# Opioid-induced changes in cerebral blood flow in the human brain during controlled breathing

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## Introduction

Studies using positron emission tomography have demonstrated opioid induced alterations in regional cerebral blood flow (rCBF). These have included increases in cortical areas such as the cingulate, orbitofrontal and medial prefontal cortex [1], and subcortical regions including brainstem (pons) [2], as well as decreases in frontal, cerebellar and temporal areas [1,3]. Recently, non-invasive MRI arterial spin labelling (ASL) methods have demonstrated their utility in quantifying opioid-related changes in rCBF [4], with opioid-induced CBF increases reported in thalamus and other areas [5]. The location of opioid-induced CBF increases is broadly consistent with the pattern of μ-opioid binding in the human brain [6]. Most previous studies of CBF have not fully accounted for confounding effects of opioid-induced respiratory depression which can increase rCBF as a result of the rise in arterial partial pressure of $CO_2$ [4]. However, we recently employed control strategies during opioid administration to map BOLD signal reactivity following opioid administration [7], to identify networks engaged in the control of breathing [8] and their modulation by opioid administration [9].

The present study examines the effect of remifentanil, a potent μ-opioid agent, on CBF while volunteers to control their breathing to suppress the respiratory depressive effects of the drug. We hypothesize that remifentanil increases CBF in areas of have high opioid binding (e.g. thalamus) and, by virtue of the sustained breathing task, in areas engaged in the control of breathing [8,9].



Fig 1. Group mean CBF

5 ml/100g/min 80

## Methods

13 healthy volunteers (5 female; mean age 26.5; range 21-35) underwent single-shot pulsed ASL perfusion measurements before and during intravenous infusion of remifentanil, each scan lasting for 5 mins. Remifentanil was delivered by target controlled infusion pump to achieve a steady-state plasma concentration of 1.5 ng/ml. During ASL measurements volunteers controlled their rate and depth of breathing [7]. Following training, they were asked to maintain their end-tidal $CO_2$ at a target value displayed on a screen alongside their current value. This procedure mitigated the rise in arterial $CO_2$ normally caused by opioid-induced respiratory depression. The target end-tidal $CO_2$ was set to 1-2mmHg below the volunteer's resting value to ensure compliance with the task both before and during the remifentanil infusion.

Imaging was performed on a 3T GE HDx system using pulsed ASL QUIPSSII [10] with GE-EPI readout. 16 slices (7 mm thick, 1mm gap) provided whole brain coverage with a 64x64 matrix (3.75mm in-pane resolution, TR/TE=2200/19.8ms, single inversion time with TI1/TI2=700/1350ms, 136 volumes). A 1x1x1mm T1 weighted structural scan was acquired for image registration.

The perfusion timeseries were motion-corrected (MCFLIRT [11]) and CBF maps computed using in-house software. Following affine registration of EPI data (FLIRT [11]) to the Montreal Neurological Institute template, mean grey matter flow was computed. A voxel-wise paired group analysis was performed comparing the drug infusion period with that preceding it (FEAT, [11]), incorporating individual scan-mean end-tidal $CO_2$ as a regressor of no interest to account for residual differences in arterial $CO_2$. Results are quoted as mean ± standard deviation.

## Results

Group mean grey matter perfusion was 32.5±5.7 ml/100g/min preceding remifentanil infusion and 33.4±8.6 ml/100g/min during infusion ($p$>0.2 1-tailed $t$-test). Before infusion, group mean end-tidal $CO_2$ was 38.5±3.3 mmHg, increasing slightly to 39.6±3.3 mmHg ($p$<0.01 1-tailed $t$-test). Remifentanil induced a significant increase in CBF bilaterally in the ventral anterior/lateral nuclei of the thalamus and in the nuclei reticularis in the brainstem. Significant CBF decreases were found bilaterally in the putamen/globus pallidum. Mean CBF in positive flow-responding regions (Fig 2) rose from 33.4±7.8 to 42.2±10.5 ml/100g/min (up 26%) and mean rCBF in negative flow-responding regions fell from 30.1±5.8 to 25.5±8.0 ml/100g/min (down 15%).



Fig 2. Significant CBF increases and decreases during remifentanil infusion (1.5 ng/ml) compared to pre-infusion

z(mm) 6   -12   -18   -32   y(mm) -22   x(mm) -6

Put/GP   VA / VL   NRC   NR   NR,LC, KF,PB   VA / VL   NRC   NR   NRC pons medulla

Put/GP=putamen/globus pallidum
VA/VL=ventral anterior/ventral lateral nuclei of thalamus;
NRC=nucleus reticularis cuneiformis; NR=nuclei reticularis;
LC=locus coeruleus, KF=kolliker-fuse, PB=parabrachial complex

Z score, cluster corrected p<0.05
2.3   4
CBF increase
CBF decrease

## Discussion

These data demonstrate the sensitivity of pulsed ASL to opioid administration. Localised changes in rCBF were observed after controlling end-tidal $CO_2$. Flow increases in thalamus and brainstem are consistent with strong opioid binding potential in these regions. However, the putamen, also a region of strong opioid binding [6], showed a significant decrease in CBF. This is consistent with our previous opioid study (end-tidal $CO_2$ uncontrolled) in which the putamen exhibited only a small increase in CBF. Increased CBF in VA/VL thalamus, subthalamic nuclei and pons is consistent with our previous studies of breathing control [7,8] identifying these regions as more active during volitional and spontaneous changes in breathing. The observed CBF changes are potentially linked to the greater conscious control of breathing required during opioid administration.

The small average rise in end-tidal $CO_2$ (~1mmHg) in this experiment would be expected to cause an approximately uniform (in grey matter) 3% increase in global CBF [12], close to our observed increase. The global influence of $CO_2$ is unlikely to explain the larger, regionally dependent flow changes. Furthermore, we have accounted for changes in end-tidal $CO_2$, in our comparison by assuming that rCBF changes are proportional to changes in end-tidal $CO_2$ [12]. Our results demonstrate that the effects of μ-opioid administration on CBF are not uniform across the brain. These regional effects on CBF must be accounted for when considering the role of drugs in modulating stimulus-induced brain activity [9].

## References

[1] Firestone et al. Anesth Analg. 1996, 82:1247-51
[2] Petrovic et al. Science. 2002, 295:1737-40
[3] Wagner et al. Anesthesiology. 2001, 94:732-9
[4] Macintosh et al. J Cereb Blood Flow Metab. 2008, 28:1514-22
[5] Zelaya et al. Abstract No.320, Annual Meeting of the ESMRMB, Valencia, Spain, October 2-4, 2008
[6] Baumgartner et al. NeuroImage. 2006, 30:692-99

[7] Pattinson et al. J Cereb Blood Flow Metab. 2007, 27(2):414-23
[8] Pattinson et al. NeuroImage. 2009, 44:295-305
[9] Pattinson et al. J Neurosci. 2009, 29:8177-86
[10] Wong et al. Magn Reson Med. 1998, 39:702-8
[11] www.fmrib.ox.ac.uk/fsl
[12] Poulin et al. J Appl Physiol. 1996, 81:1084-95