A comparison of recent parametric neuroreceptor mapping approaches based on measurements with the high affinity PET radioligands [^{11}C]FLB 457 and [^{11}C]WAY 100635

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In positron emission tomography (PET) studies, the detailed mapping of neuroreceptor binding is a trade-off between parametric accuracy and spatial precision. Logan's graphical approach is a straightforward way to quickly obtain binding potential values at the voxel level but it has been shown to have a noise-dependent negative bias. More recently suggested approaches claim to improve parametric accuracy with retained spatial resolution. In the present study, we used PET measurements on regional D_2 dopamine and 5-HT$_{1A}$ serotonin receptor binding in man to compare binding potential (BP) estimates of six different parametric imaging approaches to the traditional Logan ROI-based approach which was used as a "gold standard". The parametric imaging approaches included Logan's reference tissue graphical analysis (PILogan), its version recently modified by Varga and Szabo (PIVarga), two versions of the wavelet-based approach, Gunn's basis function method (BFM) and Gunn et al.'s recent compartmental theory-based approach employing basis pursuit strategy for kinetic modeling (called DEPICT). Applicability for practical purposes in basic and clinical research was also considered. The results indicate that the PILogan and PIVarga approaches fail to recover the correct values, the wavelet-based approaches overcome the noise susceptibility of the Logan fit with generally good recovery of BP values, and BFM and DEPICT seem to produce values with a bias dependent on receptor density. Further investigations on this bias and other phenomena revealed fundamental issues regarding the use of BFM and DEPICT on noisy voxel-wise data. In conclusion, the wavelet-based approaches seem to provide the most valid and reliable estimates across regions with a wide range of receptor densities. Furthermore, the results support the use of receptor parametric imaging in applied studies in basic or clinical research.
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Introduction

With new high affinity radioligands, positron emission tomography (PET) studies of central neuroreceptors provide signals from brain regions with highly different structures and receptor densities. The methodology is currently widely applied to examine neuroreceptor distribution patterns in both basic and clinical research. Repeated assessments of the same receptor system can give insight into temporal changes related to physiology, the advancement of a disease, or effects of drug treatment.

In clinical studies, a common approach for the analysis of neuroreceptor images is to delineate regions of interest (ROIs) and then use the regional time radioactivity curves (TACs) to calculate binding parameters, especially the binding potential (BP). However, estimation of binding parameters at the level of individual volume elements (voxels) may provide additional information. Such parametric mapping approaches allow for analysis of the entire brain volume irrespective of anatomy, i.e. they are anatomically unbiased. Importantly, to qualify for practical use, a parametric mapping approach should provide valid estimates, be automatic, observer independent, and relatively fast.

A common approach in a ROI-based analysis is to use a linear graphical algorithm to estimate the parameter of interest, usually the BP for radioligand binding to target receptors (Gjedde and Diemer, 1983; Patlak et al., 1983; Logan et al., 1990, 1996). Hence a straightforward way to create a voxel-wise parametric mapping approach is to use the same graphical algorithm as for the ROI-based analysis but on each voxel separately (Cselényi et al., 2002). However, for small regions or single voxels, the accuracy of the estimated parameters is diminished due to noise in the time-activity curves (TACs) (Millet et al., 1996; Logan, 2000; Millet et al., 2000). To reduce this problem, novel approaches have recently been suggested. In a previous study, we validated the approach based on three-dimensional dyadic wavelet filtering (Cselényi et al., 2002). The study showed that the wavelet-based approach is accurate and confirmed that the voxel-based BP estimation using Logan's graphical approach underestimates the BP

values. Interestingly, a recently published paper suggests that Logan's graphical approach can be modified so that its noise-dependence decreases (Varga and Szabo, 2002). This modified procedure has been suggested to allow for rapid generation of BP maps on a voxel-by-voxel basis.

Another approach to calculate parametric images is offered by the basis function method (BFM) (Gunn et al., 1997). It is an extension of the simplified reference region (SRR) fit originally developed for ROI-based analysis (Lammertsma and Hume, 1996) but here further developed for voxel-wise binding parameter estimation. Its use has been illustrated on PET images obtained using various radioligands including dopamine- and 5-HT$_{1A}$-receptor ligands (e.g. Gunn et al., 1997, 1998). Comparative analysis of this approach on different radioligands is hitherto, however, lacking.

A third recently proposed approach is a successor of the BFM approach (Gunn et al., 2002). Based on the compartmental theory, it employs a so-called basis pursuit strategy for the optimal selection of kinetic basis functions then used to identify key binding parameters. In contrast to most approaches, it does not require an a priori definition of the number of compartments to be fitted. It is accordingly referred to as data-driven estimation of parametric images based on compartmental theory (DEPICT). This novel approach is also in need of comparative evaluation.

The aim of the present study was to extend the validation of the wavelet-based parametric mapping framework in two ways (Cselényi et al., 2002). Firstly, by comparing its performance to other novel approaches and, secondly, by increasing the number of radioligands used for the calculations. Beside the approaches employed in the previous study (i.e. regional binding potential estimation, simple voxel-based and dyadic wavelet-based parametric mapping), we included the voxel-based parameter mapping approach suggested by Varga and Szabo (2002), a modified (nondyadic) version of the wavelet-based parametric mapping, the basis function method (Gunn et al., 1997), and the DEPICT approach (Gunn et al., 2002). An additional objective was to assess whether any of the aforementioned approaches can be justified for routine use in applied basic research or clinical studies using well-established and tested ligands. Particular attention was given to efficiency, ease of use and computational complexity of the approach.

Methods and subjects

Choice of suitable radioligands and data sets

[^{11}C]FLB 457

[^{11}C]FLB 457 is a high-affinity radioligand for D$_2$/D$_3$ dopamine receptors in the human brain (Halldin et al., 1995; Farde et al., 1997; Delforge et al., 1999; Olsson et al., 1999; Suhara et al., 1999). The choice of [^{11}C]FLB 457 for the purpose of comparison was motivated by the fact that the human brain displays a 100-fold range of D$_2$ dopamine receptor densities across different brain regions (Kessler et al., 1993). Moreover, brain regions with different receptor densities display a wide range of size and shape that may present a further challenge to parametric imaging approaches. In the present cross-validation design, we used part of the data set from our previous study on the wavelet approach (Cselényi et al., 2002).

[^{11}C]WAY 100635

[^{11}C]WAY 100635, a 5-HT$_{1A}$ receptor antagonist, was selected for similar reasons as [^{11}C]FLB 457. It provides signals from a number of brain regions with different size and shape and varying receptor densities. However, the pattern of distribution is distinct from that of [^{11}C]FLB 457. Furthermore, [^{11}C]WAY 100635 is currently widely applied in clinical studies on the role of the serotoninergic system in neuropsychiatric diseases such as anxiety, depression, Tourette syndrome, and schizophrenia (see e.g. Lam et al., 1996; Drevets et al., 1999; Andree et al., 2000). The data set used was an extension of the one included in a previous study (Cselényi et al., 2004).

PET images

The PET studies were approved by the Ethics and Radiation Safety Committee of the Karolinska Hospital. Healthy subjects were enrolled and informed consent was obtained in line with the Declaration of Helsinki. Ten subjects were examined by PET using the radioligand [^{11}C]FLB 457 and six subjects were examined using the radioligand [^{11}C]WAY 100635. Details on subject selection and MR and PET image acquisition have recently been published in detail (Cselényi et al., 2002, 2004).

General strategy of calculations

Each of the individual data sets was analyzed by all seven approaches; the traditional ROI-based linear graphical parameter estimation according to Logan et al., voxel-wise parametric imaging using Logan's original linear graphical plot (PILogan), the version using Varga's modified version (PIVarga), the 3D dyadic wavelet-transform aided parametric imaging approach (D-WAPI), a variant of this approach using 3D stationary wavelet-filtering (S-WAPI), Gunn's basis function method (BFM), and the DEPICT approach. BP was the key parameter in the comparison. The results of the ROI-based approach served as a reference or "golden standard" for validation of the six receptor-mapping approaches. Detailed descriptions of the approaches have been published earlier (Logan et al., 1996; Gunn et al., 1997, 2002; Turkheimer et al., 2000a; Cselényi et al., 2002; Varga and Szabo, 2002). The following is a short overview of the approaches applied.

ROI-based analysis

Images were transformed into standard anatomical space using the computerized human brain atlas (HBA) (Roland et al., 1994). ROIs from the anatomical database of the HBA were positioned for a series of brain structures of interest in the dopaminergic and serotoninergic systems (see Tables 1 and 3). The cerebellar cortex was used as a reference region for free and nonspecifically bound [^{11}C]FLB 457 and [^{11}C]WAY 100635 in brain (Farde et al., 1998; Olsson et al., 1999).

The binding potential was estimated using the reference region version of Logan's linear graphical analysis (Logan et al., 1996). Distribution volume ratio (DVR) was determined by fitting a line to the linear part of the plot using traditional linear regression. This corresponded to 36–60 min for [^{11}C]FLB 457 and 40–69 min for [^{11}C]WAY 100635. The binding potential (BP) was calculated as DVR minus one (Logan et al., 1996; Farde et al., 1998; Olsson et al., 1999).