Evaluation of fMRI Signal versus Receptor Occupancy using Simultaneous PET/fMRI

Christin Y Sander[1,2], Jacob M Hooker[1], Bruce R Rosen[1,3], and Joseph B Mandeville[1]

[1]*A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, United States,* [2]*Electrical Engineering, Massachusetts General Hospital, Cambridge, MA, United States,* [3]*Health Sciences and Technology, Harvard-MIT, Cambridge, MA, United States*

Target Audience: PET/MR and functional imaging researchers, kinetic modelers.

Purpose: fMRI signal has not been compared to receptor occupancy in any previous studies. The "classical occupancy model" assumes that all receptors are either bound or available for binding, and that binding elicits function. We aim to test two predictions of the classical model: 1) function should be linearly related to receptor occupancy, 2) function and specific binding of drug should be matched in the temporal domain. We investigated these predictions with simultaneous dynamic PET and fMRI using graded doses of exogenous ligand in order to better understand mechanisms underlying fMRI signal changes.

Methods: Dynamic PET and fMRI was acquired in a non-human primate (NHP, rhesus macaque) with the radiotracer [^{11}C]raclopride (a D2/D3 dopamine receptor antagonist) on a simultaneous PET/MR scanner. Five studies were carried out with increasing doses of raclopride injected with the PET radiotracer (0.4, 1.4, 4.5, 16.5 and 41 μg/kg). An additional study was carried out with an injection of 0.3 mg/kg quinpirole (a D2 dopamine receptor agonist) at 30 min. after the start of the PET scan. Before each scan, iron oxide was injected to improve contrast and detection power of fMRI. PET/fMRI data were registered to a standardized NHP space. fMRI data was analyzed with the GLM and %CBV changes derived according to [1]. PET data were analyzed by GLM with a reference tissue model that included a term for dynamic binding changes and used the cerebellum as the reference tissue [2]. Simulations of a full reference tissue model with two tissue compartments [3] were carried out using reference data curves as inputs. Dynamic specific binding curves for comparison with fMRI data were estimated by subtracting reference time activity curves (TAC) from specific binding regions after inclusion of the flow-compensating term (R1).

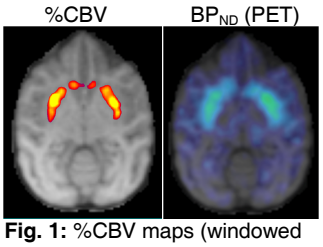

Fig. 1: %CBV maps (windowed by p<0.01) and BP$_{ND}$ maps overlaid on an anatomical MR for a 16.5 μg/kg dose of raclopride.

Results: Maps of %CBV showed positive CBV signal increases in the striatum and were co-localized with the PET specific binding regions (Fig. 1). The total occupancy of receptors measured by PET was approximately linear versus CBV signal (Fig. 2), with the slope in putamen being 2.4 times larger than the slope of caudate. Temporal responses of CBV signal were well-matched with *specific binding* from PET in striatal regions, as shown for putamen in Fig. 3 for the tracer dose and the two highest doses, and not with total PET signal or reference region. In contrast to the good temporal match obtained using an antagonist, the agonist quinpirole showed an obvious temporal divergence between the CBV response and PET measurements of binding (Fig. 4). CBV peaked at 3 min and returned to baseline by 20 minutes, whereas PET binding potential was suppressed for the duration of the scan (> 60 min).

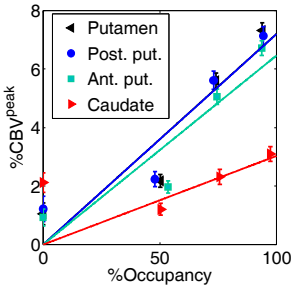

Fig. 2: Linear relation between CBV and occupancy (PET).

Discussion: This study showed for the first time that fMRI signals can be related to receptor occupancy in space, dose and time for certain cases. For the antagonist, the similarity of the time courses between CBV and the specific binding of the PET signal, and the linearity between these measurements using graded doses, both support a classical occupancy model, in which functional changes are directly related to the occupancy at the receptor level. Our data is consistent with a model whereby the fMRI signal is directly related to a decrease in dopamine occupancy at D2 receptors. In addition, the slopes of the function-occupancy relationship in Fig. 2 can be related to basal receptor occupancy, such that a 2-fold steeper slope in putamen suggests a 2-fold higher basal occupancy, or equivalently a 2-fold higher level of basal dopamine, which is supported by literature values [4]. Thus, PET/fMRI using this antagonist shows the potential for assessing basal neurotransmitter function.

In principle, one could obtain the similar information within the classical occupancy model using an agonist. However, the occupancy model breaks down with a high-dose agonist challenge directed at D2 receptors, as shown by the much faster CBV response in comparison to raclopride displacement. In an agonist challenge, the response elicited at the postsynaptic membrane may lead to internalization of D2 receptors, an established phenomenon *in vitro* and one that has been invoked in prior PET studies to explain the long duration of displacement in relation to dopamine release. Here, we show the same prolonged displacement seen in prior PET studies, but we also show that fMRI signal is highly abbreviated relative to the PET data, a result that can be explained by down-regulation of postsynaptic receptors via internalization. Thus, modifications of the classical occupancy model will be needed to explain agonist data, at least at high doses.

Conclusion: With simultaneous PET/fMRI, we showed that predictions from the occupancy model on linearity between CBV and occupancy hold and that basal occupancy levels can be inferred from fMRI/PET data. Moreover, fMRI time courses match to specific binding measures from PET in the case of an antagonist challenge. We directly related functional changes with occupancy and demonstrated that the use of dynamic simultaneous PET/fMRI can give important insights into specific receptor actions underlying functional changes.

References: [1] Mandeville et al. (1998) *MRM.* [2] Ichise et al. (2003) *JCBFM.* [3] Lammertsma et al. (1996) *JCBFM.* [4] Moghaddam et al. (1993) *Synapse.*

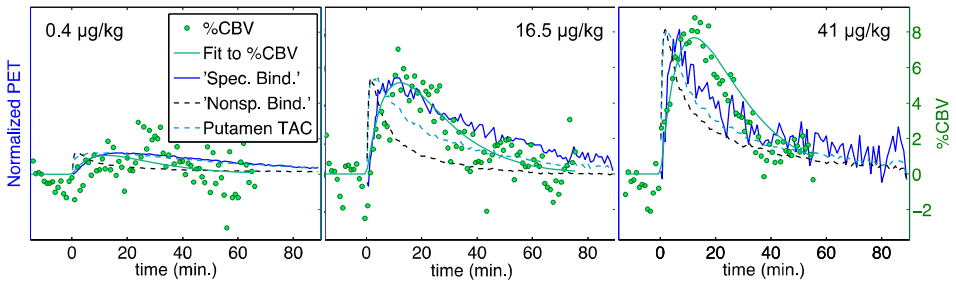

Fig. 3: Time courses of %CBV, together with PET time activity curves (normalized to max. values) of specific binding, nonspecific binding and the putamen for three doses of raclopride administration.

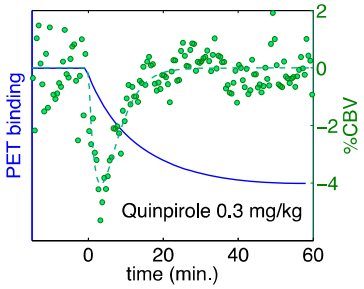

Fig. 4: fMRI time course and PET binding signal for quinpirole injection.