Does mild hypoxia modulate the stimulus-evoked BOLD response?

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INTRODUCTION

We have investigated the effects of a range of analgesic and anaesthetic drugs on pain-related brain activity, measured using BOLD fMRI (Wise et al., 2002, 2004; Rogers et al., 2004). Some agents can have unwanted and potentially confounding effects on brain physiology, such as inducing respiratory depression. This can result in an increase in arterial end-tidal carbon dioxide (PCO_2) and a decrease in end-tidal oxygen (PO_2) and arterial oxygen saturation (SaO_2). It has been reported that decreasing the concentration of arterial blood oxygen (inducing a physiological condition known as hypoxia) results in a decrease in the stimulus evoked BOLD fMRI response in humans (Rostrup et al., 1995; Kemna et al., 2001). The effect of altering this baseline physiological state on the BOLD signal response evoked by other types of stimuli activating different brain regions, such as auditory or painful sensory, stimuli remains unclear. Understanding this effect is of great importance to the planning of future pharmacological fMRI experiments where non-neuronal, physiological confounds of the BOLD response must be understood.

METHODS

This study investigated hypoxic modulations of the BOLD response evoked by 6-second duration visual (10Hz flashing checkerboard), auditory (binaural multifrequency signal) and noxious thermal (thermal resistor on left-hand dorsum) stimuli. Group mean temperature (±s.d.) of noxious thermal stimuli: 48.8 ± 2.3°C. These three stimuli were combined with alternating 300-second periods of mild hypoxia (16% FiO_2) and normoxia (21% FiO_2). Whole brain, T2* weighted, gradient echo-planar imaging (TE=30 ms, TR=3000 ms) was performed on 9 subjects (3 females, group mean age ± standard deviation; 28 ± 2.7 years) undergoing this experimental paradigm for a total of 30 minutes at 3T (Varian Unity Inova). Following every painful stimulus the subject was asked to rate the pain intensity experienced from that stimulus on a 21-point visual analogue scale (VAS), between extremes of 0 (no pain) and 100 (worst pain imaginable). Analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.42, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Time-series statistical analysis was carried out using FILM with local autocorrelation correction. Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>2.0 and a (corrected) cluster significance threshold of P<0.05. Registration to high resolution and standard images was carried out using FLIRT. A mixed effects group analysis was performed using FLAME to investigate average activation across all subjects. A region of interest (ROI) analysis of hypoxia-stimulus interactions was performed to reveal potential modulation of the stimulus evoked BOLD response. The ROI used were Visual: visual cortex; Auditory: auditory cortex; Pain matrix incorporating: anterior cingulate cortex (ACC), insular cortex, primary somatosensory areas (SI), secondary somatosensory areas (SII) and the thalamus.

RESULTS

Fig. 1 shows the mean end-tidal PO_2 trace calculated across all subjects indicating periods of normoxia and hypoxia. There was a statistically significant difference ($p<2x10^{-4}$) between the mean end-tidal PO_2 during normoxia (107 ± 10.2 mmHg) compared to during hypoxia (86.1 ± 10 mmHg). There was also a significant difference ($p<0.005$) between the mean SaO_2 during normoxia (97.5 ± 1%) compared to hypoxia (96.1 ± 1%) (paired t-tests). There was a non-significant difference in the group mean pain rating (± s.d) between normoxia (48.2 ± 8.2) and hypoxia (50.8 ± 6.7) ($p>0.35$, paired t-test). Interaction effects between visual stimulation and hypoxia and between auditory stimulation and hypoxia, showing reduced visual (Fig. 2) and auditory activation during hypoxia. These were detected from z-statistic maps and by the magnitude of the signal change from the ROI analysis. This decrease in BOLD response in visual and auditory areas during hypoxia was significant ($p<0.05$). The mean percentage signal change represented by this interaction across all subjects was -0.22 ± 0.1% in visual areas and -0.17 ± 0.1% in auditory areas. No significant interaction was detected between painful stimuli and hypoxia in any of the brain regions examined (Table 1).

	Mean during normoxia (±SEM)	**Mean during hypoxia (±SEM)**
Visual cortex	**0.66 ± 0.23 %**	0.44 ± 0.17 % *
Auditory cortex	**0.56 ± 0.05 %**	0.39 ± 0.09 % *
ACC	0.15 ± 0.045 %	**0.18 ± 0.04 %**
Bilateral Insula	0.31 ± 0.1 %	**0.28 ± 0.12 %**
Contralateral SI	0.13 ± 0.14 %	**0.16 ± 0.16 %**
Bilateral SII	0.22 ± 0.12 %	**0.23 ± 0.12 %**
Bilateral Thalamus	0.2 ± 0.1 %	**0.22 ± 0.1 %**
Pain Matrix	0.185 ± 0.07 %	0.182 ± 0.09 %

Table 1. Mean ROI stimulus-induced BOLD signals during normoxia and hypoxia. * represents significant ($p<0.05$) signal modulation during hypoxia

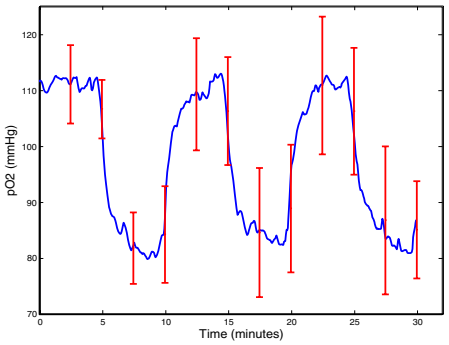

Fig. 1. Group mean end-tidal partial pressure of O_2

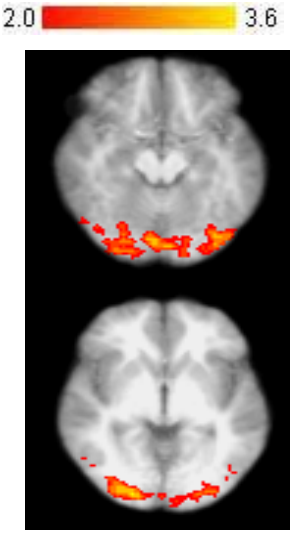

Fig. 2. Regions showing decreased BOLD response to visual stimulation during hypoxia

DISCUSSION AND CONCLUSION

We have found that the effect of mild hypoxia on the stimulus evoked BOLD response is regionally dependent. We have detected a significant ($p<0.05$) reduction in both visual and auditory brain activity during mild hypoxia. Pain activity was found to be unaffected. Measurement of a decrease in visually evoked BOLD signal during hypoxia has been previously reported (Kemna 2001), although our hypoxic challenge is considerably milder. The measurement of a decrease in auditory activity is to the authors' knowledge, a new finding. There was no significant hypoxic modulation of the BOLD pain response found in the ACC, SI, SII, the insula cortex or the thalamus. This finding suggests that a small decrease in arterial oxygenation may have a less confounding influence on the BOLD response in regions of the brain responding to pain than regions responding to visual or auditory stimuli.

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