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Ketamine modulates subgenual cingulate connectivity with the memory-related neural circuit - a mechanism of relevance to resistant depression?

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Background: Ketamine has been reported to have efficacy as an antidepressant in several studies of treatment-resistant depression. In this study, we investigate whether an acute administration of ketamine leads to reductions in the functional connectivity of subgenual anterior cingulate cortex (sgACC) with other brain regions. **Methods:** Thirteen right-handed healthy male subjects underwent a 15 minute resting state fMRI with an infusion of intravenous ketamine (target blood level=150ng/ml) starting at 5 minutes. We used a seed region centred on the sgACC and assessed functional connectivity before and during ketamine administration. **Results:** Before ketamine administration, positive coupling with the sgACC seed region was observed in a large cluster encompassing the anterior cingulate and negative coupling was observed with the anterior cerebellum. Following ketamine administration, sgACC coupling decreased with the brainstem, hippocampus, parahippocampal gyrus, retrosplenial cortex, and thalamus. **Discussion:** Ketamine reduced functional connectivity of the sgACC with brain regions implicated in emotion, memory and mind wandering. It is possible the therapeutic effects of ketamine may be mediated via this mechanism, although further work is required to test this hypothesis.

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Key Words: depression, ketamine, antidepressant, MRI, anterior cingulate

Introduction

The sgACC or Brodmann area 25 is a region of the brain densely innervated with serotonin neurons and containing an abundance of serotonin transporters (Mantere et al. 2002; Varnas et al. 2004). Decreased mean gray matter volume combined with metabolic hyperactivity and hyperconnectivity of this region have been observed in patients with major depressive disorder (MDD) (Davey et al. 2012; Drevets et al. 2008; Greicius et al. 2007; Sundermann et al. 2014). With a growing number of studies demonstrating the association between metabolic hyperactivity in this region and poor therapeutic response (Baeken et al. 2014; Konarski et al. 2009; Maletic & Raison 2009; Sheline et al. 2010; Taylor & Liberzon 2007), the activity of this region may prove important for attempts to predict treatment response in patients (Siegle et al. 2012). Furthermore, given that connectivity between the sgACC and the default mode network (particularly the ventromedial prefrontal cortex, and posterior cingulate cortex) has been hypothesised to underlie depressive rumination (Hamilton et al. 2015), therapeutic disruption of this connectivity might also be a potential target for novel antidepressant action.

Treatment resistant depression (TRD) is common, with approximately 45% of patients failing to respond to pharmacological treatment (Papakostas & Fava 2010). Currently available antidepressants are characterised by a relatively slow onset of effect ranging from weeks to months, which can make the management of patients with suicidal ideation problematic (Machado-Vieira et al. 2008). There has been great interest in the potential of ketamine as a treatment for TRD patients, given early reports of strong and rapid (within hours) antidepressant properties in patients otherwise resistant to antidepressant treatment (Fond et al. 2014; Salvatore et al. 2009; Zarate et al. 2012; Zarate et al. 2006). Ketamine has been reported to reduce

subgenual anterior cingulate activity in healthy volunteers (De Simoni et al. 2013; Deakin et al. 2008; Doyle et al. 2013; Stone et al. 2015), and responders to ketamine with treatment resistant bipolar depression have been reported to have increased glucose metabolism in this region (Nugent et al. 2014). However, the effect of ketamine on subgenual connectivity, which might be hypothesised to underlie its antidepressant effects, has not been fully investigated. To date there has only been one study on the effect of ketamine on brain connectivity in relation to potential antidepressant mechanisms. Ketamine was shown to disrupt connectivity between subgenual anterior cingulate and dorsomedial prefrontal cortex 24 hours following administration in healthy volunteers, an effect that was hypothesised to be related to its antidepressant properties (Scheidegger et al. 2012). We hypothesise that immediate effects of ketamine might also play an important part in the therapeutic effects of ketamine in TRD, and that the early modulation of circuits involved in maintenance of depressive cognitions may be necessary for the emergence of objectively measureable clinical improvement.

In this study, which is an analysis of existing resting state data (Stone et al. 2015), we investigated the effect of acute intravenous ketamine administration on functional connectivity of the sgACC in healthy volunteers.

Materials and Methods

The study was approved by the East London Research Ethics Committee. Prior to screening for the study, all participants gave written informed consent for inclusion. Thirteen healthy, right handed, male volunteers (age 21-39, mean 27, standard deviation 6.90) were selected for the study after screening. Each subject underwent medical, mental state, physical, and psychiatric

examination including electrocardiogram, urine drug screen, and taking measurements of blood pressure, pulse rate, temperature, and weight. Each volunteer underwent venous cannulation in the left antecubital fossa. We attached a 50ml syringe pump containing 4mg/ml racemic ketamine via an infusion line.

Image acquisition was conducted, as previously reported (Stone et al. 2015), at the Centre for Neuroimaging Sciences on a General Electric (Milwaukee, Wisconsin) 3-Tesla HDx MRI scanner. Pharmacological MRI (phMRI) BOLD data were acquired using gradient echo EPI (Echo-Planar Imaging) with parallel imaging accelerated by a factor of 2. Each participant was scanned continuously for 15 minutes to yield a total of 450 functional image volumes of 37, continuous top down, 3 mm thick slices with a slice gap of 0.3 mm, TR of 2000 ms, TE of 30 ms, flip angle of 75°, in-plane resolution of 3.3 mm, 64 × 64 matrix, and 21.1 × 21.1 cm field of view. The ketamine infusion commenced after 5 minutes of resting state acquisition and followed a dynamically modelled intravenous infusion with a target plasma level of 150 ng/mL determined according to pharmacodynamic properties of ketamine from the “Clements 250 model”, with a rapid bolus over 20 seconds of approximately 0.26mg/Kg followed by a slow infusion of approximately 0.42mg/Kg/Hr. Participants’ peak ketamine-induced experience was rated by a trained psychiatrist using the positive and negative syndrome scale (PANSS) immediately following their exit from the scanning room.

Preprocessing and statistical analyses were performed using Statistical Parametric Mapping software version 8 (SPM8; Wellcome Trust Centre for Neuroimaging, London, England). Functional images were corrected for slice timing effects and subsequently realigned to correct

for the effects of volume-to-volume head motion. They were then co-registered to a high-resolution T1-weighted structural image, and normalised to MNI space via unified segmentation. The normalised images were smoothed using an 8mm FWHM Gaussian kernel. Additional preprocessing was carried out using the REST toolbox for rsfMRI analysis (Song et al. 2011). Nuisance variables such as motion parameters, white matter and CSF signal were regressed from the data. The residual time-series was then de-trended and band-pass filtered (frequency range 0.08-0.01Hz) and a signal time-series was extracted from the sgACC seed (10mm sphere at [2, 28, -5] based upon a previous publication (Scheidegger et al. 2012)). The 15-minute time series was separated into three 5-minute time-series segments of pre-infusion, early-infusion and late-infusion. The early-infusion portion of the time series was disregarded as any observed connectivity would have been dominated by the phMRI response to the bolus. Finally, connectivity maps were created using regression within the REST toolbox, and the resultant r-maps underwent r-to-Z conversion again within REST.

These Z-transformed maps were taken forward into a second level random effect analyses within SPM8 and appropriate linear contrasts were used to characterise sgACC connectivity at the group level and to identify regional changes in sgACC coupling following ketamine administration. Results were considered significant if they survived family wise error (FWE) correction on the basis of cluster-extent ($p_{FWE} < 0.05$). The PANSS general score was tested for normality using the Shapiro-Wilk test prior to regression analysis with sgACC connectivity maps.

Results

Prior to ketamine administration, there was positive coupling ($pFWE < 0.05$) between sgACC and multiple brain regions including anterior cingulate, ventral striatum, and thalamus. There was negative coupling ($pFWE < 0.05$) between sgACC and regions including cerebellum, pons, precentral gyrus, superior frontal gyrus, and parahippocampus (Table 1).

Following ketamine administration, there was significant reduction in sgACC coupling with a large cluster including the hippocampus, retrosplenial cortex, and thalamus centred at $[-2 -3 6]$ ($p_{FWE} = 0.002$; $k_E = 2885$; $Z_0 = 3.69$) (Figure 1). An examination of the model coefficients indicate that this network was not correlated with the sgACC at rest, but was strongly negatively correlated with the sgACC following ketamine administration. Ketamine administration was associated with a mean (SD) increase in PANSS positive, negative and general subscales to 10.7(2.89), 10.07(3.43) and 20.15(3.53) respectively.

Multiple regression analysis using cluster forming threshold of $p < 0.01$ was performed to test for correlations between changes in whole brain functional connectivity and PANSS scores. No correlations with PANSS positive or negative scores were found, but a negative correlation between the PANSS general score and sgACC coupling was observed in the medial prefrontal cortex (mPFC) and subcallosal gyrus (SCG) ($pFWE < 0.05$). In order to further investigate this correlation, we performed a post-hoc analysis of the correlation between sgACC coupling and depressive symptoms using the 5 factor PANSS (Lindenmayer et al. 1994). The level of depressive symptoms was found to be negatively associated with coupling between sgACC and subcallosal gyrus and right dorsolateral prefrontal cortex ($pFWE < 0.05$). Level of depressive

symptoms were positively associated with coupling between sgACC and right ventromedial prefrontal cortex ($pFWE < 0.05$; figure 2).

Discussion

In this study, we examined the acute effect of ketamine on functional connectivity between the subgenual anterior cingulate and other brain regions. Our primary aim was to investigate potential mechanisms underlying the antidepressant effect of ketamine. The most striking effect of acute ketamine administration in this study is the disruption of connectivity between subgenual anterior cingulate and a large cluster encompassing midline thalamus, hippocampus, RSC. This may be of relevance to the antidepressant effect. Both thalamus and hippocampus have been implicated in the pathology of MDD (Malykhin & Coupland 2015; Yakovlev et al. 1960; Young et al. 2004), and, interestingly, NMDA receptor blockade in the RSC has been shown to be necessary for retrieval of fear memory (Corcoran et al. 2011). Furthermore, the network between subgenual anterior cingulate and the default mode network, including RSC is increased in patients with MDD, and has been suggested to underlie depressive ruminations (Hamilton et al. 2015), a process hypothesized to be of great significance in the maintenance of depressed mood (Disner et al. 2011). If ketamine is able to disrupt the tendency of the mind to return to depressive ruminations through changing the functional connectivity within this network, this may be of particular importance in its antidepressant action.

Although ketamine acutely increased rather than decreased depressive symptoms in this healthy volunteer sample (likely due to a floor effect) it is notable that changes in functional connectivity

between subgenual anterior cingulate and other brain regions correlated only with general and depressive symptoms on the PANSS, and not with positive or negative subscales. Our finding of a negative correlation between depressive symptoms and sgACC coupling with surrounding regions of the SCG is of interest as the SCG is an important node in a neural network comprising of cortical structures, the limbic system, thalamus, hypothalamus, and brainstem nuclei. MDD patients generally show increased activity in SCG, which is normalised by antidepressant treatment (Hamani et al. 2011). It is possible that this local reduction in connectivity reflects a direct consequence of the reduced BOLD activity in this brain region seen following ketamine administration (Stone et al. 2015). The positive correlation of depressive symptoms with sgACC and ventromedial prefrontal cortex connectivity is notable because increased connectivity between these regions has been hypothesised to underlie depressive ruminations (Hamilton et al. 2015).

There are a number of limitations regarding the study design. The fact we were studying healthy volunteers means that any effects we see in functional connectivity may not map directly onto those that occur in patients with MDD. Ketamine modulation of brain circuits may vary according to severity of depression and thus networks affected in healthy controls may be different to those suffering from MDD. On the other hand, the effects in this study are not confounded by differences in mood state or medication exposure. Secondly, the effects investigated in the present study occurred 5 minutes following ketamine administration, during the steady-state infusion, whereas antidepressant effect in patients do not normally arise until 40 minutes to 2 hours after ketamine administration. We hypothesise that the changes reported in the current study may be precursors to an antidepressant effect, but it is possible that changes in

functional connectivity relevant to antidepressant mechanism between other brain regions might arise at later time points. Lastly, because the volunteers in this study did not have any depressive symptoms, the correlations of change in connectivity with mood symptoms are difficult to interpret – participants had an increase rather than a decrease in depression-related symptom following ketamine administration.

Conclusion

We found that ketamine alters the functional connectivity of the sgACC in healthy controls. The regions affected suggest that these changes may be of importance in the therapeutic effects of ketamine in patients with MDD. This study suggests that ketamine may reduce depressive rumination via acute effects on sgACC- RSC connectivity.

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304 treatment-resistant major depression. *Arch Gen Psychiatry* 63:856-864.

305

306

Table 1 (on next page)

Resting state sgACC coupling prior to ketamine administration

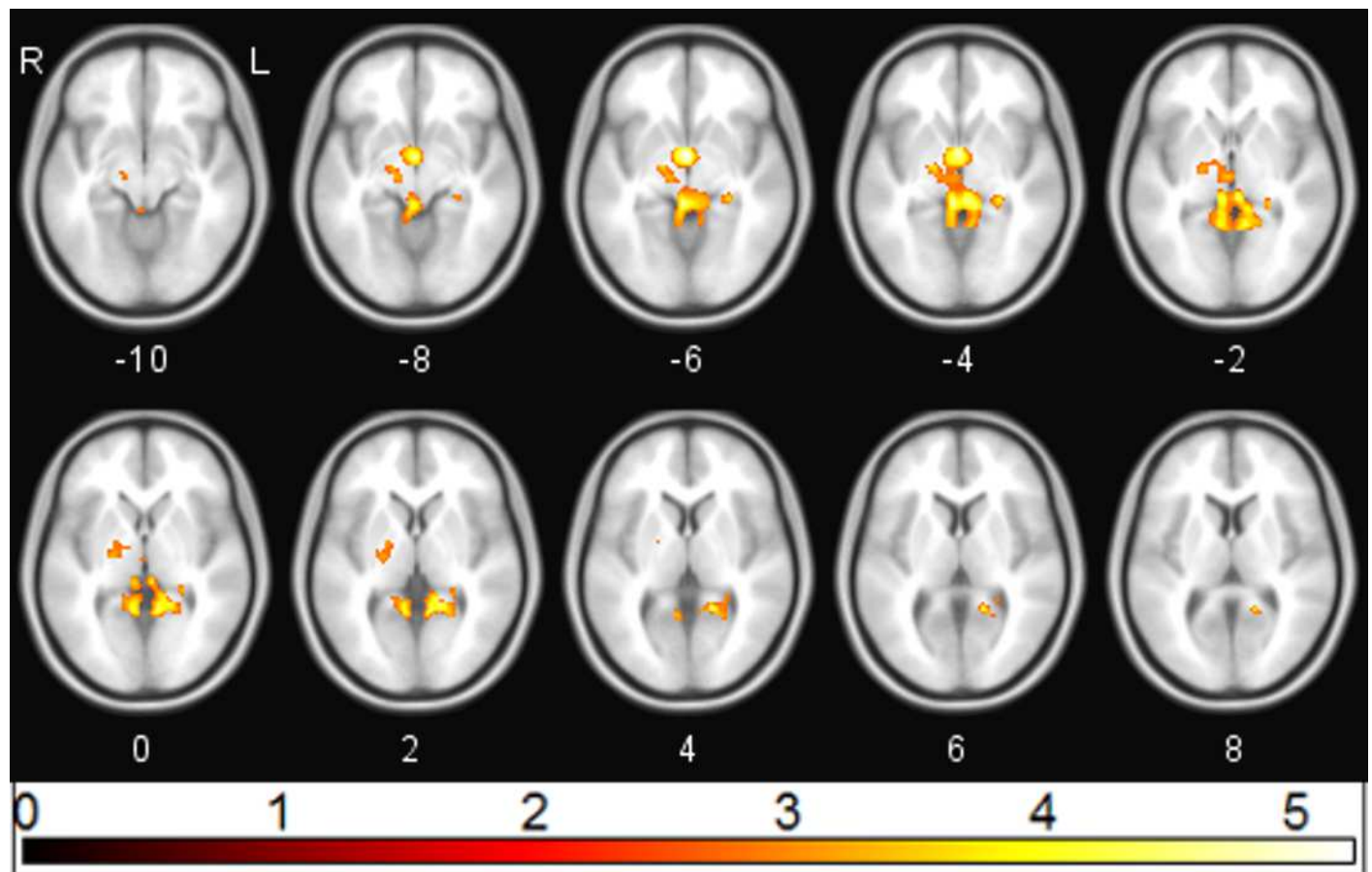
Regions showing significant coupling with sgACC prior to ketamine infusion ($p_{FWE} < 0.05$ corrected for multiple comparisons on the basis of cluster extent, using a cluster-forming threshold of $z = 3.1$).

| sgACC Coupling | Brain Region | Brodmann Area | Cluster-level | | Peak-level (Z_0) | Coordinates | | |
|----------------|----------------------------|---------------|---------------|-------|-------------------------|-------------|-----|-----|
| | | | p_{FWE} | k_E | | x | y | z |
| Positive | Ventral Anterior Cingulate | 24 | <0.001 | 12610 | 6.69 | 4 | 27 | -6 |
| Positive | Dorsal Anterior Cingulate | 32 | | | 6.23 | -6 | 35 | -3 |
| Positive | Thalamus | | | | 5.79 | -2 | -3 | -3 |
| Negative | Anterior Cerebellum | | <0.001 | 3705 | 4.69 | -12 | -37 | -27 |
| Negative | Pons | | | | 4.16 | 9 | -22 | -24 |
| Negative | Anterior Cerebellum | | | | 3.96 | 10 | -37 | -26 |
| Negative | Middle Frontal Gyrus | 9 | <0.001 | 1089 | 4.68 | 43 | 12 | 33 |
| Negative | Middle Frontal Gyrus | 9 | | | 4.50 | 42 | 3 | 39 |
| Negative | Precentral Gyrus | 6 | | | 4.03 | 51 | 0 | 40 |
| Negative | Superior Frontal Gyrus | 10 | 0.001 | 971 | 4.45 | 22 | 51 | 24 |
| Negative | Middle Frontal Gyrus | 9 | | | 4.12 | 34 | 29 | 28 |
| Negative | Middle Frontal Gyrus | 9 | | | 3.77 | 30 | 36 | 21 |
| Negative | Inferior Parietal Lobule | 40 | 0.007 | 649 | 4.17 | 66 | -46 | 31 |
| Negative | Inferior Parietal Lobule | 40 | | | 3.46 | 70 | -46 | 22 |
| Negative | Postcentral Gyrus | 2 | | | 3.44 | 61 | -30 | 43 |

1

sgACC connectivity following ketamine administration.

Regions showing significant ($p_{FWE} < 0.05$) reduction in sgACC coupling following ketamine administration (red/yellow).



2

Correlation between PANSS depression and sgACC coupling

Regions showing significant ($p_{FWE} < 0.05$) correlations between PANSS depression score and sgACC coupling (blue - negative correlation, yellow - positive correlation).

