Remifentanil-induced Activation Pattern in Rat Brain detected with phMRI and Independent Component Analysis

W. Otte[1], J. M. van Ree[2], K. V. Marel[1], A. V. Toorn[1], and R. M. Dijkhuizen[1]

[1]University Medical Center Utrecht, Image Sciences Institute, Utrecht, Utrecht, Netherlands, [2]University Medical Center Utrecht, Rudolf Magnus Institute of Neuroscience, Utrecht, Utrecht, Netherlands

Introduction

Pharmacological MRI can provide valuable information on pharmacodynamics, spatial distribution of receptor-induced activation and changes in neurophysiological drug effects. However, in most cases the pharmacological model is not known *a priori*, which hampers accurate model-based data analysis. Estimation of an appropriate activation model is complicated when infusion rates are unknown, different concentrations are used, and pharmacodynamics are influenced by other drugs. The goal of this study was to overcome these difficulties and to delineate pharmacologically induced spatial and temporal activation patterns with a probabilistic temporal model-free fMRI independent component analysis. To that aim we applied a pharmacological stimulation paradigm involving repetitive injections with increasing dose of the μ-opioid receptor agonist remifentanil, with and without prior administration of the μ-opioid receptor antagonist naloxone.

Methods

MR imaging was performed on a 4.7-T Varian Instruments horizontal-bore spectrometer. Repetitive blood oxygenation level dependent (BOLD) MRI was performed using a gradient echo multi-slice sequence: TR/TE = 500/23 ms; pulse angle = 41°; data matrix = 64 x 64 voxels; FOV = 32 x 32 mm^2; 10 x 1.5-mm slices; temporal resolution = 32 s. A spin echo MRI dataset was collected for coregistration: TR/TE = 1500/15; data matrix 128 x 128 voxels; FOV = 32 x 32 mm^2; 10 x 1.5-mm slices. Adult male Wistar rats were anesthetized and endotracheally intubated followed by mechanical ventilation with 2.0% isoflurane in air/O_2 (2:1). During the experiments, arterial blood pressure, exhaled CO_2, blood oxygen saturation, heart rate and rectal temperature were continuously monitored. Body temperature was maintained at 37.0 ± 0.5 ºC.

During BOLD MRI acquisition, 7 rats (group A) each received four consecutive remifentanil injections (i.v.) with increasing dosage (20 μg/mL in 50 μL, 150 μL, 0.5 mL and 1.5 mL (15-min injection interval)) after 10 minutes baseline measurement. A second group of 4 rats (group B) received naloxone (2 mg/kg; i.p.) 10 minutes prior to phMRI. All datasets were zerofilled to 128 x 128 voxels, realigned, coregistered to a template, and smoothed. Group-level data analysis was carried out using probabilistic independent component analysis[1] as implemented in MELODIC (Multivariate Exploratory Linear Decomposition into Independent Components), part of FSL (www.fmrib.ox.ac.uk/fsl). Input data were pre-processed as follows: masking of non-brain voxels; voxel-wise de-meaning and normalization of the voxel-wise variance. Pre-processed data were whitened and projected into a multi-dimensional subspace using probabilistic principal component analysis where the number of dimensions was estimated using the Laplace approximation to the Bayesian evidence of the model order[1,2]. The whitened observations were decomposed into sets of vectors which describe signal variation across the temporal domain (time-courses), the subject domain and across the spatial domain (maps) by optimizing for non-Gaussian spatial source distributions using a fixed-point iteration technique[3]. Estimated component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixture model to the histogram of intensity values[1]. Z statistic parametric maps were overlaid on the structural MRI template used for coregistration.

Results

In both groups remifentanil induced a significant negative BOLD response followed by a smaller positive response, primarily in the midbrain and thalamus. In the group analysis a single component showed strong correlation with the remifentanil administration pattern with resultant intracerebral activation patterns, with explained variances of 13.1% in group A and 12.4% in group B (figures 1 and 2). In group A responses to all four remifentanil injections were detected, whereas in group B only responses to the last two highest doses were evident in the response time course. After each remifentanil injections, mean arterial blood pressure rapidly decreased to a minimum of 30 mmHg and returned to baseline level in about 3 minutes.

Discussion

In this study we demonstrated the effective use of a model-free independent component analysis to detect pharmacological activation patterns in rat brain. Small and large doses of remifentanil induced significant BOLD changes in different subcortical regions in drug-naïve rats. In group B remifentanil action at low doses was blocked by naloxone. Significant BOLD changes at the two highest remifentanil doses at later time-points most likely became evident because of the short duration of action of naloxone, which has a half-life of 40 min[4]. The activated brain areas included the midbrain, dorsal thalamus and part of the hippocampus, which is in agreement with an earlier phMRI study that used a model-based approach[5]. The mean arterial blood pressure time-course and the temporal responses of the components in both groups were largely similar, although the blood pressure displayed a slower return to baseline level after each remifentanil injection. The exact relationship between systemic blood pressure changes and central effects requires further investigation.

In conclusion, this study demonstrates that phMRI data can be successfully analyzed in spatial and temporal domain using a model-free approach with probabilistic independent component analysis. This model-free analysis provides a valuable tool for phMRI studies that involve advanced administration patterns with one or more drugs.

References

1. C.F. Beckmann and S.M. Smith. Probabilistic Independent Component Analysis for Functional Magnetic Resonance Imaging. IEEE Transactions on Medical Imaging 23:137-52, 2004.
2. T. Minka. Automatic choice of dimensionality for PCA. Technical Report 514, MIT Media Lab Vision and Modeling Group, 2000.
3. A. Hyvärinen. Fast and Robust Fixed-Point Algorithms for Independent Component Analysis. IEEE Transactions on Neural Networks 10:626-34, 1999.
4. B.A. Berkowitz, S.H. Ngai, J. Hempstead and S. Spector. Disposition of naloxone: use of a new radioimmunoassay. J. Pharmacol. Exp. Ther. 193: 499-504 1975
5. C.H. Liu, D.N. Greve, G. Dai, J.J. Marota and J.B. Mandeville. Remifentanil administration reveals biphasic phMRI temporal responses in rat consistent with dynamic receptor regulation. Neuroimage 34: 1042-53, 2007.

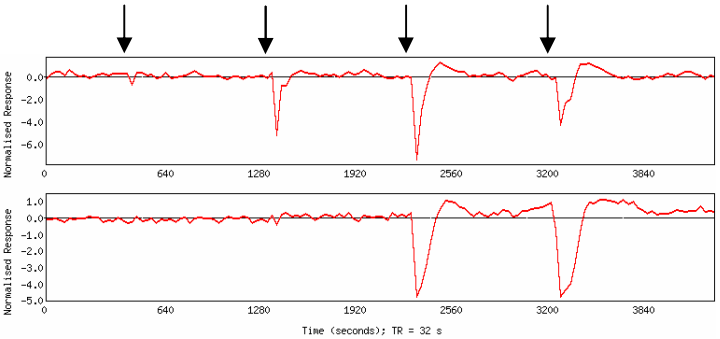

Fig 1. Normalized response time course for independent component (IC) map in group A (upper graph) and group B (lower graph). Arrows indicate repetitive remifentanil injections with increasing dose (15 min interval).

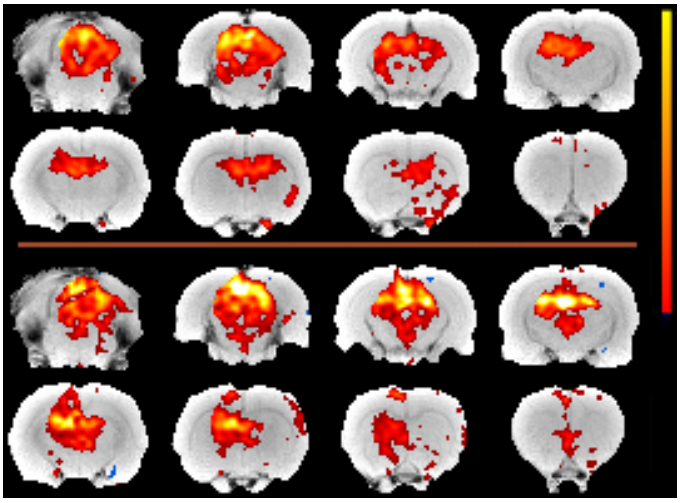

Fig 2. Thresholded IC maps for group A (upper montage) and group B (lower montage) overlaid on a multislice structural MRI template (positive Z-value range: 2.2 - 10.7).