A MODEL OF DOPAMINE-INDUCED FMRI RESPONSE INFORMED BY SIMULTANEOUS PET/FMRI
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Introduction
Regional fMRI signal kinetics, and even biphasic responses, often are observed in response to drug infusion [1-3]. However, fMRI does not furnish specific neuro-chemical information, which makes the new generation of PET-fMRI scanners particularly useful for dynamic investigations of task-induced changes in neurotransmitter levels. In this study, we performed simultaneous PET and fMRI in awake monkey to map the amphetamine-induced functional response and basal dopamine (DA) D2 receptor densities, and we use these data to motivate a physiological model of DA-induced function in basal ganglia that can accurately describe the shape of the fMRI response, while also producing approximate agreement with the sign and shape of fMRI response in rats and monkeys at various levels of DA induced by different doses and dopaminergic drugs (cocaine, amphetamine).

Methods
We employed an awake monkey model, as described previously [4, 5], based upon head fixation and behavioral reinforcement. Monkeys are placed inside a MRI-compatible chair (Fig 1, left) within a Siemens 3T Trio with a BrainPET insert. fMRI employed parallel imaging enabled by a custom 4-channel coil array, and signal changes were enhanced using Feraheme iron oxide contrast agent. A replaceable radioligand for the D2 receptor (11C-raclopride) provided measurements of specific D2R binding with and without pharmacological challenge. Simultaneous PET/fMRI scanning occurred for 90 minutes, with raclopride (3-5 mCi) injected just after the start and amphetamine (0.6 mg/kg) injected at 20 min.

Results
Figure 1 depicts two co-registered maps: a PET map of binding potential for D2R, and an fMRI map showing the percentage CBV decrease induced by amphetamine. The temporal response of CBV was accurately described across whole brain by a GLM analysis based upon two data-derived temporal components. Figure 1 shows the response (black points) and fit (red) in posterior putamen based upon the z-component (blue) analysis. Note the negative fMRI response, unlike the positive response at higher doses [6].

Model
While the phenomenological model of Fig. 1 is statistically efficient, the temporal components are neither unique nor physiologically informative. Thus, we employ a compartmental model in which a single function of amphetamine-evoked free DA (F) drives both D1 and D2 receptors (Fig 2a). Bound receptors (B) produce the well-known excitatory effect at D1R and inhibitory effect at D2R, so that temporal and dose responses are set primarily by 1) the local ratio of D1/D2 receptors, and 2) the level of invoked DA and basal occupancy, which together determine receptor saturation. The key to the multi-phasic response at high DA concentrations is that the known higher affinity of DA for D2 over D1 leads to an initially higher D2 (inhibitory) over D1 (excitatory) effect, but also a more rapid D2R saturation (Fig 2b). Fig. 3a compares model predictions for DA increases of 10x (appropriate for 0.6 mg/kg amphetamine) and 3x (0.5 mg/kg cocaine). The model reproduces both the shape and relative magnitudes of this amphetamine data and our prior cocaine data [5]. Conversely, if we use a 3x increase in DA but increase the D1/D2 receptor ratio from 1 (monkey) to 2.5 or 3 (rat), as measured by autoradiography [7], then the model reproduces the sign and shape of the cocaine response in both the monkey [5] and rat [1], as shown in Fig. 3b.

If the analysis regressors of Figure 2 are employed for voxel-wise statistical mapping and parameter estimation from data, then all coefficients associated with D2 receptor are negative and all D1 coefficients are positive. Figure 4 shows the correlation between PET-derived D2 binding potential and fMRI-derived D2 stimulation as determined by GLM using the D2 regressor.

Conclusion
A compelling model of the fMRI response to dopamimergic stimulation can be generated based upon the different affinities of DA to D1 and D2 receptors. Simultaneous fMRI and PET studies of the dynamic DA response will be required to further refine the model.