IMAGING D2-DOPAMINE RECEPTOR CONCENTRATION IN NON-HUMAN PRIMATE BRAIN USING ^{18}F-FALLYPRIDE

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ABSTRACT

In this paper, we demonstrate how to form images of D2-dopamine receptor concentration in the brain with positron emission tomography (PET).

Quantification of receptor sites within the brain is required to understand aging, diseases such as Alzheimer, and drug addiction. This quantification is performed by acquiring dynamic PET data and analyzing the tracer kinetics from the reconstructed emission data. The signal-to-noise ratio (SNR) of the reconstructed dynamic PET data is generally so low that region of interest (ROI) analysis is required to have accurate quantification. ROI analysis produces a single value of receptor concentration for each region in the brain. We recently show that it is possible to form parametric images directly from the acquired sinogram data [1]. Elimination of intermediate steps and direct reconstruction of parameters from sinograms allowed us to form dense images of parameters of interest. In this paper, we applied the direct parametric reconstruction algorithm to form images of D2-dopamine receptor concentration within monkey brain using ^{18}F-fallypride radiotracer. Our initial investigations show that our D2 receptor images are consistent with the results of the classical ROI analysis.

1. INTRODUCTION

Images of dopamine receptor concentration in the brain is an important tool for clinical and pharmacological research. The dopamine receptors have important roles on several deceases such as Alzheimer and Schizophrenia. They are also related to drug abuse and addiction. Therefore, any clinical research on these deceases and pharmacological research on the development of treatment drugs require images of receptor concentration in the brain.

The noninvasive method for measuring dopamine receptor concentration is to inject radioactive tracers (also called radioligands) that bind to these receptors and collect the signal using positron emission tomography (PET). Therefore, regions with higher concentration of receptors will also have higher concentration of radioligands and more pozitrons will be emitted from these regions. However, the number of emissions is not directly proportional to the receptor concentration. Physiological models are used to obtain the concentration of the receptors from the collected emission numbers. One of the commonly used physiological model type is the compartment models [2, 3]. The concentration of receptors can be obtained from the parameters of these compartment models.

Using compartment models, one can analyze the kinetics of the radioligand. The radioligands kinetics can only be obtained by dividing the PET data into time frames. Each frame is reconstructed separately and the radioligand distribution in the brain can be computed. However, as the PET data is divided into time frames the signal-to-noise ratio (SNR) of each time frame also decreases. This causes inaccurate and highly varying estimates of model parameters and receptor concentrations. This problem is partially solved by region-of-interest (ROI) analysis. The regions with homogeneous tissue type generally should have similar receptor concentrations. Therefore, the signal collected from this region is averaged into a single time response. This averaging operation increases the SNR of the signal. This response is then used to model the radioligand kinetics and receptor concentration is estimated for the whole region. Then it is assumed that all voxels within this region have the same receptor concentration. The ROI analysis does not estimate the receptor concentration within each voxel. Alternative methods are developed to form dense images of receptor concentration such as spatio-temporal reconstruction methods [4, 5], spatial regularization methods [6], and direct reconstruction [7].

We recently proposed a direct reconstruction method that do not require emission image reconstruction [1]. Using this algorithm, the model parameters are estimated directly from the sinogram data. In this paper, we demonstrate an application of this algorithm to form images of D2-dopamine receptor concentration within monkey brain using ^{18}F-fallypride radiotracer. Our initial investigations show that our D2 receptor images are consistent with the results of the classical ROI analysis.

2. RECEPTOR IMAGING USING COMPARTMENT MODELS

Receptor imaging studies are generally performed using three-tissue compartment models. Figure 2 illustrates this model: C_P (pmol/ml) is the molar concentration of the ^{18}F-fallypride in the plasma, C_F (pmol/ml) is the molar concentration of unbound ^{18}F-fallypride in the tissue, C_B (pmol/ml) is the molar concentration of ^{18}F-fallypride bounded to D2 receptors in the tissue, and C_{NS} (pmol/ml) is the molar concentration of ^{18}F-fallypride bounded to other receptors in the tissue.

This model describes the PET signal arising from the kinetics of the radioligand from *each* voxel of the reconstructed image. The model depends on the kinetic parameters k_1, k_2, k_3, k_4, k_5, and k_6 (all in units of inverse minutes). Because of the high molecular specificity and affinity of the ^{18}F-fallypride to D2 receptors, the non-specific binding of ^{18}F-fallypride to other receptors can be ignored [8]. This means that the parameters k_5 and k_6 have values that are very

close to zero. Hence, we used two-tissue compartment model with parameters k_1, k_2, k_3, and k_4.

The kinetic parameters specify the tracer exchange rates between the compartments. In addition to these parameters, there are two compound parameters that have ready physiological interpretations and practical application, particularly for receptor-ligand imaging tracers such as ^{18}F-fallypride . These compound parameters are binding potential (BP), and total volume of distribution (VD). BP is proportional to the concentration of the D2 dopamine receptors and VD represents the steady state distribution of tracer between the plasma and tissue. BP and VD can be expressed in terms of k_1, k_2, k_3, and k_4

$$BP = \frac{k_3}{k_4} \tag{1}$$

$$VD = \frac{k_1}{k_2}\left(1+\frac{k_3}{k_4}\right) . \tag{2}$$

The tracer concentration in the plasma, C_P, is not a function of voxel position. However, the values of the kinetic parameters and the compound parameters will be allowed to vary for each voxel. Using these assumptions, the time variation of the concentration for each voxel s is governed by the following ODEs:

$$\frac{dC_F(s,t)}{dt} = k_{1s}C_P(t) - (k_{2s}+k_{3s})C_F(s,t) + k_{4s}C_B(s,t) \tag{3}$$

$$\frac{dC_B(s,t)}{dt} = k_{3s}C_F(s,t) - k_{4s}C_B(s,t) \tag{4}$$

In general, $C_P(t)$ is measured directly from arterial plasma samples. As an alternative, it may also be estimated simultaneously with the kinetic parameters [9].

If $C_P(t)$ is known, it is possible to compute $C_F(s,t)$ and $C_B(s,t)$ by solving the ODEs given in (3) and (4).

Let $\varphi_s = [k_{1s}, k_{2s}, k_{3s}, k_{4s}]$, N be the number of voxels, and $\varphi = [\varphi_0, \varphi_1, \cdots, \varphi_{N-1}]$. Using this notation the total activity concentration (nCi/ml) for voxel s at time t is

$$f(\varphi_s,t) = (1-V_B)[C_F(s,t)+C_B(s,t)]S_A e^{-\lambda t} + V_B C_{WB}(t) .$$

where S_A is the initial specific activity of the tracer (nCi/pmol), λ is the decay rate of the isotope (min^{-1}), V_B is a known constant for the volume fraction of the voxel that contains blood, and C_{WB} (nCi/ml) is the tracer activity in whole blood.

3. DIRECT RECONSTRUCTION METHOD

Our direct reconstruction method creates the parametric images from the sinogram data using the entire PET data set. Let K be the number of time frames that the data were collected, and $t_0, t_1, \cdots, t_{K-1}$ be the time frames. Then the emission rate at voxel s for each time frame is given by

$$f(\varphi_s) = [f(t_0,\varphi_s), f(t_1,\varphi_s), \cdots, f(t_{K-1},\varphi_s)]^T . \tag{5}$$

Furthermore let

$$F(\varphi) = [f(\varphi_0), f(\varphi_1), \cdots, f(\varphi_{N-1})] \tag{6}$$

be the function that maps the parametric image to the activity for each voxel at each time. Given φ and $F(\varphi)$, it is possible to compute the log likelihood of the sinogram data which is based on a Poisson model. The log likelihood of the sinogram data, Y, given the parametric image, φ is

$$LL(Y|\varphi) = \sum_{k=0}^{K-1}\sum_{m=0}^{M-1} Y_{mk}\log(A_{m*}F(\varphi,t_k)) - (A_{m*}F(\varphi,t_k)) - \log(Y_{mk}!) , \tag{7}$$

where Y_{mk} denotes the sinogram measurement for projection $0 \le m < M$, $F(\varphi,t_k)$ is the k^{th} column of $F(\varphi)$, and A_{m*} is the m^{th} row of the forward projection matrix (system matrix), A. Using this log likelihood, we can form the following cost functional

$$C(Y|\varphi) = -LL(Y|\varphi) + S(\varphi) , \tag{8}$$

where $S(\varphi)$ is a stabilizing function added to regularize the inversion. The stabilizing function is obtained from an assumed prior distribution for the parametric image. We model the distribution of the parametric image as a Gaussian Markov random field (GMRF) with a Gibbs distribution. We choose the negative logarithm of this distribution as our stabilizing function of the form

$$S(\varphi) = \sum_{\{s,r\}\in\mathcal{N}} g_{s-r}\|T(\varphi_s) - T(\varphi_r)\|_W^2 , \tag{9}$$

where $\mathcal{N}$ is the set of neighboring voxels, g_{s-r} is the coefficient linking voxels s and r, W is the diagonal weighting matrix, and $T(\cdot)$ is a transform function. By choosing an appropriate transform function, $T(\cdot)$, the regularization can be done in the space of the physiologically relevant parameters. Typically, we select $T(\cdot)$ to regularize k_1, k_2, k_3, k_4, BP, and/or VD. However, any well-behaved one-to-one transformation, $T(\cdot)$, is suitable for our algorithm.

In this framework, the maximum a posteriori (MAP) reconstruction is given by

$$\hat{\varphi} = \arg\min_{\varphi} C(Y|\varphi) . \tag{10}$$

This optimization problem is solved by parametric iterative coordinate descent (PICD) algorithm, which is described in detail at [1]. PICD algorithm is shown to compute $\hat{\varphi}$, given in (10), very efficiently and it has fast convergence [1]. When $F(\varphi)$ is a nonlinear function, the PICD algorithm reduces the computation by decoupling the dependencies between the compartment model nonlinearities and the forward tomography model.

4. DATA ACQUISITION

A healthy male rhesus monkey (*macaca mulatta*) was scanned using an EXACT HR+ scanner in 3D mode. A 5-min transmission scan using ^{68}Ge/^{68}Ga rod sources was acquired prior to administration of the radiopharmaceutical. The data were collected into 40 time frames consisting of 6×0.5 min., 7×1 min., 5×2 min., 4×5 min., and 18×10 min. frames following the administration of ^{18}F-fallypride . Total acquisition time was 220 min.

The raw data were corrected for randoms, deadtime, scatter, attenuation, and normalization. The data were then rebinned into 2D data sinograms using Fourier rebinning (FORE) [10]. [1]

[1] Thanks to CTI for correction and rebinning code.

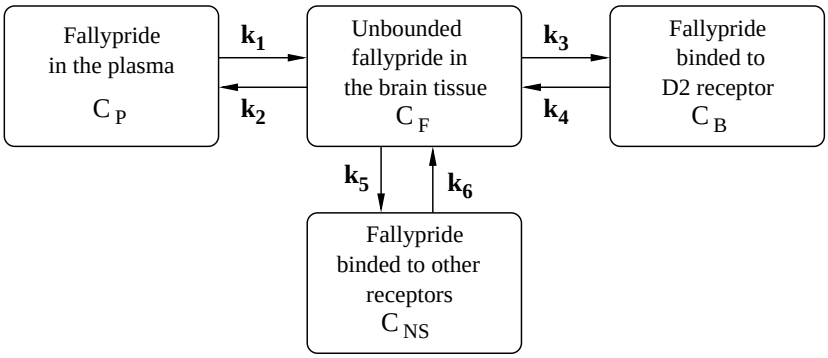

Figure 1: The three-tissue compartment model used in receptor-ligand studies.

Arterial blood samples were collected following the injection of radioligands to provide a measure of the plasma ^{18}F-fallypride concentration. (See [11] for further details on plasma function measurements.)

5. RESULTS

Two slices of the data are chosen for reconstruction: Slice 25 and slice 33. Slice 25 contains the striatum region, and slice 33 contains the amygdala region. Both regions have high concentration of D2 receptors.

Figures 2 and 3 show the reconstructed kinetic parameters for slice 25 and slice 33 respectively. Same set of regularization parameters are used for the reconstruction of the kinetic parameters. These regularization parameters are the diagonal elements of W in (9), ie.

$$W = diag\left\{\frac{1}{2\sigma_{k_1}^2}, \frac{1}{2\sigma_{k_2}^2}, \frac{1}{2\sigma_{k_3}^2}, \frac{1}{2\sigma_{k_4}^2}, \frac{1}{2\sigma_{BP}^2}, \frac{1}{2\sigma_{VD}^2}\right\}, \quad (11)$$

where $\sigma_{k_1} = 0.02$, $\sigma_{k_2} = 0.01$, $\sigma_{k_3} = 0.06$, $\sigma_{k_4} = 0.01$, $\sigma_{BP} = \infty$, $\sigma_{VD} = 10$. By adjusting these regularization parameters, we can change the smoothness of the reconstructed parameter images.

The D2 dopamine receptor concentration images of slice 25 and slice 33 are given in figure 4. In this figure, the striatum region in slice 25 and amygdala region in slice 33 are marked. These regions have higher D2 receptor concentration and they are brighter than surrounding regions in these reconstructions. However, these numbers need to be validated with the results of the classical methods. Our initial investigations show that our images are consistent with the D2 receptor concentration values obtained by classical ROI analysis [12].

6. CONCLUSIONS

In this paper, we demonstrate that we can form dense images of D2 dopamine receptor concentration in monkey brain. The dense images can be formed using the direct parametric reconstruction algorithm. Images of D2 dopamine receptor concentrations are formed for two slices; one with the striatum region and one with the amygdala region. These regions can be seen visually at the images. However, the concentration values of the D2 receptor images need to be validated with the classical ROI analysis results.

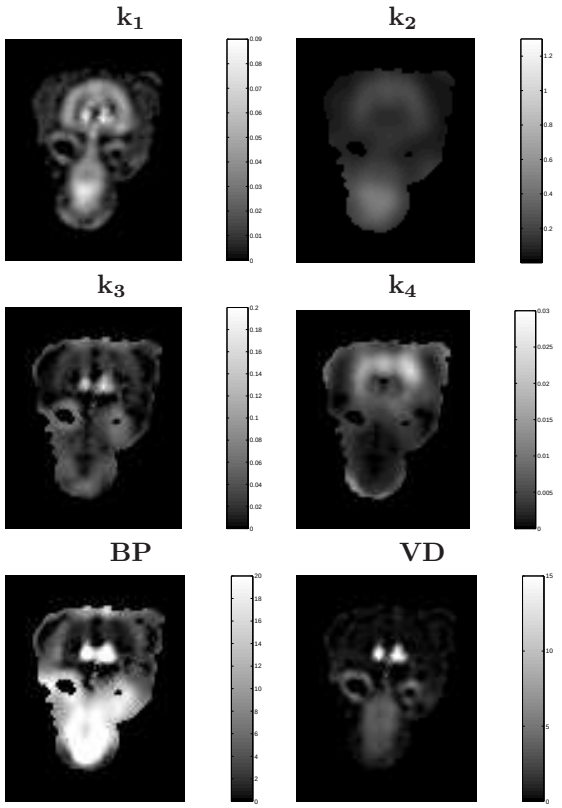

Figure 2: Directly reconstructed parametric images of slice 25.

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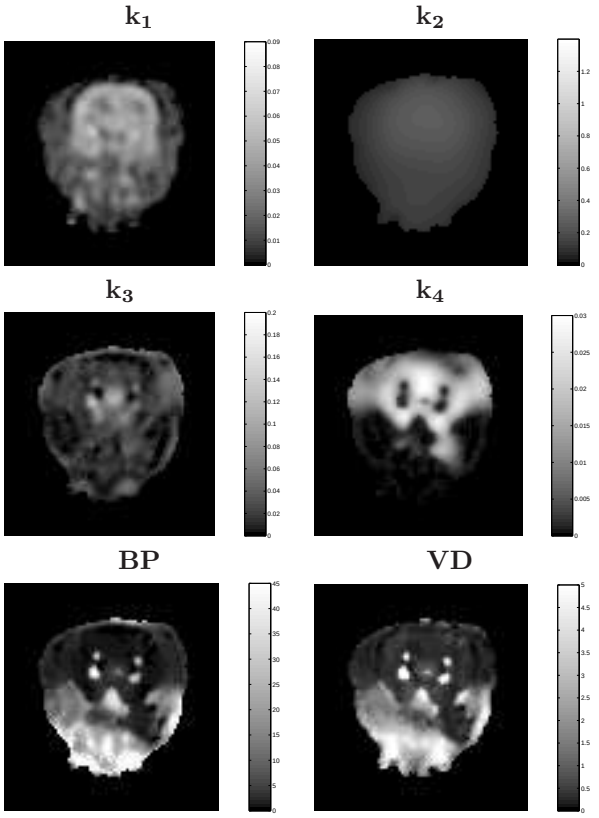

Figure 3: Directly reconstructed parametric images of slice 25.

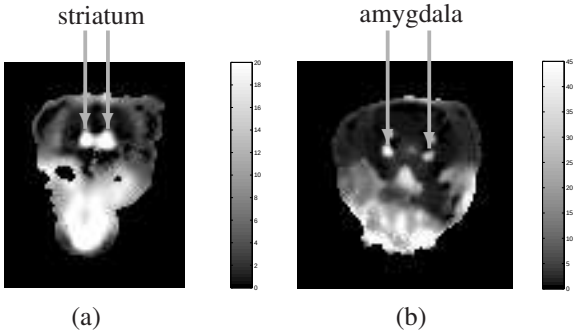

Figure 4: Concentration images of D2 dopamine receptors in (a) slice 25 (b) slice 33.

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