline (control); we found that the standardized uptake values (SUVs) of the prefrontal cortex (PFC), supplementary motor area (SMA), and dACC in patients with TRD provided with the low-dose ketamine infusion were higher than those in the control group (Li et al., 2016). We also demonstrated that increased glucose metabolism in the PFC was significantly associated with improved depressive symptoms (Li et al., 2016). Furthermore, recent clinical studies have revealed that the rapid antidepressant effect of ketamine not only occurred within hours after a single-dose infusion but may also persist for days and even up to 2 weeks, which is a considerably longer period than the half-life of ketamine and its metabolites (Zunszain et al., 2013; Lener et al., 2016). The persistent antidepressant effect of ketamine and related changes in brain function remain unclear, despite our knowing that activations in specific brain regions, such as the PFC, hippocampus, SMA, and dACC, contribute to the rapid antidepressant effect of ketamine. The question as to whether the aforementioned brain regions or other potential regions that are involved in the brain circuit of depression are responsible for the persistent antidepressant effect of ketamine requires further study.

In the current study, we followed the same protocol as in our previous study (Li et al., 2016) and enrolled a new group of 24 patients with TRD, who were divided randomly into three treatment groups: 0.5 mg/kg ketamine, 0.2 mg/kg ketamine, and normal saline infusion. Moreover, ^{18}F-FDG PET was performed at the baseline and 1 day after a 40-min low-dose ketamine or normal saline infusion. On the basis of the results of our previous study, we hypothesized that a persistent increase in the SUVs of glucose metabolism in the PFC, SMA, and dACC may contribute to the persistent antidepressant effect of ketamine in TRD.

1.1. Experimental procedures

1.1.1. Inclusion criteria of subjects

We followed the same study inclusion criteria and the study procedures of our previous study (Li et al., 2016). In all, 24 adult patients aged between 21 and 65 years with a Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR) diagnosis of major depressive disorder who had failed to respond to at least three different antidepressants with adequate dosage and treatment duration were enrolled in our current study. The enrolled TRD patients did not have major medical or neurological illnesses or a history of alcohol or substance abuse. This study was performed in accordance with the Declaration of Helsinki and was approved by the Taipei Veterans General Hospital Institutional Review Board. Informed consent was provided by all of the participants.

1.1.2. Study procedures

Each enrolled patient underwent a detailed psychiatric and medical history-taking, a diagnostic interview. Following at least 2-week concomitant stable antidepressant treatment, patients received an add-on intravenous ketamine infusion using a randomized, double-blind, placebo-controlled design. Each patient received a single dose of ketamine infusion with A: 0.5 mg/kg, B: 0.2 mg/kg, or C: normal saline (placebo), which was administered over 40 min. First ^{18}F-FDG-PET scan was performed immediately before a single dose of ketamine infusion. Depressive symptoms were rated using the 17-item Hamilton Depression Rating Scale (HDRS-17) at baseline (immediately before the first ^{18}F-FDG-PET scan) and at 40, 80, 120, 240 min, and 1 day (second day) post-ketamine administration. To investigate the persistent antidepressant effect of a single dose of ketamine infusion, the second ^{18}F-FDG-PET scan was performed at 1 day later after ketamine infusion. The current study primarily focused on the persistent antidepressant effects of the low-dose ketamine infusion and neuroimaging findings between the baseline and one day later after ketamine infusion. Primary outcomes, such as 24-h HDRS-17 scores, were correlated with imaging results. Responders were defined as having at least a 50% decrease in their HDRS-17 score from baseline.

1.1.3. Imaging procedures

MR images were acquired with a 3.0 GE Discovery 750 whole-body high-speed imaging device. High-resolution structural T1-weighted images were acquired, for improving co-registration of the PET images, in the sagittal plane using a high resolution sequence (repetition time (TR), 2530 ms; echo spacing, 7.25 ms; echo time (TE), 3 ms; flip angle 7°) with isotropic 1 mm voxels and FOV = 256 × 256 mm. Two volumes of ^{18}F-FDG PET scans (i.e., before and 1 day after ketamine injections; the brain acquisition time for each PET volume is 15 min) of at rest glucose utilizations were acquired on a PET/CT scanner (Discovery VCT; GE Healthcare, USA) with the 3D brain mode. All PET scans were done in the morning (9.00–12.00 h); all subjects fasted for at least 8 h before the 1st PET examination. The 1st 15-min PET scan was acquired while staying awake in a deem-light room 45 min after an intravenous injection of about 222 MBq of ^{18}F-FDG. Around 1 day after the 1st PET imaging, another 15-min PET scan was acquired under the same condition (i.e., fasting condition for at least 8 h and 45 min' rest after iv bolus of about 222 MBq of ^{18}F-FDG while staying awake in a dim-light room). The system produces 47 consecutive slices over an axial length of 15.7 cm, with a slice thickness of 3.75 mm and a transaxial FOV of 70 cm. PET images will be then reconstructed, and corrected for attenuation with the ordered-subset expectation maximization iterative reconstruction algorithm (6 iterations and 14 subsets). Then the axial images will be realigned to yield sagittal and coronal images.

1.1.4. Voxel-wise analysis of PET data

PET data were analyzed using Statistical Parametric Mapping version 8 software (SPM8; Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, London, England) implemented in Matlab 7.1 (The Mathworks Inc., Sherborn, MA, USA). A group-specific MRI-aided ^{18}F-FDG template was created (Signorini et al., 1999; Gispert et al., 2003; Li et al., 2016) and used to normalize each subject's PET images, followed by smoothing with a 3D Gaussian kernel (FWHM = 8 mm). The smoothed and normalized PET images in the standardized brain space were created and then submitted for further analysis. Since relative changes of the brain metabolic activity within one hour were our primary interests, we used the standardized

uptake value (SUV), which is a validated semi-quantitative method (Lucignani et al., 2004), to correct for the FDG activity at the injection time for each of the two FDG scans before and 40 min after ketamine injections. Specifically, we calculated a parametric whole-brain SUV image by dividing the radiotracer activity concentration of the normalized PET image (MBq/kg) by the FDG dose at the injection time (MBq) divided by the body weight (kg). The total FDG dose at the 2nd injection time also considered the residual dose from the 1st FDG injection. Voxel-based partial correlations were performed to investigate the association between HDRS-17 scores and the 1st SUV image after controlling for age, gender, and global gray matter values (Friston et al., 1990). A paired *t*-test was separately used to compare the relative changes between the 1st and 2nd SUV images in the three groups (i.e., A: 0.5 mg/kg, B: 0.2 mg/kg, and C: normal saline). The significance thresholds were all set at a cluster-level FWE (family-wise errors)-corrected $p < 0.001$.

1.1.5. Statistical methods

We used one-way analysis of variance (ANOVA) for continuous variables and Fisher's chi-square tests for nominal variables to assess the differences of demographic and clinical data among three subgroups (0.5 or 0.2 mg/kg ketamine and placebo). A value of $P < 0.05$ was used to indicate statistical significance. To determine whether the changes of SUV of the SMA and dACC were a result of the interaction between time (i.e., before and after ketamine treatment) and ketamine group (i.e., A, B, and C), two-way repeated measures ANOVA was conducted, with time as the within-subject factor and ketamine groups as the between-subject factor, whereas age and sex were treated as covariates. The interaction between group and time and the main effects of group and time were reported, with $P < 0.05$ (2-sided test, corrected by family-wise errors (FWE) for multiple comparisons) considered to be statistically significant. The Least Significant Difference (LSD) method was used for post hoc analyses. Finally, linear regression was performed, with age, sex, baseline HDRS-17 scores, before-versus-after SUV changes of the dACC, and ketamine groups (low-dose ketamine or placebo group) included as independent factors. The HDRS-17 scores at 1 day later after ketamine infusion was the dependent variable. A P-value < 0.05 (2-sided test) was deemed statistically significant.

2. Results

All 24 subjects (8 subjects in each group) were recruited from Oct 2014 to Oct 2015 and participated in the entire study. Baseline demographic and clinical features (i.e., age, sex, psychiatric comorbidities, duration of illness, and baseline HDRS-17 scores) were similar among the three groups (Table 1).

Only 0.5 mg/kg ketamine group exhibited a significant reduction in total depressive scores at 240 mins ($-42.7\% \pm 13.4\%$ vs. $-15.9\% \pm 15.0\%$ vs. $-16.1\% \pm 9.8\%$, $F(df) = 11.41\ (2,21)$, $P < 0.001$) and 1 day later ($-50.0\% \pm 16.5\%$ vs. $-25.3\% \pm 22.0\%$ vs. $-11.5\% \pm 10.5\%$, $F(df) = 10.56\ (2,21)$, $P = 0.001$) after ketamine infusion and had a significant treatment response at 240 mins (37.5% vs. 0% vs. 0%, $\times^2(df) = 6.86\ (2)$, $P = 0.032$), and 1 day later (50% vs. 12.5% vs. 0%, $\times^2(df) = 6.57\ (2)$, $P = 0.037$) after ketamine infusion compared with 0.2 mg/kg ketamine and normal saline control groups (Table 1).

The results of the whole-brain voxel-wise analysis showed that there was not a significant main effect of the group. But, the post-hoc analyses showed that after treatment, TRD patients receiving 0.5 kg/mg ketamine had an increased SUV ($P = 0.014$) in SMA and dACC compared with those receiving 0.2 kg/mg ketamine (Fig. 1). The SUV increase in the dACC was negatively correlated with depressive symptoms at 1 day later after ketamine infusion measured by HDRS-17 scale ($P = 0.034$) (Fig. 2). The ANOVA analysis did not reveal a significant main effect of time or a significant interaction between group and time.

3. Discussion

Consistent with our hypothesis, our findings from the present study supported the hypothesis that the activation in the SMA and dACC could persist 1 day after a 0.5 mg/kg ketamine infusion and may contribute to the persistent antidepressant effect of ketamine considerably beyond its half-life. The supporting evidence is that increased glucose metabolism in the SMA and dACC was observed at 1 day after a 40-min 0.5 mg/kg ketamine infusion. In addition, a persistent increase in the SUV of glucose metabolism in the dACC was significantly associated with lower depressive symptoms at 1 day after ketamine infusion. However, the PFC that played a crucial role in the rapid antidepressant effect of ketamine in our previous study was not found to be responsible for the persistent antidepressant effect of ketamine in the current study.

The main finding that the SMA may play a critical role in TRD is consistent with those of previous studies (Luu and TuckerTucker, 2001; Schrijvers et al., 2008; Halari et al., 2009; Peng et al., 2014; Li et al., 2015). For example, our previous study revealed that compared with patients with MDD, who responded favorably to antidepressant treatment, patients with TRD had considerable hypometabolism in the PFC and SMA (Li, Su et al., 2015). Such hypometabolism in the PFC and SMA was considered a characteristic feature of TRD and was significantly correlated with their poorer performance in attentional tasks (Li, Su et al., 2015). Growing evidence suggests that the SMA may play a critical role in human volition; executive function; and integration of affective, behavioral, and cognitive functions (HaggardHaggard, 2008; Nachev et al., 2008; Leisman et al., 2016). Many behavioral and cognitive problems, such as psychomotor retardation, attentional problems, executive dysfunction, and even suicidality, have been found to be prominent in patients with TRD and can be modulated by the supplementary motor complex (i.e., the SMA and pre-SMA). Schrijvers et al. reported that severely depressed patients with psychomotor retardation exhibited impaired action monitoring function measured as an error negativity (Ne)/error-related negativity (ERN) amplitude (Schrijvers et al., 2008). The Ne/ERN amplitude, an index of SMA and ACC function, was significantly correlated with the severity of psychomotor retardation (Luu and TuckerTucker, 2001; Schrijvers et al., 2008). Peng et al. investigated the brain functional connectivity of the SMA in depressed patients, and they found that reduced functional connectivity between the SMA and thalamus was related to the symptom of helplessness in major depression (Peng et al., 2014). Halari et al. assessed the abnormalities of the fronto-cingulate circuitries mediating cognitive control functions in medication-free patients with depression; they demonstrated that poor attention and cognitive control function measured using the switch task was correlated with reduced BOLD activation in the SMA and ACC (Halari et al., 2009). As mentioned in the introduction, a 0.5 mg/kg ketamine infusion could activate glucose metabolism in the SMA and several other brain regions and could thus rapidly attenuate depressive symptoms within hours. In our current study, we further found that the persistent antidepressant effect of a 0.5 mg/kg ketamine infusion, which was considerably beyond the half-life of ketamine and its active metabolites, was associated with a persistent increase in activation in the SMA and dACC.

In addition to the SMA, a persistent increase in glucose metabolism in the dACC 1 day after a 0.5 mg/kg ketamine infusion was another major finding and could be a critical hub mediating the antidepressant effect of the 0.5 mg/kg ketamine infusion. The dACC is a critical hub that integrates the emotional and cognitive domains of emotional and behavioral regulation, thereby connecting the PFC, SMA, and limbic system (Bush et al., 2000). The dACC synergically works with the DLPFC in attentional and cognitive control and in emotional regulation through the inhibition of the hyperactive limbic system and subgenual ACC, a feature of TRD, in a top–down regulatory manner (Ressler and MaybergMayberg, 2007; De Raedt et al., 2015). During the resting state of TRD, dACC activity was reduced and tended to become normalized with successful treatment (De Raedt et al., 2015). A recent resting-state

Table 1
Baseline characteristics and antidepressant responses following a single dose of ketamine or normal saline infusion.

	A: 0.5 mg/kg ketamine infusion (n = 8)	B: 0.2 mg/kg ketamine infusion (n = 8)	C: placebo normal saline (n = 8)	p-value
Age (years, SD)	51.13 (13.59)	49.75 (11.08)	46.25 (8.14)	0.672
Female (n, %)	8 (100)	5 (62.5)	5 (62.5)	0.135
Duration of illness (years, SD)	11.88 (9.40)	11.63 (6.61)	12.44 (8.73)	0.980
Psychiatric comorbidities (DD/PD/SP/PTSD/GAD, n%)	5/2/1/0/1	3/1/0/0/3	4/1/1/0/3	0.607/0.741/ 0.580/-/0.466
Current antidepressant treatments[a] (1ATD, 2ATDs, ATD + others)	5/2/1	4/2/2	5/3/0	0.657
HDRS-17 score at baseline (SD)	24.00 (1.93)	27.13 (3.23)	24.63 (4.63)	0.182
Antidepressant responses following ketamine infusion (n, %)				
Responders (240 mins)	3 (37.5)	0 (0)	0 (0)	0.032
Responders (1 day)	4 (50)	1 (12.5)	0 (0)	0.037
HDRS-17 score changes (SD)				
240 mins vs. baseline	−42.7% (13.4%)	−15.9% (15.0%)	−16.1% (9.8%)	< 0.001
1 day vs. baseline	−50.0% (16.5%)	−25.3% (22.0%)	−11.5% (10.5%)	0.001

SD: standard deviation; HDRS: *Hamilton Depression Rating Scale; ATD: antidepressant;* DD: Dysthymic disorder; PD: Panic disorder; SP: Social phobia; PTSD: Post-traumatic stress disorder; GAD: Generalized anxiety disorder.

[a] Current antidepressant uses included one ATD, two ATD combinations, and one ATD in combination with atypical antipsychotics (i.e., quetiapine and aripiprazole) or mood stabilizers (i.e., lithium and valproic acid).

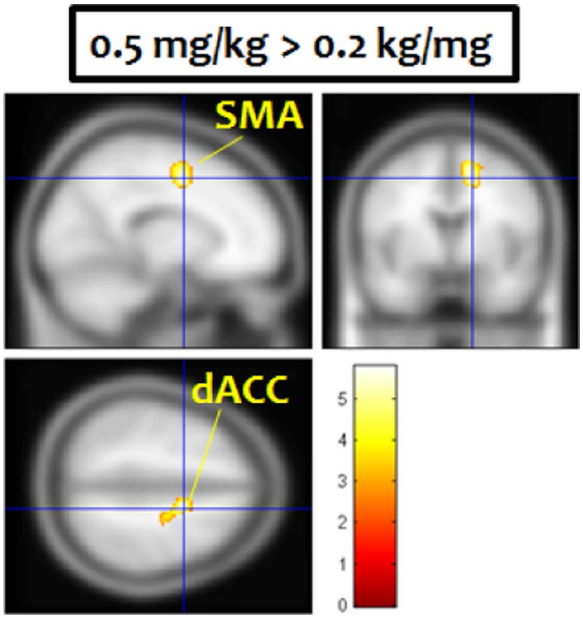

Fig. 1. SMA and dACC activation of 0.5 mg/kg ketamine infusion compared with 0.2 mg/kg ketamine infusion (FWE-corrected P = 0.014).

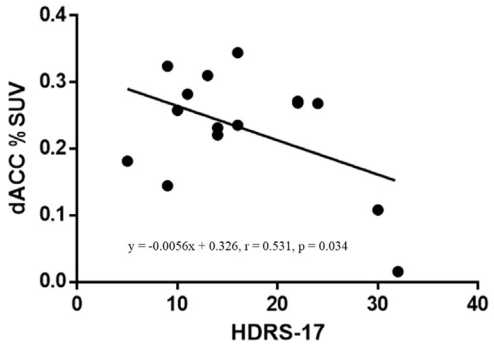

Fig. 2. The SUV increase in the dACC was negatively correlated with depressive symptoms at day 1.

function MRI study in healthy controls who were administrated an intravenous low-dose esketamine infusion indicated ketamine-dependent increases in neural activation in the midcingulate cortex, dACC, insula, and thalamus (Hoflich et al., 2016). Previous open-label PET studies investigating changes in brain function after a 0.5 mg/kg ketamine infusion indicated that an improvement in anhedonia was correlated with an increase in glucose metabolism in the dACC and hippocampus in patients with TRD (Lally et al., 2014; Lally et al., 2014, 2015). Our previous study also found that patients with TRD who responded favorably to a single dose of ketamine infusion experienced an immediate increase in glucose metabolism in the dACC, PFC, and SMA (Li et al., 2016). Downey et al. further compared changes in brain function between ketamine and lanicemine, a nonselective NMDA receptor antagonist, and observed increased BOLD activity of the ACC following infusion of the two different NMDA compounds, and this effect predicted improvements in mood 1 and 7 days post-infusion (Downey et al., 2016). They also suggested that the initial site of antidepressant action for NMDA antagonists may be the ACC, and that the ACC could be a treatment target for a low-dose ketamine or NMDA antagonist infusion in TRD (Downey et al., 2016). Consistent with previous studies, our previous and current studies have revealed that a single dose of 0.5 mg/kg ketamine infusion could lead to an SUV increase in the dACC at 40 min and 1 day after ketamine infusion, and further demonstrated that the persistent increase in the SUV in the dACC was related to reduced depressive symptoms at 1 day after ketamine infusion.

Notably, the whole-brain voxel-wise and ROI analyses in our current study did not support one of the study hypotheses that the PFC may be responsible for the persistent antidepressant effect of a 0.5 mg/kg ketamine infusion. Indeed, a growing body of evidence suggests that hypofunction in the PFC is one of key features of TRD, and a previous high-frequency repetitive transcranial magnetic stimulation (rTMS) study stimulating left DLPFC revealed a prominent antidepressant effect in TRD (Kimbrell et al., 2002; Li et al., 2013). However, the increase in glucose metabolism in the PFC after 2 weeks of rTMS treatment is not a consistent finding. Most previous studies have found that left prefrontal rTMS increased glucose metabolism in the ACC but did not activate glucose metabolism in the PFC after rTMS treatment (Baeken et al., 2009; Li, Wang et al., 2010; Li et al., 2013). These findings may suggest that a rebalance between the PFC and limbic system or reconnection between the PFC and ACC through repetitively stimulating the PFC could be more significantly responsible for the antidepressant effect of high-frequency rTMS. Such arguments may imply that the PFC is a kindler that can initiate and facilitate sequential brain function changes to achieve the antidepressant efficacy (Baeken et al., 2009; Li et al., 2010; Li et al., 2010, 2013). Following a similar concept, our previous

study revealed that an increase in glucose metabolism in the PFC immediately after a 40-min ketamine infusion was associated with an improvement in depression (Li et al., 2016). However, in our current study, we did not find persistent activation in the PFC 1 day after ketamine infusion. Consistent with our findings, two other PET studies have not observed increased glucose metabolism in the PFC 2 h after ketamine infusion, but they have reported that the rapid antidepressant effect of ketamine infusion was mediated by activation in the dACC (Carlson et al., 2013; Lally et al., 2015). Taking the preceding pieces of evidence together, we can state that the effect of ketamine infusion on PFC activation rapidly occurred within 1 h and then rapidly disappeared approximately 2 h later. A short activation in the PFC engendered by 0.5 mg/kg ketamine infusion may be a kindler, facilitating the persistent increase in glucose metabolism in the SMA and dACC; therefore, the PFC may be still considered to play a key role in improving TRD.

Several study limitations are listed here. First, our study was an add-on ketamine study because the medications used by patients with TRD were not discontinued during ketamine treatment and the PET procedure. Therefore, the observed responses to ketamine could have resulted from a combinative or a regulatory effect of ketamine and the medications that the patients were already using. However, the medications were not changed between ketamine treatment and the PET procedure; therefore, the current study findings can be appropriately explained by the add-on effect of a low-dose ketamine infusion. Furthermore, the add-on study design was ethically more appropriate in such severely depressed patients, and it could provide more naturalistic data. Second, only 24 patients with TRD (8 cases in each treatment group) were enrolled in the current study, which may decrease the statistical power in the analyses. However, with a strict statistical threshold in the PET analysis, we could still observe a prominent finding that a persistent increase in glucose metabolism in the SMA and dACC, but not in the PFC, produced the persistent antidepressant effect of a 0.5 mg/kg ketamine infusion. The finding involving the SMA is a replication because it was reported in our previous study using the same study design (except a different PET imaging timing) with an independent cohort of patients with TRD. Third, in our previous study, both the 0.5 mg/kg and 0.2 mg/kg ketamine groups achieved more significant antidepressant responses than the normal saline control group did, but in our current study, only the 0.5 mg/kg ketamine group achieved the treatment response state within hours and 1 day after ketamine infusion. The potential reason may be that we enrolled more severely depressed patients (HDRS-17 total score: 25.25 ± 3.57 vs. 22.04 ± 4.63, $p = 0.004$) in our current study. This result may indicate that 0.5 mg/kg ketamine infusion is necessary for very severely depressed patients and 0.2 mg/kg ketamine infusion may be an optimal dose for less severely depressed patients. However, whether changes in brain function caused by ketamine infusion vary in depressed patients with varying severity levels requires further investigation.

In conclusion, a 0.5 mg/kg ketamine infusion had both rapid (within 240 min) and persistent (beyond 1 day) antidepressant effects in our study. The persistent antidepressant effect of ketamine may be mediated by increased glucose metabolism in the SMA and dACC. The increase in the SUV of glucose metabolism in the dACC was significantly associated with lower depressive symptoms at 1 day later after ketamine infusion. A 0.5 mg/kg ketamine infusion could facilitate the glutamatergic neurotransmission in the SMA and dACC, which may be responsible for the persistent antidepressant effect of ketamine considerably beyond its half-life.

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