The effect of remifentanil upon the conscious control of breathing

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INTRODUCTION: Opioid drugs (e.g. morphine) are widely used for pain relief in millions of patients every day. Their use is limited by potentially fatal depression of breathing. Opioids affect 'unconscious' and 'conscious' respiratory control mechanisms. 'Unconscious' effects are mediated in the brainstem, whereas the conscious control of breathing is also mediated in cortical centers [1]. The neural mechanisms of opioids on conscious respiratory control have not been investigated. The main difficulty with imaging opioid effects in the brain is that respiratory depression leads to a rise in arterial carbon dioxide tension ($PaCO_2$) causing a rise in baseline cerebral blood flow (CBF), which affects BOLD responses [2]. In this study, we investigated the effect of remifentanil (remi) (a short acting μ-opioid agonist), upon a conscious breathing task, a short expiratory breath hold. We included control measures (short CO_2 challenges, finger tapping and visual stimulation) in order to help disentangle the global vascular effects from those that are neuronal in origin. Changes in baseline CBF were measured using a whole-brain ASL protocol[3]. We hypothesized that the remi induced rise in CO_2 and baseline CBF would attenuate the activation-related BOLD responses to our stimuli, but that there would be a greater neuronally related reduction in the BOLD response in opioid sensitive respiratory areas.

METHODS: Experiment. Twelve healthy subjects took part in this study performed on a Siemens 3T scanner. T2* weighted gradient-echo EPI scanning (TE=30 ms, TR=3000 ms) for 13 minutes 21 seconds (voxel size 3x3x3mm) and whole brain ASL (6 minutes 30 seconds) were performed, before and during a target-controlled infusion of 1ng/ml remi (figure 1). The order of the BOLD and ASL sequences were randomized between subjects. 10 minutes were given for remi to reach stable effect site concentrations. During the EPI sequence the subjects performed a series of tasks each lasting 15 seconds (figure 2): visual stimulation (8Hz flashing checkerboard), self-paced finger tapping (right hand), and expiratory breath hold. The subjects also received 15 second 5% CO_2 challenges. After each breath hold the subject rated the "urge to breathe" using a 0 (no urge) to 100 (severe) rating scale. The following physiological parameters were measured: Non-invasive blood pressure (before and after each scan), pulse oximetry, tidal O_2 and CO_2. End-tidal oxygen ($PETO_2$) was maintained at 225mmHg by manual control of the gas mixture that was delivered to subjects via a tight-fitting facemask. During the ASL scanning, the subjects were asked to remain awake with their eyes open, but no stimuli were delivered. **Analysis.** Analysis of the BOLD data was carried out using FSL [4]. Voxel-wise statistical analysis was extended to a second (group) level in a mixed effects analysis using cluster threshold of Z>2.0 and a (corrected) cluster significance threshold of P=0.05. The $PETCO_2$ values during the breath hold were modeled based upon the $PETCO_2$ rise per unit time measured from breath holds performed prior to the experiment. As we saw a strong decrease in all the positive BOLD activations during remi, we used a region-of interest (ROI) approach to further analyze the remi arm of the experiment. The ROI's were defined from the mixed effects activation maps during the no drug condition. Physiological measurements and subjective ratings were compared using two-tailed t-tests and $P<0.05$ was considered significant.

RESULTS: With breath holding in the no-drug condition we observed right hemisphere signal increases in the dorsolateral prefrontal cortex (DLPFC), operculum, insula and supramarginal gyrus (figure 3). For the finger tapping task we observed strong activations in the left motor cortex and in the right cerebellum, for visual stimulation we observed strong activations in the visual cortex, and for the CO_2 challenges, we observed a generalized increase in BOLD signal throughout the grey matter (also not illustrated). With remi administration we observed strong decreases in BOLD responses in all the above ROI's ($P<0.001$) (figure 4). Comparison of the change in BOLD between the ROI's revealed a significantly greater reduction in BOLD response to breath hold in the DLPFC ($P<0.01$) and operculum ($P<0.05$) than the global reduction in the BOLD responsiveness to CO_2. In contrast the reduction in BOLD responses to finger tapping and visual stimulation were of a similar magnitude to the reduction seen with BOLD responsiveness to CO_2. This suggests a neural effect in the operculum and DLPFC beyond the global reduction in BOLD responsiveness. Furthermore the changes in the operculum were strongly correlated with changes in the "urge to breathe" rating scale ($r^2=0.85$, $p<0.01$) which was not observed in any other ROI. With remi administration there were no observed changes in blood pressure, heart rate, SpO_2 or $PETO_2$. $PETCO_2$ rose from 42±2.9mmHg to 51±3.2mmHg ($P<0.001$). Cerebral blood flow rose from 55±14.5 ml/100g/min to 70± ml/100g/min ($P<0.05$). Subjective "urge to breath" ratings fell from 24±12 to 12±8 ($P<0.001$).

DISCUSSION: We have shown that remi has profound effects upon the cortical substrates of conscious respiration, and that areas mediating the subjective and awareness components of breath holding (operculum, DLPFC) are more strongly affected than those mediating sensorimotor components of the breath hold (supramarginal gyrus). We propose a specific role for the operculum in mediating "urge to breathe". BOLD responses to CO_2 are unchanged if baseline $PETCO_2$ is maintained at normal levels during remi administration [5], thus validating our control tasks, which have helped us disentangle the global effects of increased baseline CBF from the specific opioid related effects upon respiration. Such methodology is directly applicable to studies of drugs with profound physiological effects. We conclude that specific cortical areas are associated with remifentanil induced respiratory depression.

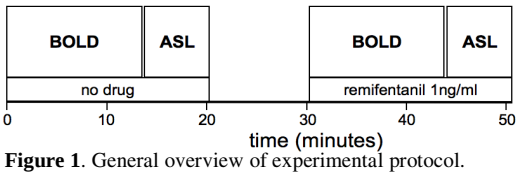

Figure 1. General overview of experimental protocol.

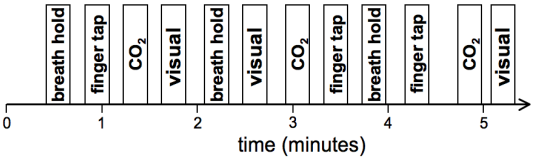

Figure 2. Stimuli presentation during BOLD experiment

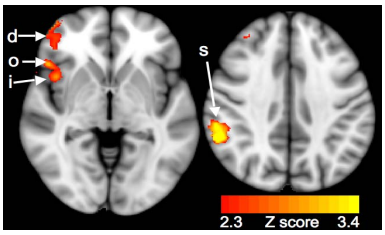

Figure 3. Group map of BOLD response to breath hold after accounting for CO_2 changes. (12 subjects, mixed effects analysis. Significant regions displayed with Z>2.3 and cluster probability threshold of $P<0.05$ (corrected).

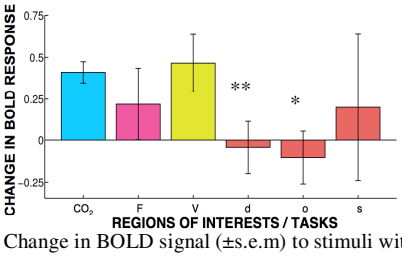

Figure 4. Change in BOLD signal (±s.e.m) to stimuli with remifentanil, expressed as proportion of BOLD response during the no drug condition ($\Delta BOLD_{REMI}$ / $\Delta BOLD_{NO\ DRUG}$). ROI's compared with CO_2 response (left bar). **Abbreviations:** *P<0.05, **P<0.01. **F**= finger tapping activations, **V**=activation from visual stimulation in visual cortex. Activation from breath holding: **d**=dorsolateral prefrontal cortex, **o**=operculum, **s**=supramarginal gyrus, **i**=insula).

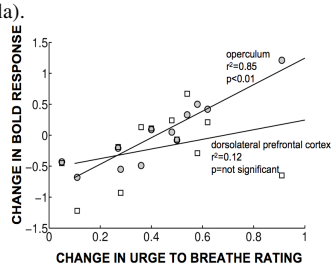

Figure 5. Relationship between change in "urge to breathe" rating and ΔBOLD to breath hold with remifentanil. Each data point represents a different subject. Circles represent operculum and squares represent dorsolateral prefrontal cortex.

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