Anaesthetic interactions in the phMRI resposne to acute ketamine challenge

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Introduction

Pharmacological-challenge MRI (phMRI) is an exciting new tool enabling researchers to map the effects of neuroactive drugs *in vivo*. To employ this technique pre-clinically, head movements are often reduced by maintaining animals under general anaesthesia. However, interactions between the drug of interest and the anaesthetic employed may potentially confound data interpretation. NMDA receptor (NMDAR) antagonists used widely to mimic schizophrenia have recently been shown to interact with the anaesthetic halothane. [1]. Here we investigated the phMRI response to NMDAR antagonist ketamine in rats maintained by the anaesthetic agents; α-chloralose and isoflurane.

Methods

A total of 24 male Sprague-Dawley rats (230-310 g) were each assigned to one of four challenge arms ***(Figure 1)***. MRI data were acquired using a Magnex Scientific 7T system interfaced to SMIS console, with a custom-made RF transit birdcage coil. For each study, a T_2-weighted anatomical volume was acquired via FSE sequence (TR=2000ms, TE=32ms, FOV=40mm, 256 x 256 matrix, 11 contiguous 1mm slices), followed by an optimized T_2^*-weighted BOLD-sensitive time-series with the same spatial coverage but a lower resolution (TR = 272 ms, TE = 15 ms, 128 x 128 matrix). The resulting in-plane pixel dimensions were 312.5 μm^2, with a temporal resolution of 70s per scan. Data analysis was conducted in SPM5, and individual subjects were spatially normalised to a stereotaxic rat brain MRI template set [2]. All functional data were smoothed to a FWHM 0.8mm (~2.5 x 2.5 in-plane pixel dimensions), and multiplied by a brain parenchyma mask from the template set to remove extra-cranial and CSF contributions. Time-series analysis was performed using the pseudoblock analysis method described previously [3, 4]. This method enables accurate assessment of the drug-related changes by direct-phMRI in humans [4] and animals [5]. *T* - statistic images were thresholded using a significance value of $p < 0.05$ corrected, and a 3 voxel cluster extent threshold. Volume of interest (VOI) analysis was conducted using a 3D digital reconstruction of a rat brain atlas (Paxinos and Watson (1998)) co-registered with the MRI template [2], and mean VOI time-courses of significant BOLD clusters were then extracted by the SPM toolbox MarsBaR [6].

Results

We observed qualitative differences in the phMRI response to ketamine under the two anaesthetic regimes. In Group A, positive BOLD signal changes were observed in the prefrontal cortex (including the cingulate, medial-prefrontal, orbitofrontal, and retropslenial cortices), the limbic cortex (entorhinal and piriform cortex), with extension into the parietal-temporal association cortex, and the sensorimotor cortices. Subcortical areas of activation were localized to the dorsolateral- and midlinedorsal thalamus, posterior hippocampus, nucleus accumbens, caudate putamen, septum, mesencephalic region, periaqueductal grey, corpus collosum, and bed nucleus of the stria terminalis. The time-dependent effects of ketamine were similar across most regions, with the positive response reaching a plateau 20 or 30mins after ketamine administration, and remaining sustained thereafter ***(Figure 2a)***. Group B showed no significant positive BOLD signal changes, although large areas of cortical deactivation were observed. The time-course of the ketamine-evoked signal decreases, showed the effect peaked rapidly within 10min of drug administration, then slowly diminished towards the saline vehicle ***(Figure 2b)***.

Discussion

This study shows that a drug-anaesthetic interaction does occur between ketamine and isoflurane compromising the overall phMRI response. A similar dose-dependent interaction has been demonstrated between PCP and halothane [1]. However, under α-chloralose anaesthetic the positive BOLD response of ketamine is very similar to the pattern seen in healthy volunteers [4] and in metabolic maps of the rat brain [7].

References

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Acknowledgements

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Figure 1: Study design & treatment arms.
1) Group A: α-chloralose anaesthesia, challenged with vehicle (saline, 1ml) ($N = 6$)
2) Group A: α-chloralose anaesthesia, challenged with ketamine (30mg/kg) ($N = 6$)
3) Group B: isoflurane anaesthesia, challenged with vehicle (saline, 1ml) ($N = 6$)
4) Group B: isoflurane anaesthesia, challenged with ketamine (30mg/kg) ($N = 6$)

Figure 2: Statistical parametric map of the two characteristic responses to ketamine challenge with **(a)** α-chloralose, and **(b)** isoflurane anaesthesia. *T*-statistic thresholding levels are reported on the right. The range of coronal slices is approximately -7mm to +4mm bregma as indicated in the panel. The histograms show extracted time-series of ketamine (K) –vehicle (V) responses from areas of significant main effects of the drug. Time blocks of 10 min are shown, and error bars represent 90% confidence intervals.

Figure 2a: group A positive response profile to ketamine

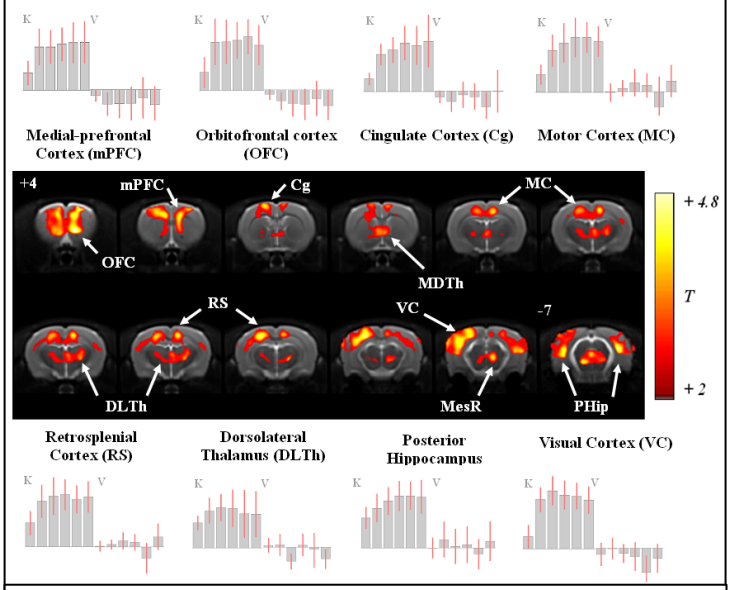

Figure 2b: group B negative response profile to ketamine