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A framework for designing dynamic lp-ntPET studies to maximize the sensitivity to transient neurotransmitter responses to drugs: Application to dopamine and smoking

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ABSTRACT

The "linear parametric neurotransmitter PET" (lp-ntPET) model was introduced to capture the time course of transient endogenous neurotransmitter response to drug stimulus from dynamic PET data. We previously used this novel analysis tool to probe the short-lived dopamine (DA) response induced by cigarette smoking in the PET scanner. It allowed us to find a sex difference in the DA signature of cigarette smoking. To make best use of this tool to characterize neurotransmitter response to drug stimulus, the sensitivity of lp-ntPET to detect such responses must be maximized. We designed a series of simulation studies to examine the impact of the following factors on the sensitivity of lp-ntPET using smoking-induced DA release as an example application: tracer delivery protocol, pre-processing for image denoising, timing of the smoking task, duration of the PET scan, and dose of the radiotracer. Our results suggest that a Bolus paradigm could replace a more difficult B/I paradigm without sacrificing the sensitivity of the method. Pre-processing the PET data with the de-noising algorithm HYPR could improve the sensitivity. The optimal timing to start the smoking task is 45min in a 90min scan and 35min in a 75min scan. A mild shortening of the scan time from 90mCi to 75min should be acceptable without loss of sensitivity. We suggest a lower dose limit of a bolus injection at 16mCi to limit underestimation of DA activation. This study established the framework to optimize the experimental design for reaching the full potential of lp-ntPET to detect neurotransmitter responses to drugs or even behavioral tasks.

1. Introduction

The "linear parametric neurotransmitter PET" (lp-ntPET) method was introduced (Normandin et al., 2012; Kim et al., 2014) to characterize the temporal patterns of time-varying neurotransmitter release induced by drug stimulus from dynamic PET data. We used this novel analysis tool previously to estimate DA response to cigarette smoking in the PET scanner. It allowed us to identify a sex difference in the brain's DA signature of cigarette smoking (Cosgrove, Wang et al., 2014). We found that nicotine-dependent men responded rapidly and consistently to cigarette smoking in the right ventral striatum, the locus of the reinforcement effect of drugs such as nicotine. Women did not. A secondary finding was that, women responded faster than men in a part of the dorsal putamen, which has been implicated in habit formation (Porrino et al., 2004; Everitt and Robbins, 2013). These findings are consistent with the established notions that men smoke primarily for the reinforcing drug effect of nicotine (Perkins et al., 2001), while women tend to smoke cigarettes for other reasons, such as to alleviate stress and negative mood or out of habit.

None of the temporal differences that we observed could have been discovered without lp-ntPET. To make best use of this novel analysis tool to characterize neurotransmitter response to stimulus, the sensitivity of lp-ntPET to detect such responses must be maximized. We experienced several challenges that may have weakened the power of lp-ntPET. One obstacle was getting sufficient radioactivity dose. In our smoking study, our tracer delivery protocol was set to deliver 20mCi of [^{11}C]raclopride in a 90 min bolus plus constant infusion scan with a K_{bol} of 105 min. It is quite a demanding burden on us to produce sufficient radioactivity following this protocol. Lower radioactivity dose could lead to greater noise and lower sensitivity of our method. Another challenge was the high noise level of voxel-by-voxel analysis. We believe lower noise in the voxel-level time activity curves (TACs)

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from the PET data will lead to more reliable parameter estimation. In addition, to better inform the neuroimaging community of the use of lp-ntPET, two remaining design parameters are the timing of the task and the duration of the scan.

Our goal in this study was to address these challenges by optimizing the experimental design and image processing procedure to achieve maximum sensitivity of lp-ntPET in detecting transient neurotransmitter response induced by stimulus. To this end, we designed a series of simulation studies to assess the impact of the following factors on the sensitivity of lp-ntPET: (1) tracer delivery protocol, (2) preprocessing for image denoising, (3) timing of the challenge/task, (4) duration of the PET scan, and (5) dose of the radiotracer.

Among many possible applications, one application of lp-ntPET is to probe the short-lived DA response to cigarette smoking. Smoking remains the leading preventable cause of death in the US. Quitting smoking is extremely hard and current therapies to aid in smoking cessation are not effective enough. The primary addictive chemical in tobacco is nicotine. Nicotine, along with most drugs of abuse, has been shown to cause DA release (Di Chiara and Imperato 1988). Dopamine has been critically implicated in the reinforcing effects of nicotine and tobacco cigarette smoking. A number of PET imaging studies attempted to measure smoking-induced striatal DA release (Barrett et al., 2004; Brody et al., 2004, 2006; Scott et al., 2007), but with highly variable results. We believe these inconsistencies observed were due to reliance on conventional PET methods that were really only appropriate to detect sustained DA release (Sullivan et al., 2013) (e.g., in response to amphetamine administration). But, the DA response to cigarette smoking is brief (lasting only minutes).

In addition, it has been suggested that a drug's addictive liability may be dependent on the timing of DA release (Volkow and Swanson, 2003), something that cannot be assessed in humans with conventional PET analysis methods. To probe the short-lived neurotransmitter response to drug stimulus in PET data on a voxel-by-voxel basis, we developed lp-ntPET (Morris et al., 2005, 2008, 2013; Normandin and Morris, 2008; Normandin et al., 2012; Kim et al., 2014). This method allows us to characterize the important temporal patterns of transient DA release with parametric images of DA parameters and "DA movies" (Morris et al., 2013) of the brain from [^{11}C]raclopride PET scans. The strength of lp-ntPET over conventional methods has two main parts. One, it is designed to detect short-lived time-varying neurotransmitter response, and is thus ideal for imaging the DA response to cigarette smoking. Two, the resulting parametric images contain timing information about DA activation that was not previously measurable *in vivo*.

By optimizing the experimental design and image processing procedure to maximize the sensitivity of the lp-ntPET method to detect short-lived neurotransmitter response, we found in our simulation studies: 1. a tracer delivery protocol that saves radioactivity, 2. a preprocessing algorithm that reduces noise, 3. an optimal timing of the task that yields maximum sensitivity, 4. a shorter scan duration that preserve performance, and 5. a minimum dose of the radiotracer to maintain a consistently high sensitivity. The application of lp-ntPET is not limited to imaging DA release or cigarette smoking. This study established the framework to optimize the experimental design for use with lp-ntPET analysis in a broader field of neuroimaging research to detect neurotransmitter responses to drugs or even behavioral tasks.

2. Materials and methods

2.1. Lp-ntPET model

Eq. (1) shows the operational equation of lp-ntPET (Normandin et al., 2012). The first three terms are the MRTM model (Ichise et al., 2003) that considers endogenous DA to be time-invariant. The additional term (dashed in Eq. (1)) describes the pattern of transient DA release induced by smoking/drug challenge by extending the LSRRM of Alpert et al. (2003) using a basis function approach.

$$C_T(t) = R_1 C_R(t) + k_2 \int_0^t C_R(u)du - k_{2a} \int_0^t C_T(u)du - \gamma \int_0^t C_T(u)h_i(u)du \quad (1)$$

C_T and C_R are the concentrations in the target and reference region, respectively. R_1 is delivery ratio, k_2 is a transfer rate constant between the free compartment and the plasma, and k_{2a} is the apparent transfer rate constant between the target tissue (taken as one compartment) and the plasma. $h_i(t)$ is one of the possible response functions in a predefined library. The coefficient γ is the magnitude of the time varying response $h_i(t)$.

The library of possible response functions includes gamma-variate functions [Eq. (2a)] and pure exponential functions [Eq. (2b)].

$$h_i(t) = \left(\frac{t - t_D}{t_P - t_D}\right)^{\alpha} exp\left(\alpha\left[1 - \frac{t - t_D}{t_P - t_D}\right]\right) u(t - t_D) \quad (2a)$$

$$h_i(t) = exp(\beta(t - t_D))u(t - t_D) \quad (2b)$$

The variable t_D is a response start time (relative to the start of the tracer), t_P is a peak response time (relative to the start of the tracer), α represents sharpness of the function, and β is the exponential time constant. During the curve fitting process, only one of the response functions from the library is used for a given fit. The response function with the best fit is chosen.

The lp-ntPET model is applied voxel-by-voxel to all the PET data. Using an F test, at each voxel the fit with lp-ntPET is compared to the fit with MRTM. This generates an F statistics map as a measure of the improvement of the fit achieved by lp-ntPET over MRTM, corrected by degrees of freedom. The F statistics map is first thresholded by an F statistics value that translates to a p-value < 0.05 and then thresholded by a cluster size threshold to correct for multiple comparisons and controls the false positive rate < 10%. The remaining voxels after the thresholding processes are identified to contain significant DA release. The details of the theory and implementation of lp-ntPET have been described by Kim et al. (2014).

2.2. Simulations

Noisy and noiseless striatal [^{11}C]raclopride time activity curves (TACs) with DA release at various time points were simulated for scan durations of 90 and 75 min in 3-min frames. To best represent the real data, our simulated noisy data used a similar noise level as was found in voxel-level TACs from a real human [^{11}C]raclopride scan. The noiseless TACs were simulated using the full 'ntPET' model (Morris et al., 2005), which is a nonlinear model of tracer binding to a receptor in the presence of a time-varying endogenous competitor. The simulations were implemented in Matlab (R2012b, MathWorks, Inc., Natick, MA) using modeling functions provided by a library of COMKAT (Muzic and Cornelius, 2001).

2.2.1. Input function

Different input functions were used for simulating different injection protocols. (1) Input function for simulating bolus data. The simulated Bolus data used an input function (Fig. 1a) taken from [^{11}C]raclopride rest scan following a Bolus injection of 20mCi into a male subject (85.45 kg). The simulation of 90 min and 75 min data used the first 90 min or 75 min of the input function, as needed. The simulation of Bolus data with varied delivered doses used the above input function scaled by dose (scale factor = delivered dose/20mCi). (2) Input function for simulating bolus plus constant infusion data. The input function following a bolus plus constant infusion (B/I) protocol (Fig. 1b) with a K_{bol}=105min, a scan duration T=90min and delivered dose of 20mCi (equivalent to a dose of 29.36 mCi at the beginning of the scan) was calculated using the Eq. (3) (Carson et al., 1993),