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A method of generating image derived input function in quantitative ^{18}F -FDG PET study based on the monotonicity of the input and output function curve

Shan Zhou^{1,2,a}, Kewei Chen^{3,4,5,a}, Eric M Reiman^{3,5}, De-min Li¹, and Baoci Shan^{2,*}

¹Physical Science and Technology College, Zhengzhou University, Zhengzhou 450052, China

²Key Laboratory of Nuclear Analytical Techniques, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing 100049, China

³Banner Alzheimer's Institute, Banner Good Samaritan Positron Emission Tomography Center, Phoenix, AZ, USA

⁴School of Mathematics and Statistics, Arizona State University, Tempe, AZ, USA

⁵Arizona Alzheimer's Consortium, Phoenix, AZ, USA

Abstract

Objective—A method for defining image-derived input function (IDIF) has been introduced and evaluated for the quantification of the regional cerebral metabolic rate of glucose in positron emission tomography studies.

Methods—The voxels in the brain vasculature are extracted based on the different monotonicity between the input and output function curves. The TACs of such voxels are averaged to get the uncorrected TAC of the brain vasculature. The IDIF was obtained from the raw TAC after correcting for the partial volume and spillover effects by an empirical formula in conjunction with single blood sample and the TAC of the brain tissue. Data from 16 human subjects were used to test the proposed method. The Patlak approach is used to calculate the net FDG clearance with plasma-derived input function (PDIF) and our generated IDIF, respectively.

Results—the net FDG clearances calculated with the image-derived input function generated by our approach are not only highly correlated (correlation coefficients close to 1) to, but also highly comparable (regression slopes close to 1, and intercepts close to 0) with those calculated with plasma-derived input function.

Conclusion—The method used in the present work is feasible and accurate.

Keywords

regional cerebral metabolic rate of glucose; ^{18}F -fluoro-2-deoxyglucose; image derived input function; positron emission tomography

*Corresponding author. Baoci Shan, Ph.D., Professor, Key Laboratory of Nuclear Analytical Techniques, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing 100049, China, shanbc@ihep.ac.cn, Tel.: +8610-8823-3185.

^aThese two authors contribute equally to this article

Conflict of interest

There is no conflict of interest.

Introduction

In brain dynamic ^{18}F -fluro-2-deoxyglucose (^{18}F -FDG) positron emission tomography (PET) studies, a 3-compartment model [1] is often used to describe the dynamic behavior of the FDG tracer, and the regional cerebral metabolic rate of glucose (rCMRglc) can be obtained by estimating the micro-parameters of this 3-compartment model. A number of approaches for the rCMRglc estimation have been reported [2–6], among which the nonlinear least square (NLS) approach [7] is regarded as the gold standard. NLS, on the other hand, are computationally expensive and sometimes dependent on the initial values to get adequate rCMRglc. To overcome the disadvantage of NLS approach on the calculating speed, Feng et al [5] developed a linear least square (LLS) approach which is much faster than the NLS method but with some unwanted bias. To get the unbiased estimation of dynamics parameters, Feng and his colleagues proposed the general linear least square (GLLS) [4, 6]. In addition to these approaches of estimating micro-parameters, Patlak et al [2, 3] developed a graphic method to get rCMRglc in a computationally efficient manner. In all of these quantification methods, the plasma time activity curve (PTAC) is needed as input function to quantitatively estimate the rCMRglc. The PTAC is usually obtained by multiple arterial or arterialized venous blood sampling. In human studies, the process of frequent blood sampling not only causes the patient discomfort, but also increases the complexity of the experiment and increase the infection risk for personnel handling the blood samples. Furthermore, frequent blood sampling is not possible in small animal (such as mouse) PET. A number of reports have discussed various approaches [8–16] as alternatives to the invasive arterial or arterialized venous blood sampling.

The alternative approaches can be categorized into two classes: (1) This class of methods is to replace the blood input function with what referred to as reference region [16]. Approaches of this nature, however, only provide relative rCMRglc with respect to the reference region. (2) This class of methods is to derive the input function from the blood pool/vessel areas over dynamic PET images sequences [17]. These methods can be classified into two subclasses: (a) These methods, which usually include defining the ROI containing the blood pool/vessel, are originally introduced in cardiac PET studies in which the input function is obtained by placing an ROI within the very visible and large cavity of the left ventricle [17–19]. Attempts also have been made to measure the activity from the abdominal aorta in hepatic and renal PET studies [20, 21]. In all these methods, a few blood samples are needed to correct the image derived TAC. In spite of the fact that there is no large blood pool in brain, researchers [11, 13, 14] have also successfully introduced and applied similar methods of deriving the TAC from carotid artery or other blood vessels in the brain from PET images. These methods, however, usually rely on physical identification of the targeted blood vessels. For example, these methods often need a some what subjective threshold to determine the boundary of the carotid artery and the neighboring tissue [11]. These errors associated with the physical identification directly affect the quality of the image-derived input function (IDIF). For example, in case the threshold is inappropriately chosen, the spatial extent of the carotid artery will be determined poorly, thus making the IDIF inaccurate. (b) These methods identify the blood/vessel voxels using temporal tracer kinetic information, including cluster analysis [22], dynamic factor analysis [23, 24] and the independent component analysis algorithm (ICA) [12, 14, 25].

In the present work, we proposed a method to get the TAC from whole brain in PET studies. An empirical formula is proposed for correcting the raw brain vasculature TAC in conjunction with the brain tissue TAC. The method determines rCMRglc with only single blood sample. Therefore, it is more potentially feasible in clinical application.

Methods

In this study, the widely accepted Patlak approach [2, 3] was used for the rCMRglc estimation in conjunction with the IDIF or the plasma derived input function (PDIF, i.e. the PTAC). In deriving Patlak approach, the process of dephosphorylation of FDG-6-P in brain tissue is assumed to be negligible, and the formula is

$$C_i(t) = K \int_0^t C_p(\tau) d\tau + W C_p(t) \quad (1)$$

where $C_p(t)$ is the input function, $C_i(t)$ is the summation of the TACs of FDG and FDG-6-P in tissue, i.e. output function. K is the net FDG clearance from blood to tissue, and W is another constant which is related to the spillover from blood pool to the tissue pool. In this study, the sampling time for fitting the K -values will be chosen after 15 min.

The metabolic rate of glucose is expressed by [26]:

$$R = (C_g / LC) K \quad (2)$$

where C_g is the cold glucose concentration in plasma, and LC is lumped constant which reflects the difference between glucose and FDG in transportation and phosphorylation. In this paper, we only concentrate on the net FDG clearance K for methodology validation purposes.

In this work, the K -values estimated with the PDIF and the IDIF are denoted as K_{PDIF} and K_{IDIF} , respectively. The difference of K_{PDIF} and K_{IDIF} is described by the relative error percentage defined by:

$$E_{rel}(\%) = 100 * (K_{IDIF} - K_{PDIF}) / K_{PDIF} \quad (3)$$

PET imaging and blood samples

Data of 16 normal human subjects, which is a subset of the 29 subjects used in [11], are used to evaluate the proposed method. The data from these 16 subjects were shared with researchers at Key Laboratory of Nuclear Analytical Techniques, Institute of High Energy Physics, Chinese Academy of Sciences by the co-authors from Banner Alzheimer's Institute with approval of local IRB and with subject identities anonymized. The experimental procedure was described in [11] and briefly below.

After at least 4-hour (minimum) fast, subjects were positioned in the PET scanner in a darkened room and directed to lie quietly with their eyes closed. At the start of an intravenous injection of 370 MBq of FDG, the dynamic PET scan was initiated.

The PET scanner and the associated computer system (Siemens, Knoxville, TN, U.S.A) were configured so that images with frame duration as short as 2 seconds could be acquired. Acquisition started at the time of the tracer injection and lasted for a total of 60 minutes. The acquisition protocol was as follows: one frame of 12 seconds, eight frames of 2 seconds each, two frames of 10 seconds each, one 12-second frame, one 30-second frame, two 60-second frames, two 90-second frames, one 3.5-minute frame, two frames of 5 minutes, one frame of 10 minutes, and one frame of 30 minutes.

A filtered back-projection method was used to reconstruct the PET images with the Hanning filter of 0.4 cycle per pixel. Attenuation was corrected in reconstruction process using a 20-minute transmission scan acquired before the emission scan. The reconstructed image set

consisted of 31 horizontal slices with in-plane resolution of approximately 9.5 mm full width at half maximum (FWHM) and an interslice distance of 3.375 mm.

The matrix size of PET images is 128*128*31, and the voxels size is 1.876cm*1.876cm*3.375cm. The patients were positioned to make sure the field of view (FOV) of PET scan included part of the carotid artery, which is very important for the image derived input function using our method.

Sequential arterial blood samples were also drawn every 5 seconds for the first minute, every 10 seconds for the second minute, every 30 seconds for the next 2 minutes, then at 5, 6, 8, 12, 15, 20, 25, 30, 40, 50, and 60 minutes. The PTAC is obtained from this discrete artery blood sampling. Plasma glucose levels were measured at the beginning, middle, and end of the scan.

Analysis

In the following, the early frames which have not enough event counts in PET scan to form images (called noise frames in the following) are discarded, and we refer to the 'new' first frame as the one in the rest frames.

Over the first 60 minute period, we noted that the difference between the PTAC (i.e. input function) and tissue TAC (i.e. output function) is that the former rapidly rises to its maximum which is followed by a sharp decrease to form a sharp peak (due to rapid injection of the tracer as a bolus) and then with a gradual decrease over a relative long period of time (see Fig. 1, the left panel). The tissue TAC, on the other hand, slowly increases over time without any appearance of peak except some small ones due to measurement noises and/or the blood to tissue spillover (see Fig. 1, the right panel). The unit of the input/output function is the counts per minutes calibrated with the measurements from the scanner. Our procedure proposed in this study for the construction of the IDIF depends on the determination of the timing of the sharp peak of the input function. For the data used in this study, the sharp peak of the PTAC formed in the first 3 frames (for this acquisition scheme and after discarding the noise frames).

The image-derived input function

The aim of this work is to find a function to substitute the PTAC. Obviously, the useful voxels, the TAC of which can be used to substitute the PTAC, lie in the brain vasculature such as carotid artery. Thus, the first step is to select the voxels in brain vasculature.

(1) The criterion for identifying the voxels of the brain vasculature and the brain tissue—The voxel value of the last frame is subtracted from the average of the first three frames (the frames around the sharp peak of the input function). Denote frame i as f_i , we define the criterion frame F as

$$F = \sum_{i=1}^3 f_i - f_N \quad (4)$$

where N is the total number of frames.

Based on the **Analysis**, the voxels with positive values in the criterion frame F , provided that the data is noise free, are most likely in brain vasculature whereas the negative ones in brain tissue. In this study, the sign of the voxel value in the criterion frame is used as the criterion for identifying the voxels in brain vasculature (mostly vascular) and brain tissue (mostly tissue).

However, the data noise may cause the voxels to be ‘misabeled’. In fact, there is continuum between a voxel representing only mostly blood and one representing only mostly tissue (referred to as mixed voxels below). Furthermore, it also makes the voxels in the blank region (out of head and neck) to be nonzero. The mixed, the mislabeled and the blank voxels must be excluded to obtain the correct TACs of brain vasculature and brain tissue.

(2) Determining the noise level in the criterion frame—In order to exclude the mislabeled voxels, the estimation of the noise level of the criterion frame is needed. Note that the nonzero values of the blank voxels are caused by data noise, so they can be used to measure the data noise level. In our method, the spatial position of the blank voxels is identified in the last frame because its signal-to-noise ratio (SNR) is the highest (for the longest scan time) in all frames. Generally speaking, the voxels with negative values in the last frame can be considered to lie in the blank region. Although these voxels are only a part of all blank voxels, they are enough for measuring the noise level in the criterion frame.

Denote the values of the q^{th} voxel in frame i and the criterion frame as $v(q, t_i)$ and $v_F(q)$, respectively. The voxel value set which measures the noise level in the criterion frame is defined by:

$$\{v_F(q) | v(q, t_N) < 0\}, \quad (5)$$

The values in this set are arranged into a row vector $\tilde{X}$. For symmetry, the vector $\tilde{X}$ and its negative are concatenated to form a new vector:

$$X = [\tilde{X}, -\tilde{X}] \quad (6)$$

The vector X is used to determine the noise level in the criterion frame to exclude the mixed, the mislabeled and the blank voxels.

(3) Excluding the mixed, the mislabeled and the blank voxels—In our method, the voxels whose values satisfy the following condition

$$|v_F(q)| < 3 * \text{std}(X) \quad (7)$$

are excluded, where $\text{std}(X)$ is the standard deviation of the vector X .

(4) Selecting the voxels in brain vasculature (mostly vascular) and brain tissue (mostly tissue)—The mostly vascular voxels are defined as the ones which satisfy

$$v_F(q) > 3 * \text{std}(X), \quad (8)$$

and the mostly tissue voxels in brain are defined as the ones which satisfy

$$v_F(q) < -3 * \text{std}(X) \quad (9)$$

The TACs of the voxels satisfying the condition (8) are averaged to get the raw brain vasculature TAC (we use the phrase ‘the raw brain vasculature TAC’ as ‘the uncorrected brain vasculature TAC derived in PET images’ in this paper), and the TACs of the voxels satisfying the condition (9) are averaged to get the raw brain tissue TAC (i.e. the uncorrected brain tissue TAC derived in PET images). We compared in our calculation the numbers of voxels satisfying the condition (8) and (9). And we found that the proportion of the voxels in brain is about 3%, which is consistent with the reported vascular volume in the literature. In

this study, the brain tissue TAC is used to correct the raw brain vasculature TAC especially for the contamination due to the tissue-to-blood spillover.

TACs correction

(1) Correcting the raw brain tissue TAC—An example of the raw brain tissue TAC is displayed in Fig. 2(a). An unwanted sharp peak, which is caused by measurement noise and/or blood to tissue spillover, appears in the early time of the curve. Therefore, the raw brain tissue TAC must be corrected.

Our measure is to find an appropriate function to substitute the early part of the raw brain tissue TAC while the later part is retained. We find in Fig. 2(a) that the curve looks like a power function if the sharp peak is neglected. The situations for other subjects are the same as this one, so we use a power function to fit the later part of the curve, and use the power function to substitute the early part of it.

A power function is defined as

$$y=at^b \quad (10)$$

where a and b are parameters. Denote the raw brain tissue TAC as $C_{\text{TTAC}}^{\text{raw}}(t)$. Provided that the unwanted sharp peak appears at frame I , the later part ($t > t_{2*I}$) of $C_{\text{TTAC}}^{\text{raw}}(t)$ is used for the fitting of the power function in our method. The time t_{2*I} is an experiential choice based on the shape and width of the peak in Fig. 2(a).

The corrected brain tissue TAC is defined as

$$C_{\text{TTAC}}(t)=\begin{cases} at^b, & t < t_{2*I} \\ C_{\text{TTAC}}^{\text{raw}}(t), & t \geq t_{2*I} \end{cases} \quad (11)$$

The corrected brain tissue TAC is shown in Fig. 2(b).

(2) Correcting the raw brain vasculature TAC—An example of the image derived raw brain vasculature TAC (i.e. the uncorrected brain vasculature TAC derived in PET images) and the PTAC of the same subject are displayed in Fig. 3. The difference between the raw vasculature TAC and the PTAC is caused by the tissue-to-blood spillover and partial volume effects (PVE). In this study, we try to find an empirical formula to correct the raw brain vasculature TAC with only one blood sample.

Denote the TAC of the q^{th} voxel as $v(q)$. Generally speaking, the IDIF depends on the TAC of every voxel, that is, the IDIF is a functional of the TACs of all the voxels

$$C_{\text{IDIF}}(t)=\hat{F}[\{v(q)\}] \quad (12)$$

where $\{v(q)\}$ denotes the TACs of all the voxels and the square brackets denote functional. The equation (12), however, is much too general to be used for detracting the IDIF. An alternative idea is that the IDIF approximately depends on the raw brain vasculature TAC (the average of the TACs of all the brain vasculature voxels) and the brain tissue TAC (the average of the TACs of all the brain tissue voxels), that is

$$C_{\text{IDIF}}(t)=F[C_{\text{VTAC}}^{\text{raw}}, C_{\text{TTAC}}] \quad (13)$$

where C_{VTAC}^{raw} denotes the raw brain vasculature TAC. The next step is to find the form of the functional (13).

Due to the partial volume effect, the magnitude of the raw brain vasculature TAC is significantly reduced especially at its early part thus making it flatter than the PTAC (see Fig. 3). On the other hand, because the brain tissue TAC is an increasing function, the tissue-to-blood spillover contaminated the brain vasculature TAC making it higher at the later portion of the curve. Thus, we suggested that the raw brain vascular TAC could be corrected by some inverse function of the tissue uptake, and tried to correct the raw brain vasculature TAC by defining

$$C_{IDIF}(t) = \frac{s * C_{VTAC}^{raw}(t)}{C_{TTAC}(t)} \quad (14)$$

where s is a constant, which can be determined with single blood sample, for adjusting the scale of the IDIF and adding the dimension of the concentration of FDG. Fig. 4 shows the brain vasculature TAC corrected with equation (14) for one subject.

The correction result in Fig. 4 is encouraging. The results for other subjects are similar to the one showed in Fig. 4. Therefore, equation (14) provides the starting point of finding an appropriate formula for correcting the raw brain vasculature TAC. After several amendments based on equation (14), we find that the following form of the functional (13) is appropriate to improve the IDIF according to visual comparing the IDIF with PTAC and the calculating results (see Results)

$$C_{IDIF}(t) = s * C_{IDIF}^{(1)}(t), C_{IDIF}^{(1)}(t) = \frac{C_{VTAC}^{raw}(t)}{\exp\left(\frac{0.7C_{TTAC}(t)}{\max(C_{TTAC})}\right) - 1}, \quad (15)$$

where $\max(C_{TTAC})$ is the maximum of C_{TTAC} , and s is a constant factor determined with single blood sample

$$s = \frac{C_{PDIF}(T)}{C_{IDIF}^{(1)}(T)}, \quad (16)$$

where C_{PDIF} is the plasma-derived input function (PDIF), i.e. the PTAC. T is the blood sampling time used for correcting the raw brain vasculature TAC. In this study we choose

$$T = 30 \text{ min.} \quad (17)$$

Results

Fig. 5 shows the comparison between the IDIF and PDIF for one subject.

To estimate the error between the K-values calculated with the IDIF and the PDIF, we selected 42 Brodmann areas (ROIs) in brain gray matter using the software Wfu_PickAtlas Tool Version 2.4[27, 28]. In order to select the areas in gray matter with the software Wfu_PickAtlas, all the 3D PET images are normalized to the coordinate space of the MNI template with SPM5 (Wellcome Department of Cognitive Neurology, London, UK), which match with the atlas of Wfu_PickAtlas. The TAC of an ROI is obtained from the average of the TACs over all voxels within the ROI.

K-values estimated with each of the two input functions were obtained for all the ROIs of every subject. The relative error percentage of metabolic rate of an ROI is defined by equation (3). The K-values estimated with PDIF and IDIF are fitted with linear regression method for every subject. To evaluate the IDIF method, we calculate the average of the absolute values of relative error percentages of the 42 ROIs for every subject (shown in Fig. 6). The correlation coefficients, the slopes and intercepts of linear regression for all subjects are also shown in Fig. 6.

To validate the IDIF in the present work, the K-values are also calculated voxel-by-voxel for the gray matter of all subjects. For every subject, the K_{PDIF} -values and K_{IDIF} -values are fitted with linear regression method, and the correlation coefficient between the two K-values is also worked out. Fig. 7 shows the average of $|E_{rel}(\%)|$, the correlation coefficients, and the slopes and intercepts of linear regression for all subjects.

The K-values of the whole brain (using the whole gray matter as one ROI), the relative error percentage and the constant s in equation (15) for every subject are shown in Table 1. In addition, we also calculated the intraclass correlation coefficient of the 16 paired global K-values to demonstrate the reproducibility ($ICC=0.9975$, $p<1.2\times10^{-7}$).

Discussion

This study proposed an alternative method for the construction of the image derived input function to generate the rCMRglc. The useful voxels are selected based on the different monotonicity of the input and output functions and the procedure is performed in the whole brain region of PET images. We proposed an empirical formula for correcting the raw TAC of brain vessels derived in PET images and only one blood sample is needed. The procedure is simple, automatic and can be easily implemented and carried out by a user.

We note that the data used in this study were acquired 13 years ago and were with lower resolution compared to the modern PET scanners. We used these data because there are available blood sample data for acquiring the PTAC which is used to compare with our IDIF. We believe that our blood vessel identification approach is applicable to data acquired from scanners with better resolutions.

The results in Fig. 6~7 and Table 1 showed that the net FDG clearances calculated with the image derived input function generated by our approach are not only highly correlated (correlation coefficients close to 1) to, but also highly comparable (regression slopes close to 1, intercepts close to 0, and highly significant ICC results) with those calculated with plasma derived input function. This demonstrates that the method introduced in the present work is feasible and accurate.

In this study, a manually defined cubic volume containing the carotid artery is not needed. This characteristic not only simplified the procedure of deriving the input function in PET images, but also avoided the errors associated with any method of defining the carotid artery region. In addition, our method doesn't contain any manual steps except for discarding the first few frames which don't have enough counts above the background noise. Therefore, this method greatly reduces the complexity of estimating the rCMRglc and improves the efficiency which is extremely important in clinical application.

The main reasons that the raw brain vasculature TAC decreases more slowly are the tissue-to-blood spillover and the brain tissue TAC is an increasing function. Since we approximated the tissue TAC via power function fitting (a numerical procedure to correct the blood-to-tissue spillover), we only need to correct the tissue-to-blood spillover with the assumption that such spillover (to the raw vascular TAC) inversely proportional to the tissue

TAC. Equation (14) is thus proposed. Our results showcased this alternative. Of course, its eventual acceptance requires additional and more careful validations.

Note that there is an empirical factor 0.7 in equation (15). In our calculation, the results are robust with this factor changing from 0.3 to 1.0. Though we noticed the robustness of the resultant corrected IDIF and the estimated K for the variation of scalar (currently we used 0.7) in equation (15), we realized this numerical values was based on the data from 16 subjects used in this study. Furthermore, its generalization requires additional validation.

In this study, the correcting time point is chosen at 30 min after the tracer injection. We noticed that the calibration time can be any one after 25 min; the results are essentially unchanged with corresponding “s” values. Although we used one arterial blood sample for correcting the image-derived raw brain vasculature TAC, the arterialized venous sample have been validated [1] as a replacement of arterial sample. Therefore, an arterialized venous sample is adequate for correction. For the FDG tracer, the later-time arterial-venous equilibrium makes this approach feasible even with some possible inclusion of a few venous voxels when determining the input function. However, additional studies are needed for its generalization to other tracers.

In our method, the net FDG clearance can be determined with only a single blood sample. We note that the cold glucose concentration in the plasma is needed to determine the rCMRglc (see equation (2)) but not the net FDG clearance K. Thus, this single blood sample can also be used to determine the cold glucose concentration in the plasma in clinical application for rCMRglc quantification. In other words, we suggest that a single blood sample is drawn 30 minutes after the tracer injection with dual purposes: measuring the blood glucose concentration and the FDG concentration in the plasma used for correcting the raw brain vasculature TAC.

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Abbreviations

PDIF	plasma-derived input function
rCMRglc	regional cerebral metabolic for glucose
¹⁸F-FDG	¹⁸ F-fluoro-2-deoxyglucose
IDIF	image derived input function
GLLS	general linear least square
LLS	linear least square
NLS	nonlinear least square
PET	positron emission tomography
ROI	region of interest
TAC	time activity curve
PTAC	plasma time activity curve
PVE	partial volume effect

SNR	signal-to-noise ratio
ICA	independent component analysis

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Fig. 1.
the input function (a) and output function (b) of an ROI for one subject

Fig. 2.
(a) the raw brain tissue TAC, (b) the corrected brain tissue TAC

Fig. 3.
image-derived raw brain vasculature TAC and the PTAC of one subject

Fig. 4.

An attempt of correcting the raw brain vasculature TAC. The “s” value is determined by a blood sample at time 30 min

Fig. 5.
the IDIF and PDIF of one subject

Fig. 6. ROI-wise comparisons between K_{PDIF} and K_{IDIF} for all subjects: the average of $|E_{rel}(\%)|$ (a), the correlation coefficients (b), the slope (c) and the intercept (d) of linear regression

Fig. 7. Voxel-wise comparisons between K_{PDIF} and K_{IDIF} for all subjects: the average of $|E_{rel}(\%)|$ (a), the correlation coefficients (b), the slope (c) and the intercept (d) of linear regression

Table 1 Comparisons between K_{PDIF} and K_{IDIF} of the whole brain for all subjects

Subject number	K_{PDIF}	K_{IDIF}	$E_{rel}(\%)$	Constants
1	0.0228	0.0224	-1.65	1.6461
2	0.0264	0.0254	-3.70	1.2225
3	0.0364	0.0345	-5.22	1.1946
4	0.0366	0.0366	-0.00	1.1084
5	0.0260	0.0250	-3.82	1.2011
6	0.0355	0.0335	-5.88	1.2129
7	0.0368	0.0353	-4.14	1.1818
8	0.0316	0.0334	5.68	1.4363
9	0.0333	0.0323	-3.15	1.5769
10	0.0455	0.0473	3.90	0.9339
11	0.0269	0.0277	3.03	0.9776
12	0.0331	0.0330	-0.34	1.0411
13	0.0299	0.0282	-5.68	1.6574
14	0.0363	0.0355	-2.22	1.2239
15	0.0905	0.0883	-2.37	0.3916
16	0.0799	0.0796	-0.29	0.7744