

Ketamine administration reduces limbic reactivity during emotional stimulation – An fMRI study in healthy subjects

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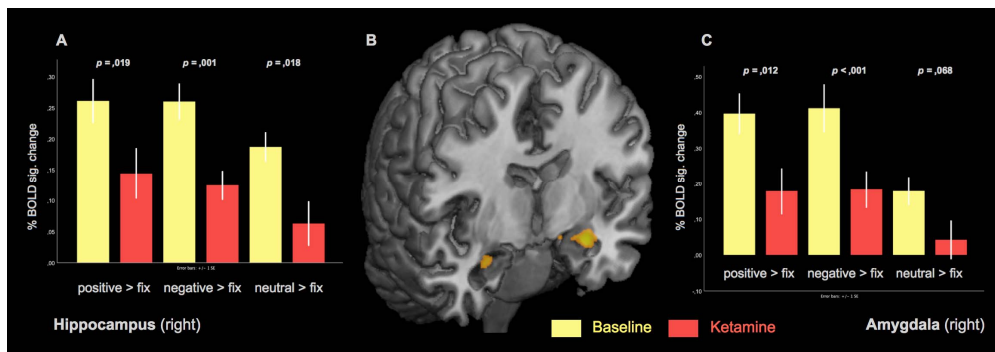
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INTRODUCTION

Previous studies using emotional fMRI paradigms reported enhanced responses in brain structures involved in mood regulation like the amygdala, hippocampus, insula, and orbitofrontal cortex in depressed patients compared with healthy controls (for review see [1]). Many related neuroimaging findings are compatible with the hypothesis that limbic hyperactivity, e.g. in the amygdala, during evaluation of emotional stimuli, combined with prefrontal hypoactivity, which is reflecting a failure of cortical control, might cause negative emotional biases in depressed patients [2]. An elevated amygdala activation to emotional stimuli was specifically observed in carriers of the short (S) allele of the serotonin transporter linked polymorphic region (5-HTTLPR) gene who also show an increased risk for depression in the context of environmental stress [3]. While cognitive psychotherapy has been shown to decrease amygdala hyperactivity (possibly through increasing inhibitory executive control via the prefrontal cortex), antidepressant drug treatment might target limbic regions directly: Both limbic reactivity to emotional faces and depressive symptoms decreased following treatment with serotonergic antidepressants (SSRIs) (for review see [4]). Recently, the NMDA-receptor antagonist ketamine has been established as a tool compound for the investigation of novel antidepressant drug targets [5]. **In this work**, the effect of ketamine as a glutamatergic agent on cortico-limbic activity during emotional stimulation is investigated. To that we combined fMRI at baseline and during pharmacological challenge with an intravenous antidepressant dose of ketamine.

METHODS

A total of 23 healthy subjects (mean age, 25.5y \pm 5y (SD); 12 males) with no history of neurological or psychiatric illness completed two separate fMRI sessions (baseline and pharmacological intervention respectively) on a Philips Achieva 3T whole-body MR unit equipped with an 8-channel head coil. Functional time series were acquired with a sensitivity-encoded single-shot echo-planar sequence (SENSE-ssHPI) during an emotional task condition. In one of the sessions, S-ketamine was administered as an intravenous bolus of 0.12 mg/kg approximately 15 minutes prior to the fMRI task, followed by a continuous infusion of 0.25 mg/kg/h during the task period. The subjects were asked to judge photographs from the International Affective Picture System (IAPS) by button press according to their valence. The stimuli were presented in a blocked design (5 positive, 5 negative and 5 neutral blocks; task periods: 5-7 pictures, durations: 21-27 sec; alternating with resting periods: fixation cross, duration: 9 sec). The following acquisition parameters were used in the fMRI protocol: TE = 35 ms, TR = 3000 ms (\approx 82°), FOV = 22 cm, acquisition matrix = 80 x 80 interpolated to 128 x 128, voxel size = 2.75 x 2.75 x 4mm, 32 contiguous axial slices (placed along the anterior-posterior commissure plane), and sensitivity-encoded acceleration factor R = 2.0. A 3-dimensional T1-weighted anatomical scan was obtained for structural reference. The functional imaging data were analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm/). For the ROI analysis effect sizes (% signal change) and fitted responses for the different conditions were extracted for each subject separately using Marsbar.



A: Reduced positive BOLD responses during emotional stimulation in right hippocampus (extracted using AAL MNI ROI library and Marsbar SPM8 region of interest toolbox) after ketamine administration compared to baseline (paired t test, n=23, error bars: \pm SEM). **B:** Cluster of voxels in amygdalo-hippocampal region showing reduced BOLD responses after ketamine administration (condition: 'negative > fixation', n=23, paired t-test map, baseline > ketamine' thresholded at t=3-5; p = .0066 - .0001 uncorrected). **C:** Reduced positive BOLD responses during emotional stimulation in right amygdala following ketamine administration (statistics: s. Fig. A).

RESULTS

Based on previous reports of altered cortico-limbic function in MDD patients we extracted % BOLD signal changes in a priori determined regions of interest from the AAL ROI library (in Marsbar) including the amygdala, hippocampus, insula, orbitofrontal, mediofrontal and dorsolateral prefrontal cortices. Ketamine administration significantly reduced functional activation in the right (ANOVA; significant main effect of drug condition (Pillai's Trace): $F_{(1,22)} = 13.1$, $p = .002$) and left ($F_{(1,22)} = 15.7$, $p = .001$) amygdala (AR/AL), as well as in the right ($F_{(1,22)} = 11.8$, $p = .002$) and left ($F_{(1,22)} = 21.8$, $p < .001$) hippocampal formation (HR/HL) during emotional stimulation compared to baseline (n=23; paired t tests (condition): AR: $p = .012$ (positive), $p < .001$ (negative); AL: $p = .005$ (positive), $p < .001$ (negative); HR: $p = .019$ (positive), $p = .001$ (negative); HL: $p = .003$ (positive), $p < .001$ (negative); s. Fig). The effect size for the drug difference was larger in response to negative pictures ($d = 0.81-1.16$) compared to positive ($d = 0.50-0.66$) or neutral ($d = 0.37-0.61$) valenced pictures. In contrast, no significant effect of drug condition was found in the insula, orbitofrontal, mediofrontal and dorsolateral prefrontal cortex by ANOVA testing.

DISCUSSION & CONCLUSION

Our findings show that in healthy subjects an antidepressant intravenous dose of ketamine reduces limbic reactivity in the amygdalo-hippocampal complex during an emotional processing task but has no significant effect on insular or prefrontal parts of the cortico-limbic neurocircuitry of mood regulation. A reduction of limbic reactivity to emotional stimulation has been observed in previous fMRI studies with antidepressant drug treatment and is in line with the hypothesis that antidepressant medication might target limbic regions directly, rather than relying on inhibition through the prefrontal cortex (for review see [4]). However, an increased inhibitory cortico-limbic modulation following ketamine administration cannot be ruled out solely due to the lack of significant BOLD signal alterations. Similar to other antidepressants, a reduction of limbic reactivity after an antidepressant dose of ketamine resembles a neurodynamic pattern of normalization with regard to MDD, where limbic hyperactivity could be observed frequently. Nevertheless, the relevance of an acute reduction of limbic reactivity as an early biomechanism of antidepressant drug action has to be further evaluated in post-challenge fMRI studies, since the antidepressant effect of ketamine starts to build up during the first 1-2 hours post-infusion and remains significant for 3-7 days [5, 6]. In conclusion, our findings suggest that pharmacologically modulating limbic neurocircuits might be an important therapeutic strategy to restore parts of the disrupted neurobehavioural homeostasis in MDD.

REFERENCES

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