Short Report

Perceptual distortions and delusional thinking following ketamine administration are related to increased pharmacological MRI signal changes in the parietal lobe

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James Stone[1], Vasileia Kotoula[1], Craige Dietrich[1], Sara De Simoni[1], John H Krystal[2,3,4] and Mitul A Mehta[1]

Abstract

Ketamine produces effects in healthy humans that resemble the positive, negative and cognitive symptoms of schizophrenia. We investigated the effect of ketamine administration on brain activity as indexed by blood-oxygen-level-dependent (BOLD) signal change response, and its relationship to ketamine-induced subjective changes, including perceptual distortion. Thirteen healthy participants volunteered for the study. All underwent a 15-min functional MRI acquisition with a ketamine infusion commencing after 5 min (approx 0.26 mg/kg over 20s followed by an infusion of approx. 0.42 mg/kg/h). Following the scan, participants self-rated ketamine-induced effects using the Psychotomimetic States Inventory. Ketamine led to widespread cortical and subcortical increases in BOLD response (FWE-corrected $p < 0.01$). Self-rated perceptual distortions and delusional thoughts correlated with increased BOLD response in the paracentral lobule (FWE-corrected $p < 0.01$). The findings suggest that BOLD increases in parietal cortices reflect ketamine effects on circuits that contribute to its capacity to produce perceptual alterations and delusional interpretations.

Keywords

Ketamine, psychosis, fMRI, BOLD

Introduction

Ketamine is an uncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist that produces effects in healthy volunteers which resemble the positive, negative and cognitive symptoms of schizophrenia (Krystal et al., 2005). The brain basis for these subjective changes is only beginning to be understood (Anticevic et al., 2012; Deakin et al., 2008; Stone et al., 2012). Animal pharmacological magnetic resonance imaging (PhMRI) studies have reported increases of blood-oxygen-level-dependent (BOLD) signal in frontal, hippocampal and thalamic regions following ketamine administration (Littlewood et al., 2006). In humans, phMRI studies have reported ketamine-induced elevations in mid-posterior cingulate, thalamus and temporal cortex BOLD, which correlated with brief psychiatric rating scale scores, and a decrease in subgenual cingulate BOLD, which correlated with dissociative effects (Deakin et al., 2008), and decreased posterior cingulate and medial prefrontal deactivations during a working memory task which correlated with negative symptom ratings (Anticevic et al., 2012). These findings are supported by earlier studies of regional brain metabolism following ketamine administration using 14C-2-deoxyglucose (2DG) and FDG positron emission tomography (PET), showing increase in uptake in medial prefrontal, ventrolateral orbital, cingulate and retrosplenial cortices in rats (Duncan et al., 1998), and thalamus, frontal and parietal cortices in humans (Langsjo et al., 2004).

We recently developed an improved method for detecting ketamine-induced change in BOLD response, accounting for the modeled neural response to acute administration of ketamine as a single vector as well as nuisance variables (head movement and scanner drift) (De Simoni et al., 2012). In developing the methods, we used a dose of ketamine that produced relatively mild dissociative effects (target plasma level: 75 ng/mL) and, perhaps for this reason, we found no significant relationship between ketamine-induced changes in BOLD response and psychopathology, despite high reliability of both the phMRI and psychopathology ratings (De Simoni et al., 2012). In this study, we repeated our earlier study design but used a higher dose of ketamine (target plasma dose of 150 ng/mL) to investigate the relationship between ketamine-induced psychopathology and BOLD response.

[1]Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
[2]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[3]Psychiatry Services, Yale-New Haven Hospital, New Haven, CT, USA
[4]Clinical Neuroscience Division, VA National Center for PTSD, VA, USA Connecticut Healthcare System, West Haven, CT, USA

Corresponding author:
James Stone, Centre for Neuroimaging Science, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, London SE5 8AF, UK.
Email: james.m.stone@kcl.ac.uk

Methods

Thirteen healthy male volunteers (age 18–50) were recruited by advertisement. Exclusion criteria included positive urine drug screen for drugs of abuse, the consumption of more than five cups of coffee per day, smoking more than five cigarettes per day, taking prescription drugs, and any history of mental illness or serious medical condition that, in the opinion of the study doctors, prevented participation in the study. Fulfillment of inclusion and exclusion criteria was assessed by a psychiatrist who completed a full psychiatric, neurological and medical examination of each participant (including electrocardiogram and urine drug screen). Written informed consent was provided by all participants prior to their inclusion in the study, which was approved by the East London Research Ethics Committee

Study design

The study was an open-label, within-subjects design. Prior to entering the scanner, participants rated their baseline psychopathology using the Psychotomimetic States Inventory (PSI; 48 items consisting of six subscales—Delusional Thinking, Perceptual Distortion, Cognitive Disorganization, Anhedonia, Mania and Paranoia) (Mason et al., 2008). All participants then underwent MRI scanning on a 3.0T GE HDx scanner (GE Medical Systems, Milwaukee, WI, USA). After an initial localizer scan we acquired structural images including an axial 2D T2-weighted fast spin echo scan and an axial fast fluid-attenuated inversion recovery scan (total scan time = 5 min). These were followed by a whole-brain three-dimensional coronal inversion recovery-prepared spoiled gradient echo (IR-SPGR) scan, giving isotropic 1.1-mm voxels in a scan time of approximately 6 min (echo time (TE) = 2.82 msec; repetition time (TR) = 6.96 msec; inversion time = 450 msec; excitation flip angle = 20°).

Participants then underwent a 15 min BOLD acquisition using gradient echo EPI (450 image volumes of 38 slices with 3 mm thickness, interslice gap = 0.3 mm; TE/TR = 30/2000 ms; flip angle (FA) = 75°; in-plane voxel size = 3.3 mm; matrix size = 64 × 64; field of view = 21.1 × 21.1 cm). During this acquisition they were asked to look at a small fixation cross displayed on the screen in front of them. A dynamically modeled intravenous infusion of ketamine was commenced 5 min after the start of the BOLD acquisition (target plasma level: 150 ng/mL) driven by a pump situated outside the scanner room, with participants having no indication that the infusion had started. The rate of infusion was controlled over the full period of infusion by a laptop computer running Stanpump software (www.opentci.org) driving a Graseby 3400 syringe driver. The rate was determined based on the pharmacodynamic properties of ketamine from the "Clements 250 model" (Absalom et al., 2007; Clements and Nimmo, 1981). In practice, this translated to a rapid bolus over 20 s of approximately 0.26 mg/kg followed by a slow infusion of approximately 0.42 mg/kg/h.

After being disconnected from the ketamine infusion and leaving the scanner, blood levels for ketamine and norketamine were taken, following which participants rated peak ketamine-induced effects using the PSI. Corrected PSI subscale scores were calculated by dividing the total subscale score by the number of items for each subscale (range for each subscale after correction: 0–3).

Data analysis

Data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Slice-timing correction and two-pass realignment of the time series image volumes was followed by spatial normalization to the SPM EPI template. Data were smoothed using an 8 mm full width at half maximum (FWHM) Gaussian kernel. A high-pass filter of 1200 s was applied to minimize the influence of very low frequency noise present in phMRI BOLD data.

The phMRI response to ketamine was modeled using a gamma-variate regressor based on the results of a previously published ketamine phMRI study in humans (Deakin et al., 2008) and validated in an independent cohort (De Simoni et al., 2012). The regressor was flat for the first 5 min and then rose after commencement of the ketamine infusion, peaking at 240 s, and decreasing to 50% of its maximum by 10 min post-infusion. In addition, a Singular Value Decomposition of the three translational and three rotational head movement traces, a white matter regressor, and a linear drift regressor were included as nuisance variables.

Whole-brain voxel-wise contrast maps were generated for each subject and analyzed in a single-sample group analysis to investigate the effect of ketamine on BOLD response. For statistical inference we used cluster-corrected statistics at family-wise error (FWE) $p < 0.05$ with a cluster-forming threshold of $p < 0.001$ at the voxel level. The relationship between ketamine-induced BOLD response and psychopathology was investigated by regression of the change in PSI subscales from baseline against whole-brain individual t-contrasts, using the same statistical thresholds.

Results

Ketamine administration led to a significant ($p < 0.05$) [mean(SD)] increase from baseline in subjective ratings on Perceptual Distortion [0.74(0.47)], Cognitive Disorganization [0.72(0.70)], Mania [0.48(0.45)], Anhedonia [0.41(0.34)] and Delusional Thinking [0.29(0.40)] PSI subscales, but there was no significant increase in PSI-rated Paranoia [0.08(0.15)]. With the exception of Anhedonia and Paranoia, these were significantly greater than the subjective effects reported with the lower target dose of 75 ng/mL plasma ketamine from our earlier study ($p < 0.05$, Figure 1) (De Simoni et al., 2012). After leaving the scanner, ketamine and norketamine [mean(SD)] levels were 113.8(27.6) ng/mL and 56.5(14.3) ng/mL, respectively. There were no correlations between ketamine or norketamine levels and clinical rating scales.

Ketamine led to widespread, significant increases in BOLD response in multiple cortical and subcortical brain regions including cingulate gyrus, hippocampus, insula, thalamus and midbrain (cluster size = 57367 voxels; FWE-corrected $p < 0.001$; Figure 2). Ketamine led to a significant decrease in BOLD response in a single cluster centered on the subgenual anterior cingulate (cluster peaks at [–2, 30, –10],[0, 38, –4],[6, 34, 12]; cluster size = 291 voxels; FWE-corrected $p = 0.008$). With whole-brain regression analysis, increase in PSI Perceptual Distortion from baseline was positively related to one cluster of increased BOLD following ketamine administration—in the paracentral lobule (cluster peaks at [–6,–24, 52], [–12, –22, 72],

[4, –28, 62]; cluster size = 376 voxels; FWE-corrected p = 0.001). Change in PSI Delusional Thinking from baseline was also positively related to one cluster of increased BOLD following ketamine administration in an overlapping region (cluster peaks at [8, –20, 58], [–2, –24, 70], [8, –30, 66]; cluster size = 489 voxels; FWE-corrected $p < 0.001$). It should be noted that change from baseline in PSI Delusional Thinking and in PSI Perceptual Distortion were correlated ($r = 0.62$, $p < 0.05$). There were no other correlations of BOLD changes with PSI subscales.

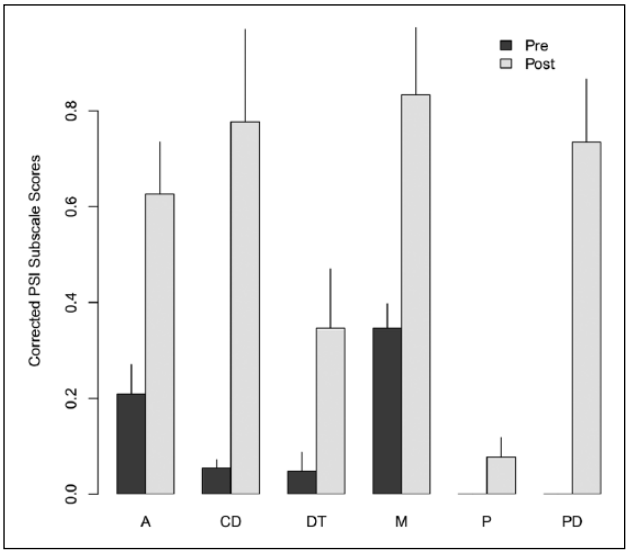

Figure 1. Subjective ratings of psychopathology (mean PSI subscales with error bars showing standard error) pre- and post-ketamine administration (A: Anhedonia; CD: Cognitive Disorganization; DT: Delusional Thinking; M: Mania; P: Paranoia; PD: Perceptual Distortion).

Conclusions

This study shows a relationship between ketamine-induced perceptual distortion and changes in BOLD activation. The study also replicates the earlier findings that ketamine administration increases cortical BOLD response in humans, with good agreement on the regions affected (De Simoni et al., 2012; Deakin et al., 2008). The reduction in subgenual anterior cingulate cortex is notable in that it is in the same brain region as reported in three earlier studies (De Simoni et al., 2012; Deakin et al., 2008; Doyle et al., 2013), and is the only region in which a reduction in BOLD was seen using whole-brain analysis. It is interesting to note that ketamine-induced changes in blood flow measured using PET did not show any reductions (Langsjo et al., 2004). While these did not measure immediate change on bolus administration due to the poor temporal resolution of PET, it remains possible that the subgenual anterior cingulate changes measured with BOLD represent ketamine-induced changes in metabolism decoupled from blood flow.

In this study, PSI-rated increases in Perceptual Distortion on the PSI rating scale were the strongest effects of ketamine. In comparison with our earlier, lower-dose study (De Simoni et al., 2012), PSI ratings were significantly higher in all categories, but the pattern of ketamine-induced changes in PSI ratings was very similar, indicating that the PSI appears to be a robust marker of the effects of ketamine across different doses. Perceptual Distortion and Delusional Thinking were both associated with the ketamine-induced effects on BOLD response in the paracentral lobule in the body area (Penfield and Rasmussen, 1950). This area may be activated in response to ketamine-induced alterations in body sensation and delusional interpretations of sensations. We also speculate that this account can also be interpreted within the forward model where a failure of feed-forward inhibition alters the experience of sensory stimuli, including bodily sensations, such that perceptions have an altered quality (Frith, 2005). Future investigations should

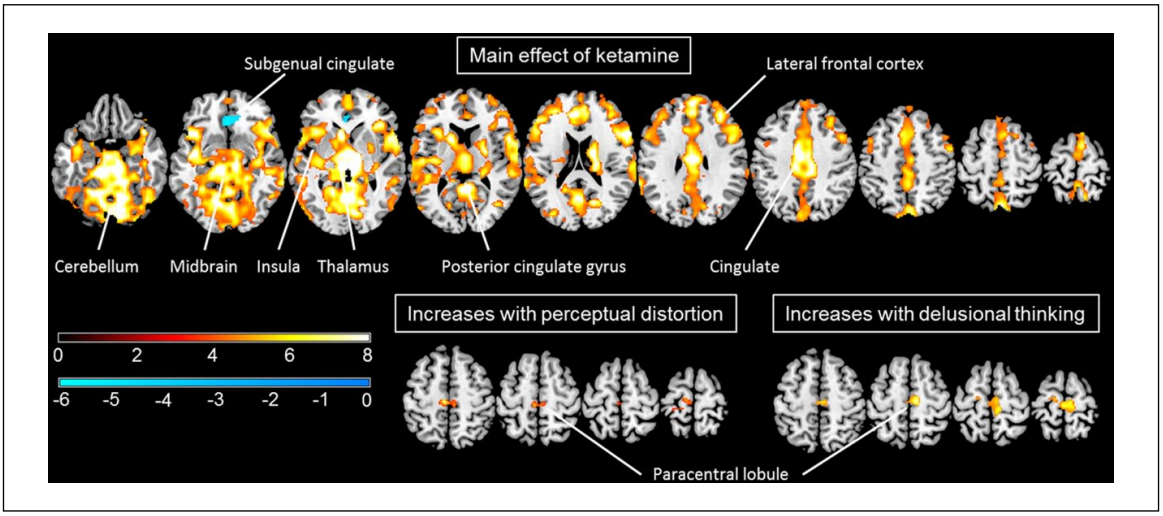

Figure 2. Main effect of ketamine on BOLD response (upper row). Image shows significant increases (red/yellow) at $p < 0.05$ cluster-corrected overlaid on the high-resolution MNI template brain from MRIcroN (www.mricro.com). A single cluster of decreased BOLD response following ketamine administration is shown in blue (whole-brain cluster-corrected $p < 0.05$). Brain slices (from left to right) are at MNI z values of –20 to 70 at 10 mm intervals. The lower row shows the clusters of significant association between BOLD signal following ketamine and self-rated perceptual distortion and delusional thinking (whole-brain cluster-corrected $p < 0.05$).

assess the forward model account of experiences on ketamine by combining ketamine administration with experimental interventions such as passive control of movements (Blakemore et al., 2003).

There are a number of potential limitations to the study. The perceptual effects of ketamine were scored retrospectively, rather than during the experience. We felt that this was unavoidable as rating experiences during the scan may have had an impact on the scan quality and possibly on BOLD response. Furthermore, during the experience, due to its intensity, participants may have found answering questions difficult or intrusive. In support of this approach, we have previously shown, using a lower dose of ketamine, that retrospective scoring using the PSI gives highly reliable ratings (ICC = 0.93). A second issue is that the regions showing the greatest BOLD change following ketamine administration did not fully overlap with the regions associated with ketamine-induced perceptual changes. Thus, it appears that the effects of ketamine on BOLD associated with perceptual changes and delusional thinking are distinct from the main effects of ketamine on BOLD signal. Third, we did not have a placebo arm. However, participants were not aware when the ketamine was started, and our earlier placebo-controlled study using an identical design did not show any effect of placebo on BOLD signal in any brain region (Doyle et al., 2013). Lastly, ketamine blood levels were taken after disconnection of the ketamine infusion (required to allow participants to leave the scanner). As ketamine is rapidly cleared from the blood, this is likely to have led to an underestimation of ketamine blood levels, and a greater variance of measures.

Although ketamine led to increases in subjective ratings in Cognitive Disorganization and Mania, these were not related to any changes in BOLD. Thus, it is possible that these effects may arise through other mechanisms, such as ketamine-induced alterations in brain connectivity (Driesen et al., 2013; Niesters et al., 2012; Scheidegger et al., 2012,). Future studies in our laboratory will investigate this possibility.

Declaration of Conflicting Interests

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