# DE NOVO BUPRENORPHINE PHMRI EFFECTS IN CONSCIOUS RATS PARALLELS BRAIN ACTIVATION IN HUMANS

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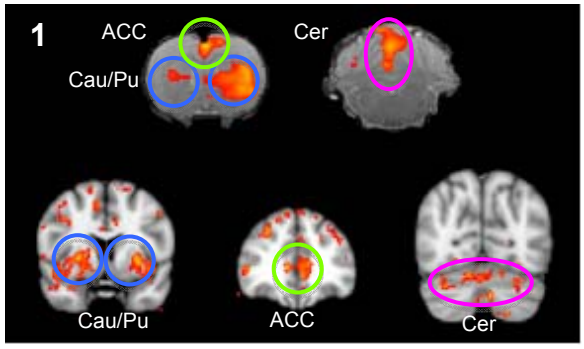
**Introduction**: Functional MRI studies of rodents are confounded by the use of anesthetics, especially for the study of analgesics. Furthermore, there are no studies comparing pharmacological brain effects in humans and rodents of the same analgesics. In this work, we present results of pharmacological MRI (phMRI) of an opioid analgesic (buprenorphine) in conscious rats and compare the brain activations with results obtained in humans (Upadhyay et al., 2009). Although brain structure and function differ between humans and rodents, some parallelism does exist and this thesis underpins much pre-clinical research. Translational results as presented here have the potential to bridge pre-clinical with clinical imaging studies.

**Methods**: Animals: Male Sprague-Dawley rats (~300g) were used for all our experiments. N=10 were injected with 0.1mg/kg buprenorphine and N=10 (controls) with saline. All rats had been habituated to the cradle and magnet noise for 5 days prior to imaging. For imaging, animals were exposed to 15 minutes of isoflurane (3%) to be loaded into the MRI cradle and regained consciousness during a 30 min recovery period prior to functional imaging. A tail vein was cannulated for drug infusion. PhMRI infusion scans lasted for 25 minutes; 5 minutes into the scan, the drug was delivered as a bolus lasting 2 minutes. A 4.7T Bruker system with a surface coil for transmit/receive was used. An EPI sequence with TR/TE=2.5s/11ms, 12 slices (1.5mm thick, FOV=3.0cm, matrix=64x64) and 600 volumes were acquired for both human and rats.
Humans: 12 Humans were administered buprenorphine (0.2 mg/70kg) and saline on different scan days (cross-over design, double blind) in a 3T Siemens scanner. A 25-minute phMRI scan was acquired with buprenorphine/saline administration spread over 7 minutes starting at minute 5 (see Upadhyay et al 2009).
Analysis: For both human and rodent phMRI data, the analysis was similar: motion correction, spatial smoothing (5 mm-humans 0.7mm-rats) and no high pass filtering. A general linear model (GLM) was used to analyze infusion data. Infusion responses were modeled by creating an explanatory variable (EV) based on the drug administration paradigm with 5 min baseline and a linear ramp to plateau during the duration of drug infusion. Variations in the infusion response in terms of the time to take off from baseline were modeled by including additional regressors in the design matrix that enable capture of these variable delay signals in an unbiased and robust fashion (Pendse et. al. 2009). A linear drift EV was also added to the design matrix to capture uninteresting drift signals.

**Results**: Group comparison (drug vs. saline) of phMRI results for the rats and humans (Figures 1 and 2) depict increased activations that were found in both human and rats and include caudate/putamen (Cau/Pu), anterior cingulate cortex (ACC), cerebellum (Cer) among others. Hippocampus (Hip) and thalamus (Th) were strongly activated in rats but only at threshold levels in humans. Similarly, insula (Ins) was strongly activated in humans and marginally in rats. Some negative activation was observed in rats in prefrontal cortex. In humans, no significant negative activation was observed.



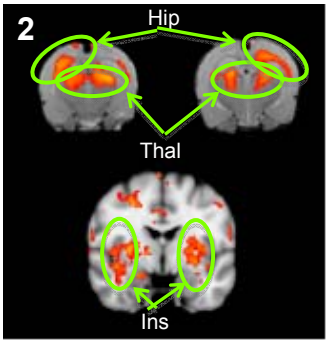




**Figure 1**: Activation in rats and humans in response to the infusion of buprenorphine vs. saline. Structures known to have high density of opioid receptors appear activated in both species. **Figure 2**: Some structures that achieved statistical significance in one species but not the other. This might be due to differences in pharmaco-kinetics and pharmaco-dynamics across species.

**Discussion and Conclusion**: Detection of activation in rat brain with phMRI following buprenorphine is similar to what has been observed with PET (Hume et al 2007) and is congruent with the distribution of opioid receptors in the brain. Congruency of activated brain structures is observed between human and rodent phMRI results for buprenorphine. Clearly a quantitative comparison is not possible since the equianalgesic dose for humans and rodents is not known. This might be the reason why some of the structures appear activated in one species and not on the other, it could also be due to differences in receptor densities in these structures. A potential approach to have a better parallelism between species would be to perform these experiments at different doses in both species. These results indicate that phMRI could be a useful tool to compare drug effects in conscious rodents (preclinical) and humans (clinical).

**References: Hume SP et al.**, Low sensitivity of the positron emission tomography ligand [11C]diprenorphine to agonist opiates. J Pharmacol Exp Ther. 2007 Aug;322(2):661-7. **Pendse, GV, et. al.** Robust, unbiased general linear model estimation of phMRI data in the presence of variance in the temporal response profile. In: Proceedings of the 17 th Annual meeting of ISMRM, Honolulu, Hawaii, 2009. **Upadhyay et al.,** Double-blind, Placebo Controlled, Dose Response fMRI Trial of Buprenorphine: Differential Valence of BOLD Response Modulation to Innocuous and Noxious Stimuli in Sensory and Striatal Regions. In: Proceedings of the 17 th Annual meeting of ISMRM, Honolulu, Hawaii, 2009