Wavelet-Aided Parametric Mapping of Cerebral Dopamine D₂ Receptors Using the High Affinity PET Radioligand [¹¹C]FLB 457

Zsolt Cselényi,* Hans Olsson,* Lars Farde,* and Balázs Gulyás†

*Karolinska Institutet, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital, S-171 76 Stockholm, Sweden; and †Department of Neuroscience, Karolinska Institutet, S-171 77 Stockholm, Sweden

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INTRODUCTION

Brain imaging of neurotransmission systems has a central role in research on normal brain functions as well as on the pathophysiology and treatment of neuropsychiatric disorders. A multitude of neuroreceptors is expressed in the human brain. Each neuroreceptor has a distinct anatomical distribution and the density of any given type varies greatly among regions. Moreover, the density also varies between individuals and it may be changed in relation to disease conditions (Farde et al., 1995). There is thus a need for accurate and precise quantification of neuroreceptor binding over a wide density range.

Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPET) are used to trace radioactivity after intravenous injection of a radioligand that binds to central neuroreceptors. Radioligand binding is often described by biological parameters, which are obtained by kinetic analyses of regional time-activity curves (TAC’s) (Farde et al., 1989; Blomqvist, 1991; Drevets et al., 1999; Olsson et al., 1999; Abi-Dargham et al., 2000). Most quantitative approaches are based on analysis of average radioactivity in regions of interest (ROIs) or volumes of interest (VOIs) (Farde et al., 1989; Koepe et al., 1996; Ito et al., 1998; Zubieta et al., 1998; Olsson et al., 1999; Kaasinen et al., 2001). The ROIs or VOIs are identified manually or by templates on the individual functional images (Abadie et al., 1992; Madar et al., 1996; Smith et al., 1998; Drevets et al., 1999; Abi-Dargham et al., 2000). A ROI-based analysis provides an estimate for the average value in a region. However, neuroreceptors may be heterogeneously distributed within a region and information regarding subregional differences may consequently be lost.

In order to obtain more detailed information about receptor distribution several attempts have been made to apply the kinetic calculations to individual pixel (or more precisely voxel) data. The generated distribution map is often referred to as a parametric image (Blomqvist et al., 1990; Frey et al., 1991; Gunn et al., 1990; Ito et al., 1998; Smith et al., 1998; Drevets et al., 1999; Abi-Dargham et al., 2000). A ROI-based analysis provides an estimate for the average value in a region. However, neuroreceptors may be heterogeneously distributed within a region and information regarding subregional differences may consequently be lost.

The application of wavelet filters has recently been proposed as a solution to handle the inherently low signal-to-noise ratio of PET images. In the present study we applied the wavelet approach to data obtained from 10 healthy subjects who were examined with [¹¹C]FLB 457. This high affinity dopamine D₂-receptor antagonist provides a signal from a range of regions with a hundredfold difference in receptor density and should thus be suitable for evaluation of the wavelet approach. For cross-validation purposes the data were analysed with four methods: a traditional region-of-interest (ROI) based analysis, a pixel-based analysis and two variants of wavelet-aided analyses. In both variants the wavelet filter was spatially applied, but a two-dimensional filter was used in one case and a three-dimensional one in the other. The same linear-graphical binding potential (BP) estimation step was used for all methods and the results of the three parametric mapping techniques were compared to the reference ROI-based method by calculating the average BP of representative ROIs. The pixel-based and the two-dimensional-wavelet-based methods yielded highly correlated but systematically lower values when compared to the reference ROI-based method. The approach utilising three-dimensional wavelet filters yielded BP maps with regional averages closely matching the values of the ROI-based method. The results show that the combination of three-dimensional spatial wavelet filtering with established parameter estimation procedures provides detailed, accurate maps of radioligand binding parameters. Such maps can be used for inter-individual or multi-condition comparisons of binding parameters at subregional levels.
Due to large computational demands of this approach it is common to use linear graphical algorithms since they allow for rapid calculations of binding parameters. Estimation of the binding potential (BP) by graphical approaches has, however, been demonstrated to be greatly affected by noise in the time-activity curves (Abi-Dargham et al., 2000; Slifstein and Laruelle, 2000). The higher the noise is the lower the estimated BP value will be when compared to the BP for the noise-free signals.

The use of wavelet filters is a new approach for pixel-based analysis (Turkheimer et al., 1999; Millet et al., 2000a; Millet et al., 2000b; Turkheimer et al., 2000a; Turkheimer et al., 2000b). This technique allows for the identification of signal patterns thereby differentiating signal from noise in the original sample. In PET studies on radioligand binding it means that the spatiotemporal patterns can be analysed to obtain a whole map of receptor density in contrast with the traditional ROI-based methods that produce one number per region only. These works establish the basic principles of working with wavelets in the context of analysing neuroreceptor imaging.

\[^{11}\text{C}\]FLB 457 is a new radioligand with very high affinity for D2/D3 dopamine receptors (Halldin et al., 1995; Farde et al., 1997). Due to its high affinity, \[^{11}\text{C}\]FLB 457 can be used to demonstrate binding even in regions with a low density of receptors (Farde et al., 1997; Okubo et al., 1999; Olsson et al., 1999; Suhara et al., 2001). Signals from a range of regions with a 100-fold difference in D2-receptor density makes \[^{11}\text{C}\]FLB 457 particularly suitable for a critical examination of the recently proposed wavelet-based analysis.

Building upon these proposed techniques, the aim of the present study is to assess the capability of wavelet-aided framework to decrease to noise-sensitivity of a parameter estimation procedure. For that reason four methods, built on the same linear-graphical parameter estimation step, were compared for cross validation purposes; a traditional ROI-based analysis, a pixel-based analysis and two variants of wavelet-aided analyses. In both variants the wavelet transform is applied spatially. The difference is whether it is applied two dimensionally to each slice of the volume or three dimensionally to the whole volume. The results of the ROI-based approach served as a reference for evaluation of the other three methods. The calculations were performed on a dataset of 10 control subjects previously examined with \[^{11}\text{C}\]FLB 457.

**METHODS**

**Wavelets in Theory**

The wavelet analysis of signals resembles the better-known Fourier analysis. In case of either technique the signal can be one-dimensional, such as a temporal sample of a sound wave, or two- or three-dimensional such as a two- or three-dimensional image. According to the Fourier theorem any function or signal can be made up by the superposition of a set of sinusoids with properly chosen amplitudes and phases. To put it in a different way, the Fourier transform allows for the description of a given signal in the frequency domain by extracting the different frequency components of the signal. However, it is not able to detect the location of non-stationary or transient components within the sample. Because of this a Fourier transform of an image, which contains a great number of transient components such as edges or boundaries, is not easily suitable for localisation of spatial features.

Wavelets, in essence, resemble sinusoids but restricted to a compact, bell-shaped envelope. This restricted nature of wavelets enables them, by contrast to Fourier sinusoids, to detect patterns in both the frequency and time domains or, alternatively, both the frequency and space domains. Therefore a coefficient of a wavelet transform is a quantity describing the signal at a certain location with a certain scale ("spatial frequency") (Mallat, 1989; Daubechies, 1992; Meyer, 1992; Turkheimer et al., 1999). Importantly because of this property the wavelet transform is capable of separating signal components (lower frequency) from noise (higher frequency) as the components show up in different coefficients of the transform.

Another property of the wavelet transform is that if the signal is well "lined-up" with the wavelet filter then the transform "accumulates" the signal in a few large coefficients whereas the noise is spread in a large number of small coefficients. This is advantageous in most of the applications of wavelets as small coefficients can be safely disregarded without the loss of the information content of the signal.

From the viewpoint of noise reduction these two properties mean that the "noise" coefficients are not only separate but also they can be identified and deleted because of their low value.

Furthermore, the wavelet transform is a linear operator and thus, if applied spatially on each timeframe of a four-dimensional radioligand study, the original temporal kinetics of the radiotracer is left undisturbed (Turkheimer et al., 2000a). In other words a kinetically homogenous region of the brain, such as a high receptor density structure with a distinct time-activity curve, will be represented with a wavelet coefficient that exhibits a time-activity curve with the same characteristics. On the other hand noise "patterns" give rise to coefficients that do not show any comprehensible temporal relationships. Noise can thus be identified and deleted when the kinetic analysis is initiated.

**Wavelets in Practice**

The wavelet transform used in the present study is realised through an iterative decomposition algorithm
known as the dyadic discrete wavelet transform (dyadic DWT), which is described in detail in the literature (Mallat, 1989; Unser et al., 1995; Turkheimer et al., 1999). The following represents a schematic overview of the wavelet algorithm. Initially we describe decomposition in one dimension (Fig. 1a) and then the reconstruction procedure (Fig. 1b).

1. Convolution. The data is passed through a low- and a highpass filter (called wavelet filters) by convolving with the wavelet filter kernels. The lowpass part or subband is called approximations (low frequency components of the signal), the highpass part is called details.

2. Downsampling. A downsampling is then performed, since the amount of information is duplicated in the first step. This means that every second coefficient of the approximations and details is thrown away. The downsampling introduces distortions that are called aliasing distortions. They are “cancelled out” during the reconstruction of the signal.

3. Iterative repetition. The first and second steps are repeated, always using the downscaled output of the lowpass filter (approximations) as input for the next iteration or next level. The details coefficients are kept, whereas the approximations are replaced with the output of the last iteration. Finally, there is one approximation and as many details as the number of iterations. The number of iterations is referred to as the depth of the decomposition. Due to the fact that the output is always downsampled at each level but the wavelet filters are the same, the cut-off frequency for the low- and highpass filtering steps is always lower and lower. Thus the final approximations part accumulates the lowest frequency components of the input sample. In other words the higher the depth the lower is the frequency of the lowest-frequency pattern extracted in the (approximations) coefficients.

The reconstruction procedure is basically the inverted version of decomposition (Fig. 1b):

1. Upsampling. The approximations and the details of the deepest level are upsampled. This means that zeros are inserted between every coefficient. This is to compensate for the downsampling step of the decomposition.

2. Convolution. The upsampled subbands are convolved with reconstruction low- and highpass filters, respectively. These reconstruction filters are close relatives of the decomposition filters, but not identical since the reconstruction filters must compensate for the aforementioned aliasing distortions.

3. Summation. The output of the two filters is summed to yield the reconstructed approximations for the next level. As we mentioned this subband was deleted during decomposition.

4. Iterative repetition. The procedure is repeated using the freshly reconstructed approximations and the corresponding details of the next level. At the coarsest level we end up with the reconstructed sample (which is an approximation of the original sample).

The procedure can be applied to two- and higher-dimensional (spatial) samples resulting in two- or higher-dimensional wavelet decompositions (Figs. 2 and 3). If employed in two dimensions, i.e., on an image, the low- and highpass filters have to be applied sequentially. They are first applied in the first dimension, on the rows of the image, resulting in two row-filtered images. Then they are applied in the second dimension, on the columns of both row-filtered images, leading to four two-dimensionally filtered subbands or quadrants. These quadrants can be visualised in a two-by-two grid (Fig. 2). One quadrant comes from the application of the lowpass filter on both the rows and the columns. This corresponds to the approximations part of a one-dimensional transform. Two quadrants come from the application of both the low- and the highpass filters. The difference between the two quadrants is whether the lowpass filter was applied on the rows of the image and the highpass on the columns or vice versa. They are also called the vertical and horizontal details, which corresponds to their placement in the grid. The final quadrant is the output of the application of the highpass filter on both the rows and the columns. It is also called the diagonal details. The input of the next level is again the approximations part or quadrant.

The method can be extended to three-dimensional samples, such as each three-dimensional timeframe of a PET study. In this case the output at each level contains eight subbands or “cubes” of coefficients corresponding to the number of permutations by which the low- and highpass filters are applied to the three dimensions separately (Fig. 3). Theoretically the procedure can be applied for any n-dimensional samples always yielding 2^n subbands of coefficients at each level.

The essential component of the procedure is the specific wavelet filter used for the transform. There are many families of wavelets, each having its own characteristics such as different filter lengths corresponding to different spatial (and frequency) detection properties. According to previous works, the wavelets best suited for analysis of emission tomographic images belong to the family of orthogonal spline wavelets, more precisely the so-called Battle-Lemarie wavelets (Battle, 1987; Lemarie, 1988; Turkheimer et al., 1999, and references therein).

A drawback of the traditional dyadic wavelet algorithm is that low-quality or noisy inputs can be distorted by the downsampling step to a higher extent than what the reconstruction filters can compensate for. This means that the reconstructed sample will contain artefacts. These artefacts are more likely to appear if an essential coefficient for the representation
FIG. 1. Schematic diagram of the dyadic wavelet transform in one dimension. (a) Decomposition of signal with two iterations (depth two). (b) Reconstruction of signal using inverse discrete wavelet transform with two iterations. Colored bars represent the signal and the decomposition structures; $S$, original or reconstructed signal; $A_1$, approximations on the first level; $A_2$, approximations on the second level; $D_1$, details on the first level; $D_2$, details on the second level. The color in general symbolizes the frequency distribution of the sample from the intuitive association of low frequency with red and high frequency with blue. Therefore the original signal, which is a mixture of low and high frequencies, is represented by purple, i.e., mixture of blue and red. The color of lowpass filtered samples is red; that of highpass filtered ones is blue. Darker colors represent deeper level of decomposition. The symbol with an “L” above stands for the decomposition lowpass filtering step, the symbol with an “H” below for the decomposition highpass filtering step. Similarly the symbols with “L” and “H” represent reconstruction low- and highpass filtering, respectively. The diamond shapes with a downward or upward arrow represent decomposition downsampling and reconstruction upsampling, respectively. Finally, the round shape with a Greek capital sigma stands for the summation step of the reconstruction algorithm.

FIG. 2. Schematic diagram of the dyadic wavelet transform in two dimensions. $S$, signal; $A$, approximations; $H$, horizontal details; $V$, vertical details; and $D$, diagonal details. Horizontal hatching symbolizes convolution along the rows of the input, vertical hatching convolution along the columns. For details on other symbols and coloring see legend of Fig. 1.
FIG. 3. Schematic visualization of decomposition structures for the three-dimensional wavelet transform. For details on symbols and coloring see legend of Fig. 1.

FIG. 4. Flowchart of the wavelet-aided binding potential estimation procedure. Blue rectangles symbolize data; pink rhombi represent procedural steps in the calculations.
of the signal was deleted during the downsampling. The presence of the artefact will be the result of a particular “constellation” of the signal and the data-points that were deleted during downsampling. As a consequence if the input is shifted by one data-point and the decomposition is performed again then the artefacts may disappear in certain locations of the sample (but others could at the same time appear in different locations).

There is a special version of the dyadic wavelet transform, which is free from this limitation. This is often referred to as the property of translation-invariance. In case of the three-dimensional transform, however, the translation-invariant approach is not workable at present due to the highly increased computational and storage requirements. On the other hand it has been shown that the three-dimensional wavelet transform, by utilising information in all the three principal axes, highly compensates for the lack of translation-invariance with regard to the quality of the decomposition (Turkheimer et al., 2000b). Also the depth of the decomposition and the length of the wavelet filter kernel have great impact on the computational load. Bigger decomposition depths and longer filter kernels imply higher computational requirements. This means that a practical trade-off has to be made between quality and performance. A realistic hardware configuration contains approximately 1 gigabyte main system memory and at least a Pentium III class processor or alike.

Subjects

The subjects and imaging procedure have been described in detail earlier in a report on quantification of \(^{[14]C}\)FLB 457 binding (Olsson et al., 1999). In short, the study was approved by the Ethics and Radiation Safety Committee of the Karolinska Hospital. Ten healthy male subjects, aged 23 to 38 years were enrolled and informed consent was obtained in line with the Declaration of Helsinki. The subjects were healthy according to history, medical examination, blood and urine screening tests and magnetic resonance imaging (MRI) of the brain. None of them were taking medications.

Magnetic Resonance Imaging

The MR system used was GE Sigma, 1.5 Tesla. Proton density and T2-weighted images were obtained for all subjects. Subjects had an individual plastic helmet that kept the head in a fixed position during data acquisition (Bergström et al., 1981).

Positron Emission Tomography

The PET system used was a Siemens ECAT Exact HR machine, which provides 47 slices with a center-to-center distance of 3.125 mm. The intrinsic spatial resolution is 3.6 mm in plain at the centre of the field of view and 4.0 mm full width at half maximum (FWHM) axially (Wienhard et al., 1994).

The same head fixation system as in the MRI measurement was used in PET to yield the same positioning of the head in both modalities. \(^{[14]C}\)FLB 457 was prepared as previously described (Halldin et al., 1995). The radioligand was injected as a bolus (t = 2 s duration) into the right cubital vein. The specific radioactivity was 1081–2086 Ci/mmol at time of injection. Total injected radioactivity was 189–299 MBq, which corresponds to an injected mass of 1.1 to 2.1 µg. After the injection the cannula was promptly flushed with 8 ml saline. After injection of \(^{[14]C}\)FLB 457 data were acquired for 63 min in consecutive time frames. The frame sequence consisted of three 1-min frames, four 3-min frames, and finally eight 6-min frames. The images were reconstructed using filtered back-projection with a Hanning filter with a cut-off frequency 0.5 of maximum, providing an in-plane resolution of 5.5 mm FWHM. Image matrix size was 128 × 128 and pixel size was 2.0 mm. Scatter correction was performed as described in the literature (Wienhard et al., 1994). Attenuation correction was performed using a transmission scan obtained for each individual.

General Strategy of Calculations

Each of the individual datasets was analysed by four methods for cross-validation purposes; traditional ROI-based graphical parameter estimation, linear graphical pixel-by-pixel analysis (parametric imaging) and two types of wavelet-aided analyses. In both types the wavelet transform is applied spatially. The difference is whether it is applied two dimensionally to each slice of the volume or three dimensionally to the whole volume. The results of the ROI-based approach served as a reference for the evaluation of the other three methods.

Calculation of Binding Potential via ROI-Based Analysis

Images were transformed into standard anatomical space using the computerized human brain atlas (HBA) (Roland et al., 1994). ROI’s from the anatomical database of this system were positioned for 10 brain structures: the caudate nucleus, the putamen, the thalamus, the frontal cortex, the anterior and posterior cingulate cortex, the temporal cortex, the parietal cortex, the occipital cortex, the substantia nigra, and the cerebellar cortex. The cerebellar cortex was used as a reference region for free and nonspecifically bound \(^{[14]C}\)FLB 457 in brain.

The binding potential of \(^{[14]C}\)FLB 457 was estimated using the reference region version of Logan’s graphical analysis (Logan et al., 1996). The equation for this plot is:
Parametric Imaging of Binding Potential Using Pixel-by-Pixel Analysis

The procedure using Eq (1) for calculation of the binding potential was also applied for a pixel-wise analysis of the datasets. To reduce the number of calculations the fitting was not applied to pixels that have total accumulated radioactivity below a certain threshold. The accumulated radioactivity of a pixel was calculated as area under the curve (AUC) of the corresponding TAC, and the threshold is defined as the mean AUC of the cerebellar cortex because any pixel that accumulates less radioactivity than the reference tissue can be safely assumed to represent an area devoid of receptors. In addition, fitting was not applied to pixels that would yield zero divisions because of zero radioactivity values.

The AUC was used with the assumption that in those locations where the radioligand is not present or accumulates only in the initial circulatory part of the experiment it will be a value close to zero. These pixels were assumed to be part of the background or nongrey matter tissues, or completely corrupted by noise and therefore the BP at those locations was set to zero. Preliminary tests have confirmed that the assumption is correct and a BP of zero is a good approximation of the estimated BP of subthreshold locations. The final product of the calculations is a parametric image of the subject’s distribution and density of dopamine D₂ receptors in brain.

The anatomical standardisation procedure using HBA was performed on the parametric images. In this way no unnecessary sources of error were introduced before the kinetic calculations. For standardisation the same warping transformations were used for each individual as in case of the ROI-based analysis. Having the images in standard space the same ROIs could be applied to determine the average binding potential of the target anatomical structures for cross-validation purposes.

Parametric Mapping of [¹¹C]FLB 457 Binding Potential Using Wavelet-Based Signal Estimation

The estimation procedure was a modification of that recently described in the literature by Turkheimer et al., 2000a). The flowchart of the procedure is shown in Fig. 4. The original images were transformed frame-by-frame to wavelet space using two approaches. Either the two-dimensional translation-invariant (2-DTI) or the three-dimensional (3-DWT) wavelet transform was applied. The filters for the transform belong to the Battle–Lemarie wavelets (Battle, 1987; Lemarie, 1988). The depth of the decomposition was 2 and the length of the filter kernels was 22. The parameters were chosen in an iterative approach, which yielded the best recovery of regional BP values as well as the lowest computational load.

Please note that when referring to a “coefficient” in this paragraph we should always in fact think of a temporal sequence of coefficients with the same position in the consecutive 2-D or 3-D wavelet transforms (similarly to a temporal sequence of voxels with the same spatial location in the original PET study). The coefficients of the resulting dynamic wavelet transform were analysed quantitatively in the same manner as in case of the pixel-based approach. The only difference was that a different strategy was required to determine the value for the thresholding step that was used to reduce the number of calculations. The mean AUC value of the reference region cannot be used as threshold in wavelet space as it is calculated on data in “normal” space. Therefore a 3-D mask image of the reference region (cerebellar cortex) was first created and transformed to wavelet space. Besides, the frame-by-frame transform of the input PET image was processed by calculating the frame-by-frame AUC of each coefficient. This AUC “transform” was then masked with the previously created WT of the 3-D mask to yield the AUC value of those coefficients that correspond to the reference region in normal space. The average value of this pool of AUC values was used as the thresholding limit. The thresholding step identified all valid coefficients. The parameter estimation was performed only on the valid coefficients. The end product of the calculations was a parametric wavelet transform describing the distribution of the binding potential. In the next step wavelet reconstruction was applied on the parametric transform to yield the 3-D parametric map of binding potential values in normal space.

Finally, for cross-validation purposes, anatomical standardisation and ROI based target structure analyses were performed on the parametric images in the same way as described above.

The parametric imaging calculations were performed on a PC (1.5 GHz Intel Pentium 4 processor) in Linux using Matlab (The Mathworks Inc., Natick, MA).
The software engine for the 3-D wavelet decomposition and reconstruction was originally developed in C++ by one of the authors (ZC). The final parametric images and the original PET images were transformed to a Silicon Graphics O2 workstation (Silicon Graphics, Mountain View, CA) to perform spatial standardization, ROI-fitting and ROI-based calculations. Extracted regional, per method binding potential values are shown in Figures 5-8.

**FIG. 5.** Regression analysis of three methods against the reference method (ROI-based analysis). Data points are mean regional binding potential values of the 10 subjects tested.

**FIG. 6.** Estimated regional binding potential values of the three parametric image methods in percentage of the corresponding value of the reference method (mean ± SD for the 10 subjects tested).
were processed in Microsoft Excel (Microsoft, Redmond, WA).

**RESULTS**

Average regional binding potential values for the four methods are given in Table 1. The traditional ROI-based analysis yielded high binding potential values for the putamen and the caudate nucleus and much lower in the extrastriatal regions. This is in good agreement with previous studies (Farde et al., 1997; Okubo et al., 1999; Olsson et al., 1999; Olsson and Farde, 2001). It must be noted that the values for the striatum are underestimated since the TAC of striatum did not reach peak equilibrium during the time-span of data acquisition (Olsson et al., 1999). The values are, however, useful for the cross validation purposes of the present comparative study.

In the pixel-based analysis the resulting parametric image (Figs. 7a and 8a) is of the same anatomical resolution as the input PET image. The image is heterogeneous due to missing pixels (“black holes”), particularly in regions of high receptor density. These missing pixels represent completely noise-corrupted locations and sudden jumps in the estimated BP values. For each region the values are unanimously lower than the corresponding ROI-based values. According to the regression plot (Fig. 5) they are only about half as high as those of the ROI-based analysis.

In general the results of the 2DTI and 3D wavelet-based analyses (Table 1; Figs. 5, 6, 7b, 7c, 8b, 8c, and 9) were in better agreement with those of the traditional ROI-based method. The regression analysis showed that the estimated regional BP values were about 78% (2DTI) and 100% (3-D) of those with the ROI-based approach (Fig. 5). Figure 6 displays the estimated BP with the three test methods for the nine highest receptor-density anatomical regions in percentage of the BP obtained with the ROI-based method. The values shown are mean and standard deviation for the 10 individuals tested.

The parametric images (Figs. 7b and 7c) obtained by the wavelet approaches show the spatial distribution of binding potential. The resolution is somewhat lower when compared to that of the input image. The parametric maps based on the 3-DWT-aided analysis showed more homogeneous patterns (especially in the axial direction) than those coming from calculations with the plane-by-plane 2-DTI wavelet transform (Figs. 8b and 8c).

**DISCUSSION**

Both clinical and nonclinical oriented research on neurotransmission has a need for accurate and precise quantification of neuroreceptor binding over a wide density range using PET in vivo. High levels of noise in PET images, however, pose a limitation when attempting to create detailed parametric images. Wavelet filters offer a promising way around this problem by differentiating the signal and noise components of the image. A thorough assessment of the performance of a wavelet-aided parameter estimation procedure should be performed on a dataset containing signals of a broad spectrum of intensities. For this reason $^{11}$C]FLB 457 is a good basis for a cross-validation approach as it is able to detect signals from a range of regions with a 100-fold difference in dopamine D$_2$-receptor density. The results show that it is possible to overcome the effects of noise by the use of the wavelet transform in the parameter estimation procedure.

The noise of the TACs representing single voxel results in a general underestimation of BP when applying a linear graphical pixel-based approach. This observation is consistent with previous findings using the radioligand $^{11}$C]WAY 100635 and $^{11}$C]NNC 112 (Slifstein and Laruelle, 2000). However, considering the high correlation between the ROI-based and pixel-
based methods ($R^2 = 0.992$) it should be feasible to correct
the results of pixel-based analysis by a factor
(approximately 2.05 for $[^{11}C]FLB$). Unfortunately
voxels in low-receptor density regions were severely
affected by noise (see leftmost regions in Fig. 6). It is
thus not likely that a corrected pixel-based approach
can be used for such regions.

One of the frequently utilised radioligands for test-
ing algorithms in a pixel-by-pixel manner is $[^{11}C]raclo-
pride. It has been shown that the average regional
values of pixel-based analysis using $[^{11}C]raclopride are
in good agreement with the results obtained by the
analysis of the same regions with the ROI-based ap-
proach (Gunn et al., 1997). Therefore, in our view,
$[^{11}C]raclopride alone is not sufficient for the validation
of parameter estimation techniques as the noise-sensi-
tivity of the method may remain unexplored. Although
Gunn's method is a highly capable technique, our
method of choice was Logan’s reference region based
graphical analysis as it can be used in both “normal
space” methods (ROI-based, simple pixel-based) and
“wavelet space” methods. On the other hand, Gunn’s
method is not applicable in the presented way of wave-
let-based analysis due to its non-linear nature. Dealing
with a large amount of data, it is also important that
the linear graphical method is much faster computa-
tionally than Gunn’s more complicated method. Nei-
ther this nor other additional “normal space” ap-
proaches were included as the aim was to assess the
capability of the wavelet-aided framework to decrease
the noise-sensitivity of a parameter estimation proce-
dure.

Two wavelet approaches were applied. In both ap-
proach the wavelet transform is applied spatially not
on the time-activity curves of individual pixels as in
other studies in the literature (Millet et al., 2000a,
2000b). The reason for this is that noise in 4-D PET
images is spatially correlated, thus it is less likely to be
eliminated if it is only dealt with in the temporal do-
main. Besides wavelets do not seem to be an optimal
functional base for PET kinetic curves. The most im-
portant difference between the two approaches used
in this study is whether the wavelet filtering is applied
two dimensionally to each slice of the volume or three
dimensionally to the whole volume. The other differ-
ence was the translation-invariant property of the 2-D
approach. The three-dimensional wavelet filtering (3-
DWT) was superior to the two-dimensional (2-DWT)
approach and the BP was in close agreement with the
traditional ROI-based analysis. Translation-invari-
ance cannot account for the systematic and big differ-
ces that we observed between the results of the
2-DTI and 3-D methods. This leads to the conclusion
that the dimensionality of the filter may have a signif-
icant impact on the quality of signal recovery for these
types of images.

The performance of the 3-DWT-aided analysis sug-
gests that using this approach a separation of signal
and noise and hence a precise estimation of BP can be
achieved because it can more accurately detect and
represent the information content of the original image
regarding the spatial patterns of signal and noise. The
accuracy was not impaired even in regions with low
receptor-density, i.e., high relative noise levels (Fig. 6).
The highest deviations from the reference values were
observed in case of the smallest region studied (the
substantia nigra). A likely explanation is that too few
voxels were averaged to achieve optimal noise reduc-
tion even for the ROI-based approach. However, given
the accuracy of all other regions the wavelet-based ap-
proach should not have been affected, thus providing
more accurate estimates. In conclusion the wavelet-aided
parameter estimation is an anatomically unbiased pro-
dure for regions with a 100-fold difference in density.

Challenging aspects of the wavelet-based analysis
include the possibly time-consuming determination of
the best settings for the wavelet transform and the
lowered resolution of the resulting parametric images.
It should be noted, however, that the maximum level to
which wavelets can determine the position and the
frequency composition of a certain feature of the signal
simultaneously is limited by the Gabor uncertainty
principle, which is the analogue of Heisenberg's prin-
ciple in the field of information theory (Gabor, 1946).
Whether the resolution of our parametric maps repre-
sents this maximum level or the sharpness can be
improved is the focus of ongoing developments. As part
of that, it is also going to be addressed if the wavelet-
filtering parameters are specific with regard to
$[^{11}C]FLB$ 457.

Noise was the major factor explaining the differences
between the examined methods. The noise in PET im-
ages is of complex nature (Pajevic et al., 1998; Turkhei-
mer et al., 1999; Abi-Dargham et al., 2000; Millet et al.,
2000b). Individual time frames of such a study can be
characterised by low spatial signal-to-noise ratio. Be-
cause of the way the reconstruction is usually per-
formed (filtered back-projection), the Gaussian white
noise of the individual detection channels becomes cor-
related in the final image. This correlated distortion of
pixel values by relatively high levels of noise cannot be
dealt with by the independent analysis of individual
TACs, multiple pixel locations must be included in any
denoising scheme. Presumably no smaller neigh-
bourhoods of pixels can be analysed independently
than the radius of effect of correlation.

In the ROI-based analysis, the problem of noise is
reduced through the use of the average value of all
pixels representing a certain brain region. In a sense,
this might be viewed as “structure-based” filtering of
noise. This approach is sufficient for regions with a
homogenous distribution of receptors. However, neuro-
receptors may be heterogeneously distributed within a
region and information regarding subregional differences may consequently be lost. Simple averaging may also lead to false results if the area of the region is so small that the effect of correlated noise cannot be overcome (possible scenario in case of substantia nigra in the present study).

Another issue regarding noise is the AUC thresholding used to “delete” locations containing noise or no receptors. In this study the criterion was realized using the mean AUC of the reference region. For situations where no reference region is available the criterion could be generalized by for instance using the AUC of the blood or white matter, i.e., any location that has an equal or smaller AUC than one containing receptors. At first glance, the problem seems to be that by this criterion the analysis would...
include locations that are devoid of receptors, but have some (interstitial) ligand accumulation. However, if the analytic procedure is good then it will produce near-zero BP for these locations so the final map could be correct. In different words, the AUC thresholding is only doing part of the job of “deleting” noise coefficients; the rest of those are in fact handled by the estimation procedure itself.

Parametric images with accurate values can be utilised in a number of applications. Among others, in contrast with simple regional values obtained they can be used in a statistical framework like SPM or GLM to compare subregional differences in receptor kinetics between different healthy or diseased populations (Friston et al., 1994; Ledberg et al., 1998; Turkheimer et al., 2000b). Besides, both cognitive and neuropsychiatric research can benefit from brain-activation-study-like applications where the aim is to map, in again a statistical framework, subregional changes of binding potential due to drug or cognitive challenge.

In sum, the usefulness of the wavelet filtering lies in being able to suppress noise by averaging over large spatial scales in a fashion that is similar to the ROI-based analyses. At the same time higher spatial frequency information is preserved in the coefficients corresponding to the detail. In short, the wavelet technique allows for the benefits of the ROI approach but does not impose prior assumptions on the exact anatomy of radioligand or receptor distribution. As such it represents a voxel-based approach that has the benefits of noise robustness usually associated with ROI approaches. The present results lead to the conclusion that the combination of three-dimensional spatial wavelet filtering with existing parameter estimation procedures enables us to obtain detailed, accurate maps of radioligand binding parameters.

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