Ketamine alters neural processing of facial emotion recognition in healthy men: an fMRI study

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Disruption of facial emotion perception occurs in neuropsychiatric disorders where the expression of emotion is dulled or blunted, for example depersonalisation disorder and schizophrenia. It has been suggested that, in the clinical context of emotional blunting, there is a shift in the relative contribution of brain regions subserving cognitive and emotional processing. The non-competitive glutamate receptor antagonist ketamine produces such emotional blunting in healthy subjects. Therefore, we hypothesised that in healthy subjects ketamine would elicit neural responses to emotional stimuli which mimicked those reported in depersonalisation disorder and schizophrenia. Thus, we predicted that ketamine would produce reduced activity in limbic and visual brain regions involved in emotion processing, and increased activity in dorsal regions of the prefrontal cortex and cingulate gyrus, both associated with cognitive processing and, putatively, with emotion regulation.

Measuring BOLD signal change in fMRI, we examined the neural correlates of ketamine-induced emotional blunting in eight young right-handed healthy men receiving an infusion of ketamine or saline placebo while viewing alternating 30 s blocks of faces displaying fear versus neutral expressions. The normal pattern of neural response occurred in limbic and visual cortex to fearful faces during the placebo infusion. Ketamine abolished this: significant BOLD signal change was demonstrated only in left visual cortex. However, with ketamine, neural responses were demonstrated to neutral expressions in visual cortex, cerebellum and left posterior cingulate gyrus. Emotional blunting may be associated with reduced limbic responses to emotional stimuli and a relative increase in the visual cortical response to neutral stimuli. *NeuroReport* 14:387–391 © 2003 Lippincott Williams & Wilkins.

Key words: Ketamine; Fear; fMRI

INTRODUCTION

Facial expressions of emotion are key regulators of social interaction and direct the appropriateness of responses between individuals. For example, the expressions of fear and disgust in a face are efficient displays to others of the presence of imminent danger [1]. Adaptive pressures guarantee that recognition of facial expressions of emotion is crucial for survival in the chosen human social environment.

More recently, the neural substrates underlying facial emotion processing have been examined with functional imaging. The perception of different facial negative emotions, including fear and sadness, evokes activation in the amygdala and visual cortex [2–8]. Inconsistent findings are reported regarding the neural substrates of happiness, but may include the amygdala [2]. The amygdala may therefore have a role in the modulation of visual cortical activity in response to emotions displayed by others [9,10].

In certain situations, emotional responses need to be inhibited in order that they remain appropriate for the context. Evidence from several studies suggests the presence of a reciprocal functional relationship between brain regions important for emotion processing including limbic regions and ventral anterior cingulate gyrus, and those important for the performance of cognitive tasks, including more dorsal regions of prefrontal cortex and anterior cingulate gyrus [10–12]. In low doses, the non-competitive NMDA antagonist ketamine has been shown consistently to produce blunting of emotional states e.g. mimicking that seen in depersonalization disorder and schizophrenia, and depersonalisation in healthy subjects [13]. In a recent study [14] there was evidence for increased ventrolateral prefrontal cortical activation (which may have a regulatory role in guiding emotional or choice behaviour [15]) and reduced limbic activation in response to aversive scenes in depersonalized patients. Drug-induced depersonalization is also reported to produce increased inferior frontal and reduced sub-cortical blood flow [16]. This may suggest that there is a shift in the relative contribution of the neural regions subserving cognitive and emotional processing in the clinical context of emotional blunting.

We hypothesised that in healthy subjects ketamine would elicit a neural response to emotional stimuli suggestive of an inhibitory emotional style. We predicted that ketamine would produce (1) reduced activity in limbic regions, including amygdala, insula and ventral anterior cingulate gyrus, and visual regions involved in processing emotional responses; (2) increased activity in dorsal regions of the prefrontal cortex and dorsal anterior cingulate gyrus (both putatively associated with emotion regulation).

MATERIALS AND METHODS

Subjects and procedure: Eight right-handed healthy male subjects were recruited by local advertisement (mean age 28.75 years; range: 23–42; mean number of years education, 16) and screened for psychiatric or medical illness by a psychiatrist (KMA). None was using any medication; all were naive to ketamine. Ethical approval was obtained and all procedures and possible side effects were fully explained to subjects by a psychiatrist or physician (KMA or MA) and subjects were given opportunities to ask questions before, and on the day of, testing. Written and witnessed informed consent was signed. No ill effects were reported after the ketamine infusion and subjects were provided with transport home.

Ketamine and placebo administration: Subjects attended 1 h before the scan and were cannulated in a forearm vein. Systolic and diastolic blood pressure and pulse were monitored at −2, 0, 5, 10, 15, 30, and 45 min throughout the infusion. Ketamine or normal saline placebo was infused into this cannula in a randomised, double-blind manner: a bolus dose of 0.23 mg/kg over 0–5 min, followed by an infusion (controlled by an I-Med pump system) of 0.5 mg/kg from 5 to 45 ($\pm$ 15) min (maximum 1 h). Subjects entered the scanner at $\sim$10 min after ketamine administration and underwent structural scans between 10 and 20 min, with cognitive tasks thereafter. The whole procedure took $\sim$45–60 min.

Drug administration was double blind, but the psychotropic effects of ketamine meant that subjects and investigators were usually able to distinguish placebo from the active drug. Test days were separated by $\geq$ 1 week and to keep the second test day blinded, subjects were told they had a one-in-three chance of receiving ketamine or placebo at each visit.

Cognitive and neurobehavioural measures: Subjects underwent assessment with the Clinician Administered Dissociative States Scale (CADSS) and BPRS as described previously [13]. In the scanner, subjects viewed 10 alternating 30 s blocks of neutral expression faces as employed in previous studies [5] and 100% fearful faces. In each 30 s block, eight faces were displayed for 3 s with an interstimulus interval of 0.75 s. Each face stimulus subtended visual angles of 10° horizontally and 8° vertically. Subjects decided upon the sex of the face as described previously [17].

Image acquisition: Gradient echo echoplanar images were acquired on a GE Signa 1.5 T Neurovascular system (General Electric, Milwaukee WI, USA) at the Maudsley Hospital, London. One hundred T2*-weighted images depicting BOLD contrast [18] were acquired over 5 min (for each task) at each of 14 near-axial non-contiguous 7 mm thick planes parallel to the intercommissural (AC-PC) line (TE 40 ms, TR 3 s, in-plane resolution 7 mm, interslice gap 0.7 mm).

Statistical analyses: BPRS, CADSS, depersonalization and accuracy data were analysed using a one-way ANOVA ($\alpha < 0.05$) with drug condition as the between-groups factor. Correlational analyses were performed using Spearman's rank order test.

Following motion correction [19], periodic change in T2*-weighted signal intensity at the (fundamental) experimentally determined frequency of alternation between A and B conditions (1/60 Hz in all experimental conditions), the standardised power of response (fundamental power quotient, FPQ), was estimated by an iterated least squares fit of a sinusoidal regression model at each voxel and its significance tested nonparametrically as described previously [17]. For group analysis, the data were transformed into stereotactic space [20] and median FPQ maps (generic brain activation maps, GBAMs) constructed following smoothing with a 2D Gaussian filter with full width half maximum = 11 mm [21]. The p-value threshold for activation at each voxel in each GBAM was < 0.004.

To estimate differences in mean power of functional activation between the two experimental conditions, we fitted an analysis of covariance (ANCOVA) model at each intracerebral voxel of the standardised power maps after their co-registration in standard space. Generally the form of the model was as described previously [17].

RESULTS

Phenomenology: Ketamine produced significant increases in CADSS ($p < 0.0001$), depersonalization ($p < 0.0001$), BPRS total ($p < 0.0001$), BPRS factor scores: thought disorder ($p < 0.0001$), withdrawal ($p = 0.012$); hostility ($p = 0.03$) and activation ($p = 0.016$).

Accuracy data: Accuracy on sex decision task did not vary significantly between the two conditions (with and without ketamine). Mean percentage correct scores were ketamine 96.4 $\pm$ 3.45; placebo 95.0 $\pm$ 6.0.

Generic brain activation maps (GBAMs): During placebo infusion, predominant regions of BOLD signal change to fearful faces included left amygdala, bilateral visual processing regions (right precuneus (BA 31), right superior temporal gyrus (BA 22), left middle occipital gyrus (BA 37) and left fusiform gyrus (BA 37)), in addition to bilateral posterior cingulate gyri (BA 23) and bilateral cerebellum. The only major regions of BOLD signal change to neutral expressions were left inferior temporal gyrus and right inferior parietal lobule (BA 40; Table 1) (Fig. 1).

During Ketamine infusion, the only region of BOLD signal change to fearful faces was the left superior occipital gyrus (BA19). Major regions of BOLD signal change to neutral expressions were bilateral visual processing regions

Table 1. Major brain regions with significant BOLD signal change with presentation of neutral *vs* fearful faces under placebo and ketamine conditions.

Region (approximate Brodmann area)	Side	x[a]	y[a]	z[a]	No. of voxels	Emotion[b]
Placebo						
Cerebellum	Right	11	−37	−7	17	Fear > Neutral
	Left	−43	−56	24	22	Fear > Neutral
Fusiform gyrus (BA 37)	Left	−43	−52	−18	16	Fear > Neutral
Middle occipital gyrus (BA 37)	Left	−40	−56	−7	13	Fear > Neutral
Superior temporal gyrus (BA 22)	Right	43	−37	20	8	Fear > Neutral
Precuneus (BA 31)	Right	21	−60	26	7	Fear > Neutral
Posterior cingulate gyrus (BA 23)	Bilateral	0	−37	20	7	Fear > Neutral
Amygdala	Left	−15	−7	−13	9	Fear > Neutral
Inferior parietal lobule (BA 40)	Right	40	−26	31	12	Neutral > Fear
Inferior temporal gyrus (BA 20)	Left	−32	−20	−35	7	Neutral > Fear
Ketamine						
Superior occipital gyrus (BA 19)	Left	−28	−63	31	15	Fear > Neutral
Cuneus (BA 18)	Right	7	−76	26	37	Neutral > Fear
Posterior cingulate gyrus (BA 23/30)	Left	−15	−56	9	11	Neutral > Fear
Caudate nucleus	Right	7	0	20	10	Neutral > Fear
Superior temporal gyrus (BA 22)	Left	−50	−46	15	9	Neutral > Fear
Precuneus (BA 31)	Left	−25	−63	26	8	Neutral > Fear
Inferior parietal lobule (BA 40)	Left	−47	−39	31	7	Neutral > Fear
Cerebellum	Bilateral	0	−67	−7	12	Neutral > Fear
Posterior cingulate gyrus (BA 23)	Left	−15	−56	9	11	Neutral > Fear
Putamen	Left	−11	−26	9	5	Neutral > Fear

[a]The cluster with the largest number of voxels within each region is reported. Talairach co-ordinates refer to the voxel with the maximum FPQ (fundamental power quotient) in each cluster. All such voxels were identified by a one-tailed test of the null hypothesis that median FPQ is not determined by experimental design. The probability threshold for activation was $p \leq 0.004$.
[b]Regions activated significantly more by fear compared with neutral (Fear > Neutral) or neutral compared with fear (Neutral > Fear).

(right cuneus (BA 18), left precuneus (BA 31), left superior temporal gyrus (BA 22)), in addition to the left posterior cingulate gyrus (BA 23), right caudate nucleus, left putamen and bilateral cerebellum (Table 1) (Fig. 1).

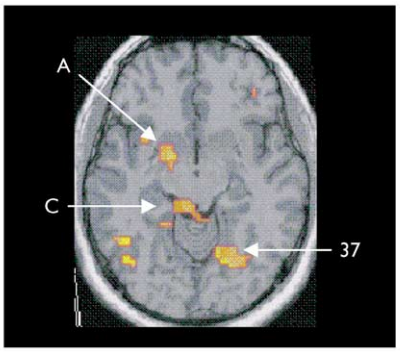
Comparison of the GBAMs relating to the two experimental conditions showed two regions with significantly greater BOLD signal change during ketamine than placebo infusion, and one during placebo compared with ketamine infusion ($p = 0.01$; search volume 393 voxels; number of expected false positively activated voxels = 3). Significantly greater BOLD signal change was demonstrated in the right cerebellum in the placebo compared with the ketamine condition in response to presentation of fearful facial expressions. Significantly greater BOLD signal change was demonstrated in the right precuneus (BA 31) and bilateral caudate nuclei in the ketamine compared with the placebo condition in response to neutral facial expressions (Table 2).

DISCUSSION

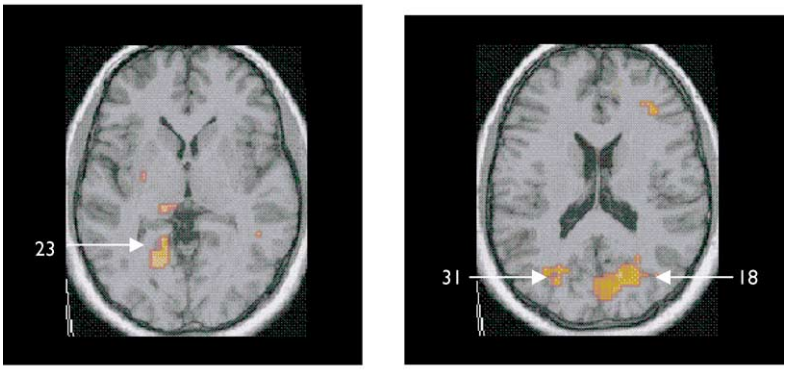
We investigated the effects of low dose ketamine in healthy men on the neural responses to facial expressions of emotion using pharmaco-fMRI. During placebo, predominant regions of BOLD signal change to fearful faces were demonstrated within the left amygdala, bilateral visual processing regions and cerebellum, findings similar to those of previous investigations of normal neural responses to fearful faces [3,5,6]. Neutral faces activated only the left inferior temporal gyrus and right inferior parietal lobule. By contrast, in the ketamine condition in the same individuals the only region significantly activated to fearful faces was left superior occipital gyrus (a visual processing region), while neutral expressions elicited activation in bilateral visual processing regions, left posterior cingulate gyrus, right caudate nucleus, left putamen, and bilateral cerebellum. Comparison of the two conditions revealed significantly greater activation to fearful faces in right cerebellum during placebo compared with ketamine, and to neutral faces within right precuneus and bilateral caudate nuclei. Our findings suggest that during ketamine infusion, fearful faces no longer activate the amygdala and other limbic regions, and the response to these faces in visual processing regions is significantly reduced compared with placebo, whilst neutral faces activate visual processing regions significantly more than during placebo.

As expected, behavioural ratings in our subjects with ketamine are consistent with emotional blunting seen in patients with schizophrenia and depersonalisation disorder [22]. In depersonalisation disorder, we have shown a similar pattern of reversal of activation in limbic areas i.e. limbic activation to neutral stimuli and no limbic or visual activation to aversive stimuli [14]. In schizophrenia, there is also a relative reduction in response to fearful facial stimuli, but not a reversal of activation [23]. Emotional blunting is common to schizophrenia, depersonalisation or subjects exposed to ketamine and therefore, may be associated with relative inhibition in limbic areas and, in the depersonalised or ketamine-exposed subjects, an apparent increase in activation in visual processing regions with neutral stimuli.

Although ketamine abolished the amygdala response to fear, in the comparison of neural responses to fear during ketamine and placebo, the decrease in BOLD signal in the amygdala during the ketamine condition did not reach statistical significance. This finding may have resulted from susceptibility-induced magnetic field inhomogeneities in



Placebo: fearful facial expressions



Ketamine: neutral facial expressions

Fig. 1. Generic activation during placebo and ketamine conditions. Generic brain activation in response to fearful facial expressions during the placebo condition is depicted in a transverse section ($z = -13$) within the left amygdala (Am), right cerebellum (C) and left fusiform gyrus (BA 37). Generic brain activation in response to neutral facial expressions in the ketamine condition is depicted in transverse sections within the left posterior cingulate gyrus (BA 23; $z = 9$), and right cuneus (BA 18) and left precuneus (BA 31; $z = 26$). These generic brain activations are superimposed upon an SPGR structural template. We would like to thank Krish Singh for use of the programme superimposing brain activation on SPGR structural template.

Table 2. Comparison data between placebo and ketamine conditions: generically activated brain regions to fear *vs* neutral faces.

Region (approximate Brodmann area)	Side	x[a]	y[a]	z[a]	No. of voxels	Emotion
Placebo						
Cerebellum	Right	9	−31	−7	5	Fear > Neutral
Ketamine						
Precuneus (BA 31)	Right	3	−58	26	12	Neutral > Fear
Caudate nucleus	Bilateral	0	0	20	7	Neutral > Fear

[a]Regions activated significantly more in the placebo *vs* ketamine, and ketamine *vs* placebo conditions are demonstrated ($p = 0.01$). The cluster with the largest number of voxels within each region is reported. Talairach co-ordinates refer to the voxel with the maximum FPQ (fundamental power quotient) in each cluster.

the amygdala region and the relatively large voxel size in the images obtained in this study, both of which can lead to signal loss in the amygdala. The employment of high-resolution fMRI and small image voxel size in future studies examining neural responses to fearful stimuli may provide solutions to this problem [24]. However, there was a significant increase in BOLD signal change in the caudate nuclei bilaterally in the ketamine condition compared with placebo. The ventral striatum (including caudate) has been implicated in the response to both positive and aversive stimuli [25].

Contrary to our initial hypotheses, we did not demonstrate increased activity in dorsal prefrontal regions. Glutamatergic NMDA receptors are most densely located in CA1 hippocampal neurons, but also throughout hippocampal, parahippocampal structures and cerebellum. Glutamatergic pathways have rich projections through the ventral perforant pathways, for example to amygdala and entorhinal cortex. PCP and ketamine psychotomimetic effects are mediated through NMDA blockade and, in non-addicted subjects, low dose ketamine increases central inhibition as assessed with prepulse inhibition [13]. Therefore, rather than producing reciprocal changes in activity in dorsal prefrontal cortex and limbic regions, ketamine may simply inhibit neurotransmission in basal limbic glutamate pathways.

During the ketamine condition there was greater BOLD signal change in visual cortex to neutral faces. One possible explanation might be that ketamine increases activation in visual cortex by increasing eye movements. However, at this dose, ketamine does not have cholinergic receptor affinity and subjects do not report visual disturbance except illusions, see [13]. Increased visual cortical activation is associated with increased visual attention to salient stimuli e.g. emotion compared to neutral stimuli in healthy subjects [9]. Our findings suggest that, with ketamine, visual attention is greater to neutral stimuli rather than emotional stimuli with associated BOLD signal increases in visual cortex and ventral striatum.

CONCLUSION

The abnormalities we find cannot be explained by non-specific effects of ketamine on BOLD signal as ketamine produces changes in response to emotional stimuli without being associated with global changes in blood flow *per se* [17]. Our results provide evidence that emotion is regulated by limbic pathways, at least in part, under the control of glutamatergic neurotransmission and that the neural correlates of emotional blunting and depersonalisation seem co-located in these limbic pathways whose connections are disrupted in disease or with NMDA antagonists. Further work is needed to address the effects of ketamine on the declarative experience of emotion, and its effects on the more subtle aspects of the reciprocal relationship between cognitive and emotion processing.

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