Unravel Neurochemical Contributions to Hemodynamic Responses using Simultaneous PET/MRI

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Target Audience Neuroimaging researchers, neuroscientists interested in multimodal imaging, pharmacologists, and addiction researchers.

Purpose Opioid drugs are the most effective analgesics for pain management, but opiates as a general class of drugs have significant abuse liability. Although the molecular mechanisms underlying the development of opioid dependence and addiction remain incompletely understood, opioid receptor regulation and opioid-modulated dopamine release have been suggested to contribute to abuse liability of opioid agonists. Functional MRI has been used extensively in neuroscience research, and could be very useful for drug development research. However, the relationship between fMRI signal changes and neurotransmitter-specific neural activation remains to be fully elucidated. In this study, we aim to investigate how changes in receptor occupancy modulate fMRI response and how different receptor systems contribute to a composite fMRI signal in space and in time. Specifically, we applied pharmacological doses of an opioid agonist (remifentanil) to nonhuman primates (NHPs), and measured changes in cerebral blood volume (CBV) and opioid and dopamine receptor occupancies using simultaneous PET/MRI.

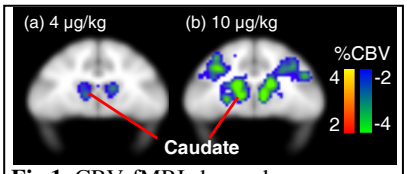

Fig 1. CBV-fMRI shows dose-response to remifentanil challenge.

Methods Dynamic PET and MRI scans were performed on two NHPs (male macaques, 8.4 kg and 14 kg). Animals were anesthetized with isoflurane and mechanically ventilated. Physiological parameters were monitored continuously and maintained within normal ranges. All images were acquired on a 3T Siemens TIM-Trio with a BrainPET insert and a custom PET-compatible 8-channel array coil. PET/MRI scans were acquired from each animal using two radiotracers, [^{11}C]carfentanil and [^{11}C]raclopride, selective for µ-opioid receptors and dopamine D2/D3 receptors, respectively. Each radiotracer (up to 12 mCi) was given as a bolus plus constant infusion to obtain steady state equilibrium. PET data were stored in list mode and binned into 1-min frames. CBV-fMRI data were obtained with iron oxide (Feraheme, 10 ug/kg, i.v.)[1,2] injection. Graded doses of remifentanil (a potent ultra short-acting µ-opioid agonist) were given intravenously as a challenge at ~35 min post radiotracer injection. All data was motion corrected, skull stripped, spatially smoothed and registered to a standard NHP atlas[3]. PET time activity curves (TACs) were analyzed for receptor binding potentials referenced to a non-displaceable compartment (BP_{ND}) using the simplified reference tissue model (SRTM)[4]. A gamma-variant function was used to model the PET and fMRI temporal response to drug challenge. The time-to-peak response of the gamma function was adjusted to minimize the χ^2/DOF of the general linear model (GLM) fit to data. Changes in fMRI signal intensity were converted to CBV changes using methods described previously[1,2].

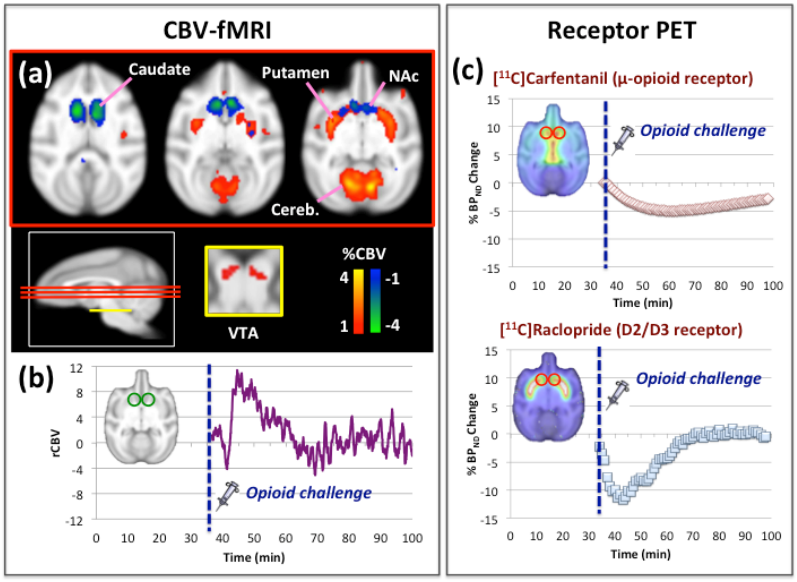

Figure 2. Simultaneously collected CBV-fMRI and receptor PET with an opioid agonist challenge. (a) GLM results of opioid-induce CBV changes. Time course of (b) CBV changes and (c) µ-opioid receptor and dopamine D2/D3 receptor binding in response to opioid agonist challenge. Figure insets in (c) show baseline receptor binding.

Results and Discussion Percent CBV changes showed a dose-response to remifentanil challenge (**Fig 1**), and a higher dose of opioid induced larger responses spatially.

Fig 2a shows robust bi-directional CBV-fMRI responses to acute opioid challenge. µ-Opioid agonist activates neurons located within VTA by reducing tonic levels of GABA (**Fig 2a**, VTA inset). Activated projection neurons release dopamine into synapses of the NAc (i.e. the mesolimbic dopamine pathway). In vitro studies suggested that induced extracellular dopamine binds preferentially to inhibitory dopamine D2/D3 receptors[5]. A reduction in functional activity within the NAc, presumably due to dopamine, is shown (**Fig 2a**). Simultaneously acquired PET data show dynamic [^{11}C]raclopride displacement after acute opioid agonist injection. [^{11}C]Raclopride displacement reflects dopamine releases in the NAc (**Fig 2c,** lower plot). Interestingly, the temporal dynamics of the opioid-induced dopamine release, as detected by PET, matches well to the negative CBV-fMRI response showing a peak response within 10 min post-remifentanil injection (**Fig 2b**). Other brain regions including putamen show a slow positive CBV-fMRI comparable to the temporal dynamic of changes in opioid receptor binding (**Fig 2c**). Collectively, our results suggest that neurotransmission modulate the fMRI responses, and specific neurochemistry underlying the fMRI signals could potentially being disentangled using PET/MRI.

Conclusions We presented simultaneous PET/MRI study with pharmacological challenges on large NHPs to investigate the engagement of the opioid and dopamine systems, and how receptor systems interaction contributes to the functional responses. In response to an opioid agonist, a dopaminergic component in limbic basal ganglia was repeatedly implicated in our PET/MRI studies. Simultaneous PET/MRI data acquisition provides the unique opportunity to directly relate neurochemical events (such as endogenous opioid and dopmamine release) to functional responses. As such, PET/MRI provides a powerful tool for studying the impact of neurotransmission on brain function, and has great potential to facilitate drug development. Work is on-going to quantitatively describe changes in opioid and dopamine receptor occupancies to the fMRI response.

References: 1. Mandeville JB, NeuroImage, 2013. 2. Sander CY, et al., PNAS, 2013. 3. McLauren et al., NeuroImage, 2010. 4. Lammertsma, NeuroImage, 1996. 5. Marcellino., et al., Synapse, 2011.