BASIS FUNCTION METHOD OUTPERFORMS GJEDDE-PATLAK PLOT IN PRODUCING PARAMETRIC MAPS FROM [F-18]FDOPA PET STUDIES

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Introduction

It has been shown that Logan analysis is more appropriate than the Gjedde-Patlak analysis for the assessment of [F-18]FDOPA PET dynamic data (Sossi et al., Kawatsu et al.).

The aim of this study was to investigate the feasibility of simplified reference tissue model, solved by basis function approach (BF-SRTM), in computation of parametric maps of dopamine turnover as its inverse, effective dopamine distribution volume (EDVR).

The potential of this approach in discriminating Parkinson's disease patients and age-matched healthy subjects is compared to the traditional analysis method, Gjedde-Patlak.

Gjedde-Patlak analysis

Habitually used method with seemingly good practical usability.

Drawback: Basic assumption: the tracer uptake is irreversible during PET imaging. This assumption is violated in FDOPA-PET-studies. Outcome of the method, net uptake rate K_i is biased because of the loss of [F-18]FDOPA metabolites from the brain (fig 1):

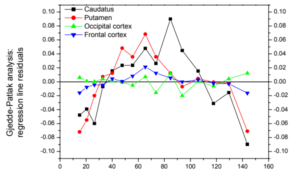

Figure 1: Violation of assumptions of Gjedde-Patlak analysis causes a curvature of the plot. This is clearly seen from the residuals of regression line fit to Gjedde-Patlak plot from one of the control subjects. Data is shown from 15-90 min after [F-18]FDOPA injection, the commonly used time range in Gjedde-Patlak analysis of [F-18]FDOPA data with reference tissue input.

Logan analysis

Recently suggested for FDOPA analysis (Sossi et al., Kawatsu et al.).

Does not require irreversible uptake.

Outcome of the method, EDVR, is relevant to neurological studies, relating to inverse of dopamine turnover, affected by both net uptake rate of [F-18]FDOPA and loss rate of [F-18]FDOPA metabolites.

Drawbacks: 1) Application requires a population average of k_2 in reference region (Kawatsu et al.). 2) The method is sensitive to measurement noise-induced negative bias.

SUGGESTED METHOD:

Simplified reference tissue model solved by basis function method (BF-SRTM)

Outcome measure = same as in Logan. No reference region k_2 needed. Less sensitive to measurement noise than Logan analysis. Software is widely available in PET centres.

Study material:

First 90 min from the prolonged 3.5 h PET studies with 6 control subjects (C) and 6 Parkinson's disease patients (PD) (Ruottinen et al.) were reanalyzed pixel-by-pixel using the two methods, BF-SRTM for producing EDVR maps, and Gjedde-Patlak analysis for producing net uptake rate (K_i) maps. Cerebellum was used as input to both models.

Results and discussion

BF-SRTM fits time-activity curves (TACs) reasonably well, demonstrated by the model fits to regional average TACs (fig 2).

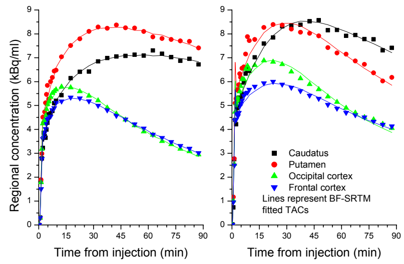

Figure 2: BF-SRTM fits well to the regional average TACs of one healthy subject (left) and one Parkinson's disease patient (right).

Parametric EDVR maps computed using BF-SRTM have a visibly good quality, especially in cortical regions (fig 3).

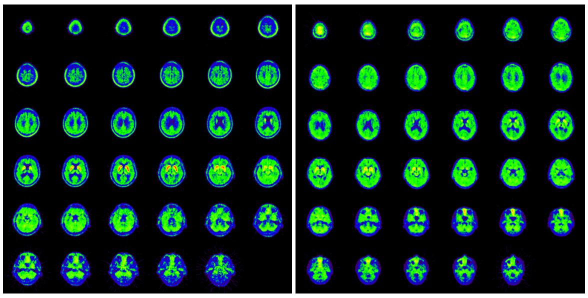

Figure 3: EDVR maps of one healthy subject (left) and one patient with Parkinson's disease (right). Maps were computed using BF-SRTM (with θ_3 between 0.01 min^{-1} and 0.1 min^{-1}).

Mean values of K_i and EDVR inside caudatus, putamen, occipital cortex and frontal cortex were calculated from the parametric maps produced using the two methods, Gjedde-Patlak analysis and BF-SRTM. Both methods separate the two study populations well in striatal areas, and neither of them gives any difference in cortical areas (Table 1).

Table 1: Regional averages (with CV% between subjects in parenthesis) of EDVR and K_i maps calculated using the first 90 min of dynamic PET data (p values from t test).

		caudatus	putamen	occipital cortex	frontal cortex
EDVR	C	2.598 (7)	3.046 (7)	0.945 (4)	0.994 (8)
	PD	2.062 (12)	1.788 (13)	0.966 (5)	0.994 (6)
	p	0.0021	0.000001	0.41	1.00
K_i (min^{-1})	C	0.0093 (8)	0.0102 (4)	0.00083 (24)	0.00133 (26)
	PD	0.0074 (15)	0.0048 (21)	0.00084 (23)	0.00136 (23)
	p	0.0056	0.000008	0.96	0.87

Although Gjedde-Patlak analysis and BF-SRTM are based on opposite assumptions (irreversible uptake vs. reversible uptake) and the outcomes theoretically represent different physiological phenomena (net uptake rate vs. distribution volume), in practise the results K_i and EDVR show good correlation (fig 4). Gjedde-Patlak analysis does not account for the loss of [F-18]FDOPA metabolites from the brain, and therefore the outcome K_i is strongly biased. K_i does not reflect "net uptake", but instead correlates to the more relevant measure, EDVR, which can be calculated using more appropriate methods, Logan analysis or BF-SRTM.

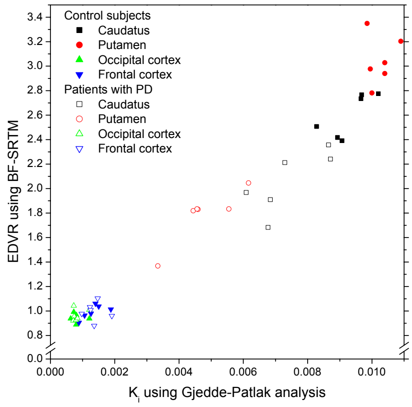

Figure 4: Correlation between outcomes of Gjedde-Patlak analysis and BF-SRTM. Regional mean values are calculated from K_i and EDVR maps.

Conclusions

BF-SRTM is useful method for producing EDVR maps from [F-18]FDOPA PET studies.

BF-SRTM separates advanced PD patients from controls at least as accurately as Gjedde-Patlak analysis.

Apparently, the K_i from Gjedde-Patlak analysis with reference tissue input does not reflect net uptake rate but is correlated to EDVR.

References:

Kawatsu S, Kato A, Hatano K, Ito K, Ishigaki T. New insight into the analysis of 6-[^{18}F]fluoro-L-DOPA PET dynamic data in brain tissue without an irreversible compartment: comparative study of the Patlak and Logan analyses. *Radiat. Med.* 2003; 21: 47-54.

Ruottinen HM, Niinivirta M, Bergman J, Oikonen V, Solin O, Eskola O, Eronen E, Sonninen P, Rinne UK. Detection of response to COMT inhibition in FDOPA PET in advanced Parkinson's disease requires prolonged imaging. *Synapse* 2001; 40: 19-26.

Sossi V, de la Fuente-Fernández R, Holden JE, Doudet DJ, McKenzie J, Stoessl AJ, Ruth TJ. Increase in dopamine turnover occurs early in Parkinson's disease: evidence from a new modeling approach to PET ^{18}F-fluorodopa data. *J. Cereb. Blood Flow Metab.* 2002; 22: 232-239.