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Validation of parametric methods for [^{11}C]PE2I positron emission tomography

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ABSTRACT

Objectives: The radioligand [^{11}C]PE2I is highly selective for dopamine transporter (DAT) and can be used in vivo for investigation of changes in DAT concentration, progression of disease and validation of treatment using positron emission tomography (PET). DAT is an important protein for regulation of central dopamine concentration and DAT deficiency has been associated with several neurodegenerative and neuropsychiatric disorders. Accurate parametric images are a prerequisite for clinical application of [^{11}C]PE2I. The purpose of this study was to evaluate different methods for producing [^{11}C]PE2I parametric images, showing binding potential (BP_{ND}) and relative delivery (R_1) at the voxel level, using clinical data as well as simulations.
Methods: Investigations were made in twelve subjects either with social anxiety disorder (n = 6) or parkinsonian syndrome (n = 6), each receiving an 80 min dynamic PET scan. All subjects underwent a T1-weighted MRI scan which was co-registered to the PET images and used for definition of regions of interest using a probabilistic template (PVElab). Two basis function implementations (receptor parametric mapping: RPM, RPM_2) of the simplified reference tissue model (SRTM) and three multilinear reference tissue models ($MRTM_0$, MRTM and $MRTM_2$) were used for computation of parametric BP_{ND} and R_1 images. In addition, reference Logan and standard uptake value ratio (SUV_r) were investigated. Evaluations of BP_{ND} and R_1 images were performed using linear regression to compare the parametric methods to region-based analyses with SRTM and cerebellar gray matter as reference region. Accuracy and precision of each method were assessed by simulations.
Results: Correlation and slope of linear regression between parametric and region-based BP_{ND} and R_1 values in both striatum and extra-striatal regions were optimal for RPM ($R^2 = 0.99$ for both BP_{ND} and R_1; slopes 0.99 and 0.98 for BP_{ND} and R_1, respectively, in striatum). In addition, accuracy and precision were best for RPM and RPM_2.
Conclusion: The basis function methods provided more robust estimations of the parameters compared to the other models and performed best in simulations. RPM, a basis function implementation of SRTM, is the preferred method for voxel level analysis of [^{11}C]PE2I PET studies.

Introduction

The dopamine transporter (DAT) is a transmembrane protein located on the presynaptic neurons responsible for re-uptake and removal of dopamine from the synaptic cleft. This process regulates the action of dopamine and has shown to be of interest in several physiological functions (Gulley and Zahniser, 2003). DAT is associated with different neurodegenerative and neuropsychiatric disorders such as Parkinson's disease (Antonini et al., 2001; Ribeiro et al., 2002), schizophrenia (Laakso et al., 2001), attention-deficit/hyperactive disorder (ADHD) (Jucaite et al., 2005; Spencer et al., 2005) and social anxiety disorders (SAD) (Warwick et al., 2012).

Positron emission tomography (PET) is a non-invasive molecular imaging method for diagnosis and monitoring treatment effects in-vivo. PET provides functional images of the body and has proven to be a powerful tool for neurotransmission studies including imaging of DAT. The cocaine analog N-(3-iodoprop-2E-enyl)-2β-carbomethoxy-3β-(4-methyl-phenyl)nortropane (PE2I) has demonstrated an excellent binding to DAT, and both in vitro autoradiography studies using [^{125}I]PE2I (Hall et al., 1999), and in vivo PET studies with [^{11}C]PE2I (DeLorenzo et al., 2009; Hirvonen et al., 2008; Jucaite et al., 2006; Seki et al., 2010) have shown marked accumulation in the striatum where concentration of DAT is high. An intermediate binding has been found in the midbrain and no, or very little, specific binding in the cerebellum. Previous studies have shown that PE2I has a high selectivity for DAT, and because of that, [^{11}C]PE2I provides high contrast PET images and appears to be sufficiently sensitive for detection of DAT in small extrastriatal brain areas (Emond et al., 2008). [^{11}C]PE2I has also

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shown a good reproducibility and reliability in test–retest PET studies (Hirvonen et al., 2008). [^{11}C]PE2I PET studies can thus be a valuable tool for early detection of neurological disorders where changes in DAT concentration are involved, for the assessment of disease progression, and for validation of treatments (Emond et al., 2008).

Applying a simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996) on regions of interest (ROIs), using cerebellum as reference region, has proven to be a robust method for parameter estimation (Hirvonen et al., 2008; Jucaite et al., 2006), showing a good correlation with compartmental modeling using a plasma input (DeLorenzo et al., 2009; Seki et al., 2010).

To further facilitate clinical use of [^{11}C]PE2I, the possibility of straightforward visual assessment of DAT availability is a prerequisite. To this end, parametric images have to be available, where the parameters of interest are estimated for each voxel. In addition to binding potential (BP_{ND}) images, showing DAT availability, images of relative delivery (R_1), reflecting regional cerebral blood flow (rCBF) may be of interest in the differential diagnosis of neurodegenerative diseases (Meyer et al., 2011). For a voxel based analysis, using standard non-linear least square fitting for estimation of the parameters is sensitive to noise and very time consuming. Parametric methods, utilizing linearization of compartment models, provide faster analyses on a voxel level than non-linear regression analysis (Gunn et al., 1997). Voxel-based analysis of BP_{ND} has been performed previously for [^{11}C]PE2I (Leroy et al., 2012; Odano et al., 2012; Ribeiro et al., 2009), but no extensive validation of parametric methods has been presented for this tracer.

The purpose of this study was to evaluate different methods for producing [^{11}C]PE2I parametric images, showing BP_{ND} and R_1 at the voxel level, using clinical data as well as simulations.

Methods

Subjects and data acquisition

Data from a total of twelve subjects were included in this study whereof six were SAD subjects (three women and three men, mean age 35 ± 11 years) and six were subjects with parkinsonian syndrome (five women and one man, mean age 68 ± 6 years). Each subject signed a written informed consent and the study was approved by the local independent ethics and radiation safety committees. In addition, the scans of subjects with SAD were part of a clinical trial that was approved by the Swedish medical products agency. Together, these two groups are expected to display a large range of DAT availability in the striatum. Each subject underwent a dynamic PET scan on an ECAT Exact HR+ scanner (Siemens/CTI, Knoxville). After a 10 min transmission scan for attenuation correction, an 80 min emission scan in 3-dimensional acquisition mode was started simultaneously with the injection of about 350 MBq [^{11}C]PE2I. Twenty-two frames of increasing durations (4×1, 2×2, 4×3, 12×5 min) were acquired. Dynamic images were reconstructed using ordered subset expectation maximization (OSEM) with 6 iterations and 8 subsets and a 4 mm Hanning post-filter, applying all appropriate corrections. In addition, each subject underwent a T1-weighted magnetic resonance image (MRI) scan (3D-SENSE) on a 3 T Achieva scanner (Philips Healthcare, Best, The Netherlands). [^{11}C]PE2I was synthesized based on previously described methods (Halldin et al., 2003).

ROI analysis

Dynamic PET images were realigned to correct for inter-frame patient motion using Voiager (GE Healthcare, Uppsala, Sweden). MRI images were co-registered to the sum of the first 3 min of the PET scan, mostly resembling a blood flow image, using statistical parametric mapping (SPM5; Wellcome Trust Center for Neuroimaging, University College London, UK). Gray matter ROIs were defined on co-registered MRI images using an automated probabilistic ROI template as implemented in the PVElab software (Svarer et al., 2005). Seven ROIs were included: the putamen, caudate, thalamus, midbrain, hypothalamus, amygdala and hippocampus, averaged over the left and the right hemisphere. ROIs were transferred to the dynamic PET images, yielding regional time-activity curves (TACs). Data were analyzed using SRTM with the cerebellar gray matter as reference tissue, since the cerebellum is a region known for low DAT concentration and thus lacks specific binding of PE2I (Halldin et al., 2003). Regions with standard error (SE) >25% for BP_{ND} estimates were excluded from further analysis.

Parametric images

For evaluation of parametric images, voxel level analyses of clinical data were performed using two receptor parametric mapping methods RPM (Gunn et al., 1997) and RPM_2 (Wu and Carson, 2002), three multilinear reference tissue models $MRTM_o$, MRTM and $MRTM_2$ (Ichise et al., 1996, 2003), reference Logan analysis (Logan et al., 1996) and standard uptake value ratio (SUV_r). In all analyses the cerebellum was used as reference region.

The three and two parameter versions of receptor parametric mapping (RPM and RPM_2) are implementations of SRTM and $SRTM_2$ (Wu and Carson, 2002) using a set of predefined basis functions to linearize the models. One hundred basis functions were predefined for each scan with a discrete set of values for the exponential variable ranging from 0.01 to 0.5 min^{-1}. For RPM_2, the estimated number of parameters was reduced to two by setting the efflux rate constant from reference tissue, k_2' (min^{-1}), to a constant value. This was performed by taking a volume-weighted mean value for k_2' including the putamen, caudate, thalamus, midbrain, hypothalamus, amygdala and hippocampus from the previous RPM analysis.

The multilinear reference tissue models ($MRTM_o$, MRTM and $MRTM_2$) estimate the parameters using multilinear regression after a certain equilibrium time that for the present analyses was set to 30 min. For $MRTM_2$, the parameters were reduced the same way as described above for RPM_2 but with the k_2' value estimated from previous MRTM analysis. The estimated parameters for these five methods were thus R_1 and BP_{ND} for each voxel.

The reference Logan model is a graphical method and the analysis was performed with a time interval of 30–80 min for which BP_{ND} was indirectly estimated as the distribution volume ratio DVR-1. Additionally, the standardized uptake value ratio (SUV_r) was estimated for the last four frames, 60–80 min, and BP_{ND} was estimated as SUV_r-1. No estimates of R_1 can be obtained by reference Logan or SUV_r.

To take into account the different counts in each frame, weights were included in the data analysis. The corresponding weighting factor for each frame was calculated as

$$w = \frac{\Delta t^2}{f^2 T}$$

where Δt is the frame duration, T is the total counts in the frame and f is the decay correction factor for the frame which is computed as follows,

$$f = \frac{\lambda \Delta t}{\exp(-\lambda t_s) - \exp(-\lambda t_e)}$$

where t_s and t_e are the start and the end time of the frame and λ is the decay constant for ^{11}C.