Dissociating the Anaesthetic and Analgesic Properties of Ketamine Using FMRI

R. Rogers[1,2], R. G. Wise[2,3], D. J. Painter[2,3], S. E. Longe[2], I. Tracey[2,3]

[1]Nuffield Department of Anaesthetics, Oxford University, Oxford, United Kingdom, [2]FMRIB Centre, Department of Clinical Neurology, Oxford University, Oxford, United Kingdom, [3]Department of Human Anatomy and Genetics, Oxford University, Oxford, United Kingdom

Introduction

Ketamine is an anaesthetic agent that is also analgesic at sub-anaesthetic doses. The clinical analgesic effect of ketamine is almost entirely NMDA mediated. Functional Magnetic Resonance Imaging (FMRI) has been used to image a "pain matrix," a network of sites within the brain, which are active in response to noxious stimulation [1]. The most commonly activated sites include thalamus, insular/SII cortex, anterior cingulate cortex, and primary sensory cortex [2]. The measured brain response to noxious stimulation, can be modulated by pharmacological agents [3]. Crucially FMRI produces objective measures of brain activity, which if compared with subjective experience have the potential to identify the neural correlates of analgesia. This study aimed to measure the analgesic effect of ketamine using FMRI and compare this with the effect of ketamine on auditory and motor processing.

Methods

Eight male, right-handed healthy volunteers, with a mean age of 28 years (range 19-37 years) were recruited. They underwent BOLD contrast FMRI scanning during a combined thermal-pain and auditory stimulus paradigm. The paradigm was repeated at estimated ketamine plasma concentrations of 0 (saline), 50 and 200 ng/ml, in that order during a single scan session. Ketamine administration was by a microprocessor-controlled target controlled infusion (TCI) pump. Four of the subjects returned for a second scan session during which a motor task was performed at the three ketamine concentrations. FMRI was performed by gradient-echo echo-planar imaging at 3T (Varian Unity Inova) (TR=3s TE=30s, in-plane resolution 4x4 mm, 24x6 mm axial slices covering the whole brain, flip angle 90°). T1 weighted structural scans were also acquired for image registration.

Noxious and auditory stimuli were presented to the subjects in a pseudo random sequence for fourteen minutes at each dose. The sequence of stimuli was randomized, with a mean stimulus interval of 41 seconds (range 27-66 seconds). The noxious stimuli were separated by a minimum delay of 59 seconds. At the end of each block of pain and auditory stimuli, the volunteers rated the pain intensity for those ten noxious stimuli on a subjective 11-point pain intensity scale. The noxious thermal stimuli were of 3 s duration and were administered to the dorsum of the volunteer's left hand using a fast-ramping (30-60^{O}C in 0.8s) home-built computer-controlled thermal resistor device. Prior to scanning and while volunteers lay in the scanner, the volunteers were "thresholded" for pain (mean temperature 56.2 ^{o}C, range 55-57.5 ^{o}C). The temperature of the stimuli was adjusted until the volunteers consistently scored the pain as eight out of ten (strong pain). The auditory stimulus was a multi-frequency tone of 3 s duration. The motor task was a block design (4 blocks of 45 s "on" alternated with 45 s "off") of button pressing. The button to be pressed ("on") or not pressed ("off") was indicated by a visual cue. Reaction times were recorded.

The imaging data was analyzed to identify regions exhibiting significant changes in BOLD signal using FEAT (FMRIB Expert Analysis Tool) [4] software. This involved motion correction, spatial smoothing using a Gaussian kernel of full width half maximum of 5.0 mm, mean-based intensity normalization of all volumes by the same factor, non-linear high pass temporal filtering (set at 100 s). The data was linearly modeled to fit a model describing the experimental design. The resulting parameter estimate for each stimulus type represents the signal change associated with that stimulus type. A fixed-effect second level group analysis was performed (FEAT). A region of interest analysis was also performed. Regions were defined by the fixed-effect group activation on saline and mean regional parameter estimates were compared (paired *t*-test) across doses for each task.

Results and Discussion

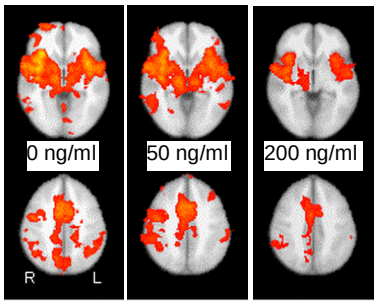

Fig. 1. **Fixed-effects group activation to painful stimulation** during 3 different plasma concentrations of ketamine. Thresholds: Z>2.3 and cluster P<0.01, n=8.

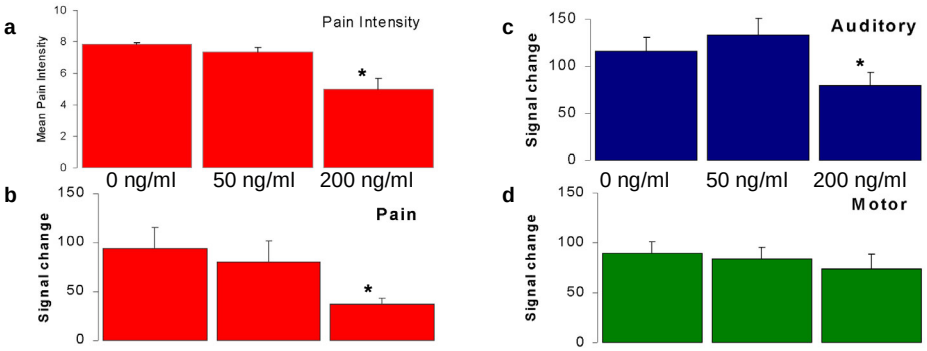

Fig. 2. **a**) **Mean subjective pain intensity scores** (with standard errors). **Comparison of activation** (mean FMRI signal change, with standard errors, in arbitrary units) during **b**) pain, **c**) auditory and **d**) motor tasks. * Indicates a significant drop in score, or FMRI response, with respect to saline (paired *t*-test, P<0.05).

Characteristic sites were activated by the noxious stimulus including the thalamus, insular cortex, anterior cingulate cortex and primary sensory cortex (Fig.1). Pain-related activity was reduced at increasing concentrations of ketamine. Reported pain intensity was significantly reduced (Fig. 2a) in agreement with the reduction of activity within the pain responsive regions (Fig. 2b). The thalamus and insular cortices showed the most significant reductions in pain-related activity at 200 ng/ml ketamine (data not shown). Auditory activity showed a non-significant rise at 50 ng/ml and a significant drop at 200 ng/ml compared to saline (Fig. 2c). There were non-significant drops in motor activity with ketamine (Fig. 2d) but with a significant (P<0.05) rise of 4 and 8% in reaction time for 50 and 200 ng/ml ketamine respectively, in comparison to saline.

The auditory and motor tasks allowed us to investigate the specificity of ketamine effects on the processing of nociceptive stimuli. The results suggest that the dose-response relationships for the three tasks differ in their magnitude and direction. It is therefore unlikely that the measured effects on the BOLD response are due to a confounding global cerebral haemodynamic effect. This is consistent with the observation of focal task-dependent effects of ketamine by Abel *et al* [5]. From studies such as ours, analgesic effects can be objectively measured and information gained about analgesic as opposed to anaesthetic effects. Further experience with different drugs will provide insight into the differing mechanisms by which analgesia can be produced in humans

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