CLASSIFICATION OF IN VIVO DRUG FUNCTION THROUGH A COUPLING MODEL AND PET/FMRI

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Target Audience: Multi-modal (PET/MR) imaging researchers, neuroscientists and neuropharmacologists.

Purpose: The efficacy of a drug (in a classical occupancy model[1]) is a property that denotes the strength of a pharmacological (functional) response at a given level of receptor occupancy. It is often determined as an in vitro measure, but can be challenging to determine in vivo as there are no ready ways to non-invasively derive efficacy[2], especially in humans. With simultaneous PET/fMRI, both occupancy and functional effects of a drug can be determined and used to predict its potency in vivo. This may provide an important tool for a functionally relevant classification of drugs that has not been possible until now.

Model: A model that predicts dynamic changes in the functional response due to ligand-receptor binding was developed and simulated in MATLAB. The model is based on the combination of a classical occupancy model (Fig. 1) that represents the number of available receptors through rate constants and affinities, with a steady-state formulation of a coupling model that relates drug occupancy to function (fcn): $\Delta fcn = \sum_{R=1}^{\#\,receptors} \sum_{L=1}^{\#\,ligands} N_R \varepsilon_{R,L} B_{max,R} \Delta\theta_{R,L}$. For the brain, a functional response can be measured by fMRI (BOLD, CBV, CBF) and is dependent of the efficacy ε and fractional occupancy θ of ligand L at receptor R. In this initial model, the neurovascular coupling constant N_R and the total number of receptors $B_{max,R}$ are assumed to stay constant. To draw comparisons with experimental data in this study, the simulations presented here are specific to neurotransmission at D2-like (inhibitory) receptors (D2R). For the specific case of a D2-like agonist and with CBV as a measure of function, the steady-state model reduces to: $\Delta CBV = N_{D2} B_{max,D2} (\varepsilon_{Agonist}\theta_{Agonist} - \varepsilon_{DA}\Delta\theta_{DA})$.

Experimental Methods: Experiments on a 3T PET/MR scanner with the radiotracer [^{11}C]raclopride were carried out in an anesthetized non-human primate model. Four D2/D3-specific drugs (quinpirole, ropinirole, compazine, raclopride) were injected at 30 min. after radiotracer injection at (minimum) two doses each to reach occupancies up to 90%. Iron oxide was administered, so that GLM analysis and conversion allowed for the computation of %CBV changes[3]. PET data were analyzed with a reference tissue model[4] to determine occupancy.

Results: Simulations of the model predict CBV temporal responses for a range of theoretical ligands with varying efficacies but similar binding kinetics (Fig. 2). For a ligand at D2-like receptors with $\varepsilon = 0$ (antagonist) or $\varepsilon = -1$ (inverse agonist) the CBV response is purely positive. In the antagonist case, this is due to displacement of endogenous dopamine at D2R[5]. In contrast, for a ligand with $\varepsilon = 1$ (a full agonist), the CBV response is purely negative (both would be reversed for an excitatory system). For ligands with efficacies $0 < \varepsilon < 1$, the sign of the response largely conformed to a steady-state prediction: (i) For efficacies larger than the basal neurotransmitter occupancy, the CBV response was similar to that of a full agonist, but with diminished amplitude. (ii) For efficacies significantly smaller than the basal neurotransmitter occupancy, the CBV response was similar to an antagonist. An interesting temporal response occurred at efficacies just below the basal occupancy (i.e., for a weak partial agonist). In this case, the simulated response was biphasic, albeit with a small overall amplitude. Experimental results agreed with model predictions, with positive CBV responses in the putamen observed for the antagonists and negative for the agonists (Fig. 3). Peak occupancies were matched at 88% for antagonists (compazine, raclopride) and 65%, 50% for agonists (quinpirole, ropinirole), respectively.

Discussion: The classification of drugs into agonists and antagonists is traditionally based on their pharmacological response and is characterized by efficacy. We have shown, with the example of the D2/D3R system, that drugs currently classified into agonists and antagonists from in vitro studies can be evaluated for their in vivo functional response with PET/fMRI. One of the challenges in pharmacology is to determine efficacy of a drug since this is a parameter that cannot be discerned from affinity in vivo with current methods. Our model predicts that we can determine efficacy based on the functional response to a drug, as long as function scales monotonically with occupancy. Of particular value may be the ability to distinguish weak partial agonism from antagonism. This can be achieved by a functional measure, as predicted by our model that shows a biphasic CBV response, with a dependency on initial basal occupancy of endogenous neurotransmitter. Further experimental evidence from a partial agonist, such as aripiprazole, will test this biphasic response in vivo. Differences in the experimental timecourse durations are likely due to affinity differences and agonist-induced receptor desensitization, which can be accounted for by model extensions. While PET can infer in vivo affinity (or K_D) from dose-occupancy curves, it may be possible to determine efficacy from occupancy-CBV curves and decouple these two quantities in vivo. Our proposed methodology and classification is not limited to neurotransmission or even the brain - it can be applied to other MR based measures of function, such as cardiac contractibility or renal perfusion/clearance to evaluate functional changes due to drug exposure.

Conclusion: A classification of pharmacological agents by an in vivo functional response as proposed here may be invaluable for predicting therapeutic effects of drugs. Especially agonists with medium in vivo efficacy may be of interest in order to maintain a homeostatic balance between extreme receptor blockage (e.g. at D2R, this can lead to parkinsonism symptoms or hyperprolactinemia) and extreme activation (e.g. resulting in psychosis) to reduce side effects compared to the action of pure agonists or antagonists.

References: [1]Laruelle *JCBFM* 2000. [2]Kenakin *Pharm. Sci.* 1999. [3]Mandeville et al. *MRM* 1998. [4]Lammertsma et al. *NeuroImage* 1996. [5]Sander et al. *PNAS* 2013.

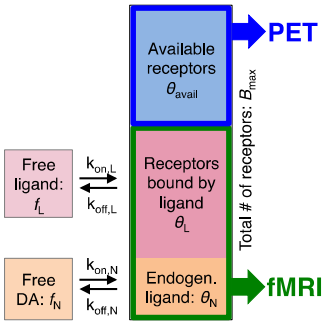

Fig. 1: Schematic of a classical occupancy model with PET & fMRI signals measurements.

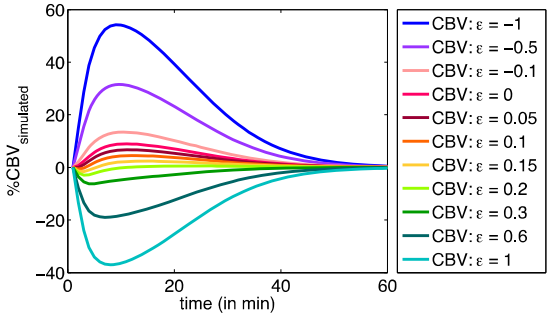

Fig. 2: Simulations of the coupling model for a range of efficacy values ($-1 \leq \varepsilon \leq 1$) that determine the functional effects of pharmacological agents.

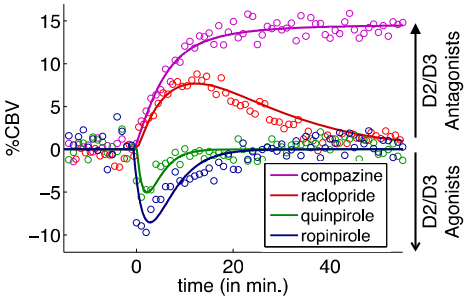

Fig. 3: Experimental data from two antagonists and two agonists that validate model predictions and allow a classification of drugs through fMRI.