EMOTIONAL PROCESSING AND BRAIN METABOLISM AFTER PHARMACOLOGICAL STIMULATION WITH KETAMINE

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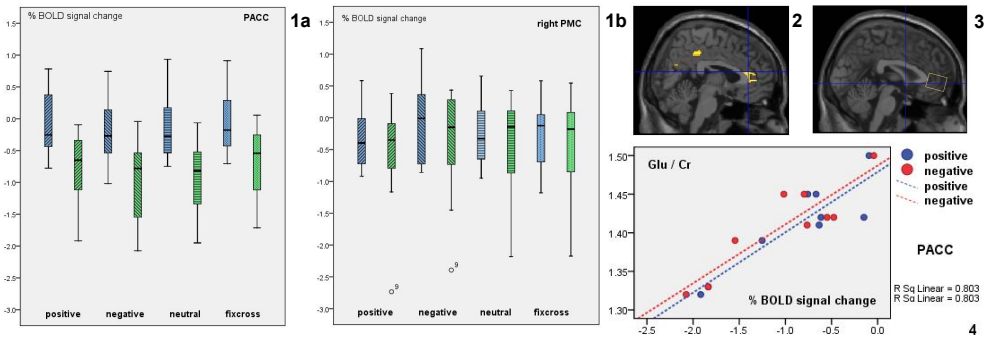
INTRODUCTION

Ketamine is a potent glutamatergic NMDA receptor antagonist with rapid antidepressant properties at subanaesthetic doses, thus providing a valuable research tool for the investigation of the neurobiology of mood disorders [1]. Increasing evidence underscores the role of glutamate dependent neuroplasticity and glutamatergic neurotransmission and metabolism in the pathophysiology of major depressive disorder (MDD)[2]. More specifically, a disturbed neuron-glia-interaction with decreased glutamate-glutamine-cycling is proposed as an explanatory model for the observed structural, metabolic and functional abnormalities associated with the disease [3, 4]. Hence, the effects of ketamine on the glutamatergic system and functional brain activity during emotional processing have to be further investigated in order to understand its rapid antidepressant properties. This multimodal imaging study in 14 healthy subjects aims at probing the neuropharmacological effects of a single intravenous subanaesthetic ketamine infusion on fMRI-BOLD responses during emotional processing and their relationship to glutamatergic metabolite concentrations assessed by proton magnetic resonance spectroscopy (^{1}H-MRS) compared to baseline conditions.

MATERIALS & METHODS

A total of 14 healthy subjects (7 women, 7 men; mean age: 26.9, SD 4.4) with no history of neurological or psychiatric illness were recruited for this study. All subjects completed two separate fMRI sessions (baseline and pharmacological intervention respectively) on a Philips Achieva 3T whole-body magnetic resonance unit equipped with an 8-channel head coil. Approximately 15 minutes prior to the fMRI task, S-ketamine was administered as an intravenous bolus of 0.12 mg/kg, followed by a continuous infusion of 0.25 mg/kg/h over 60 minutes. A 3-dimensional T1-weighted anatomical scan was obtained for structural reference. In addition, resting-state proton magnetic resonance spectra (^{1}H-MRS) from the pregenual anterior cingulate cortex (PACC) could be obtained in 9 healthy subjects immediately after the fMRI task for both experimental conditions. **Functional Magnetic Resonance Imaging (fMRI):** Functional time series were acquired with a sensitivity-encoded single-shot echo-planar sequence (SENSE-sshEPI) during an emotional task condition. 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 (θ = 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. 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. Functional BOLD responses in the PACC were related to molecular measures (^{1}H MRS) of glutamatergic metabolites and neurotransmitters before and after the pharmacological intervention with ketamine. **Proton Magnetic Resonance Spectroscopy (^{1}H-MRS):** Single voxel ^{1}H MRS data were acquired from a volume of interest (VOI: 18 x 25 x 20 mm) in the pregenual anterior cingulate cortex (PACC, Fig. 3), a brain region implicated in mood regulation and the pathophysiology of MDD. To enable unambiguous and simultaneous quantification of in vivo gamma-amino-butyric-acid (GABA), glutamate (Glu), glutamine (Gln), glucose (Glc), and N-acetyl-aspartate (NAA) concentrations MRS data were acquired using a maximum echo–sampled 2-dimensional J-resolved point-resolved spectroscopy (JPRESS) sequence and quantified using ProFit (for details cf. [5]).



*1: % BOLD signal change in PACC voxel cluster (p<.021) (**1a**) and right PMC (ns) (**1b**) before (blue) and after ketamine administration (green).*
2: Cluster of voxels in PACC showing negative BOLD responses after ketamine administration (task condition: 'rest>emotional', n=14, p<0.001 uncorr.) that was used for correlation with metabolite concentrations.
3: ^{1}H-MRS voxel placement (bilateral PACC).
4: Pearson correlation between glutamate concentrations and % BOLD signal changes (for condition 'positive' and 'negative') in PACC after ketamine administration (.896; p=.001; n=9).

RESULTS & DISCUSSION

The main finding was a brain region-specific increase in negative BOLD responses in all fMRI task conditions following ketamine administration compared to baseline (n=14, paired t-test on % BOLD signal changes, calculated relative to the mean signal intensity of ROI across the whole experiment). The most significant BOLD differences were found in predominantly limbic brain areas associated with the processing of emotional information and higher-order mental functions (e.g., bilateral PACC (Fig 1a): positive: p=.021; negative: p=.013; neutral: p=.017; fixcross: p=.021; left posterior cingulate cortex: p=.007/.005/.009/.007; right nucleus accumbens: p=.019/.017/.020/.024) compared to other brain areas associated with different sensory and bodily functions (e.g., right primary motor cortex (PMC) (Fig 1b): ns (p>.264); right superior temporal gyrus: ns (p>.666); right anterior insular cortex: ns (p>.441). The functional cluster of voxels that showed significant negative BOLD responses during the ketamine condition 'rest > emotional' (Fig. 2, n = 14, p < 0.001 uncorr.) was taken as a ROI for further analyses of the relationship between task dependent NBRs within this ROI and metabolite concentrations in the overlapping spectroscopy voxel (PACC, Fig. 3). A strong correlation between glutamate, glutamine, GABA as well as glutamine/glutamate ratios (a putative marker for glutamatergic neurotransmission) and NBRs could be found for all task conditions after ketamine administration (n=9; Glu: p<.003; Gln: p<.007; GABA: p<.015; Fig. 4) compared to baseline where NBRs showed only a trend for correlation with GABA exclusively (p=.128/.086/.048/.072) [cf. 6]. However, there were no significant changes in global metabolite concentrations in PACC after ketamine administration. To our knowledge, this is the first multimodal fMRI/MRS study, that reports a pharmacological modulation of fMRI-BOLD responses during emotional processing and probes their relationship to glutamatergic metabolism in the PACC after ketamine administration. Our findings show that, in healthy subjects, ketamine has the potential to increase negative BOLD responses which have been found to be decreased in MDD patients during an emotional processing task [4]. The regional specificity of the BOLD changes indicates a pharmacological modulation of specific neurocircuits rather than a global neurovascular effect which would have be seen also in other areas like the primary motor or auditory cortex. Future studies including arterial spin labeling (ASL) could be useful to further elucidate these effects. The correlation of NBRs with post-infusion metabolite concentrations could be interpreted in terms of a stronger metabolic relationship between glutamate, glutamine and GABA as a consequence of an increased glutamatergic neurotransmission and metabolic turnover rate after ketamine administration, finally leading to the observed altered functional BOLD reactivitiy.

REFERENCES

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***Equal Contribution**: M. Scheidegger and S. Grimm contributed equally as first authors, M. Walter and A. Henning contributed equally as last authors to this work.*