[redacted] homogeneous although there is some discussion about the optimal positioning of the region of interest in the normal brain (Unterrainer et al., 2017). Nevertheless, it cannot be excluded that physiological variations of SUV_{mean} of ^{18}F-FET uptake in background could influence TBRs and the results of semi-quantitative analysis.

It is well-known that age and gender influence cerebral metabolism as measured for example by PET using the glucose analogue ^{18}F-fluorodeoxyglucose (^{18}F-FDG) (Hsieh et al., 2012; Kakimoto et al., 2016; Van Der Gucht et al., 2015; Yoshizawa et al., 2014). Although amino acid transport in the brain as reflected by ^{18}F-FET uptake is not directly associated with metabolic processes (Langen et al., 2017), a recent study suggest that epileptic neural activity may lead to temporarily increased ^{18}F-FET uptake (Hutterer et al., 2017). Furthermore, it has been reported that pharmacotherapy with dexamethasone increases ^{18}F-FET uptake in the normal brain tissue leading to a reduction of the TBR (Stegmayr et al., 2016).

The aim of this study was to assess the effect of various physiological factors upon ^{18}F-FET uptake in the normal brain tissue. For this purpose, ^{18}F-FET uptake in the brain was evaluated in a large cohort of subjects with an inconspicuous distribution of ^{18}F-FET and which were rated as "negative scans" with respect to brain tumour diagnosis. Indeed, brains with strong abnormalities in radiotracer uptake are not compatible with whole-brain SPM analysis. SUV_{mean} of ^{18}F-FET in the brains of this cohort was correlated with different parameters such as age, gender, weight, height, injected dose, body mass index (BMI), and body surface area (BSA).

2. Materials and methods

2.1. Subjects

Out of a series of patients with suspicious brain lesions who were admitted for ^{18}F-FET PET to the Institute of Neuroscience and Medicine in Jülich (Germany) from February 2010 to April 2017, 107 scans which revealed no abnormality in ^{18}F-FET PET and which had been rated in the medical reports as "negative scans" with respect to tumour diagnosis, were retrospectively identified by two experienced nuclear physicians (AV and GS). Negative scans were defined as showing ^{18}F-FET uptake in the suspected lesion area (identified by corresponding MR images) to be indistinguishable from that of the normal brain within a TBR_{max} range of 0.9–1.1, which is in line with the expectable background SUV changes (± 8%) in the brain for this radiopharmaceutical (Unterrainer et al., 2017). Other inclusion criteria for further data evaluation were age > 18 years, no pre-treatment with radio- or chemotherapy or received therapy with dexamethasone, and [redacted] cytoma WHO grade III in six cases, oligoastrocytoma WHO grade II in two cases, oligoastrocytoma WHO grade III in one case and oligodendroglioma WHO grade II in one case. In two cases, histology revealed no evidence of tumour. For each subject, data of age, gender, weight and height were collected. Subsequently, BMI [kg/m^2] was calculated by dividing the weight [kg] by the square of the height [m^2] (Gorber et al., 2007). BSA [m^2] was calculated using weight and height and the Gehan and George formula (Gehan and George, 1970).

Subjects included in the present study were from 18 to 84 years old (45.4 ± 16.5 years old, 40 women, 41 hybrid PET/MR scans). Detailed characteristics of subjects are available in Table 1. No difference in age, type of PET scanner, injected dose, or BMI was noticed between women and men. However, weight, height, and BSA were higher in men than in women ($p = 0.01$). All subjects gave written informed consent for the investigations and the local ethics committee approved the evaluation of retrospectively collected data. Moreover, all subjects from our institution are informed that their medical data can be rendered anonymously and used for scientific purposes prior to providing consent.

2.2. ^{18}F-FET PET acquisition

The amino acid ^{18}F-FET was produced and applied as described previously (Galldiks et al., 2012). According to the German guidelines for brain tumour imaging using labelled amino acid analogues, all subjects fasted for at least 12 h before PET scanning (Langen et al., 2011). Dynamic PET studies were acquired up to 50 min after intravenous injection of 2.8 ± 0.3 MBq of ^{18}F-FET/kg of body weight. PET imaging was performed either on an ECAT Exact HR + PET scanner in 3-dimensional mode (Siemens Medical Systems) (axial field of view, 15.5 cm; image resolution, 6 mm) or simultaneously with MR imaging using a BrainPET insert. The BrainPET is a compact cylinder that fits in the bore of the Magnetom Trio MR scanner (axial field of view, 19.2 cm; optimum image resolution, 3 mm) (Herzog et al., 2011). Iterative reconstruction parameters were 16 subsets, 6 iterations using the OSEM algorithm for ECAT Exact HR + PET scanner and 2 subsets, 32 iterations using the OP-OSEM algorithm provided by the manufacturer for the BrainPET, with correction for random, scattered coincidences, and dead time for both systems. Attenuation correction for the ECAT Exact HR + PET scan was based on a transmission scan, and for the BrainPET scan on a template-based approach. This attenuation map template was obtained from 8 different subjects recorded with the ECAT Exact HR + PET (Siemens Medical Systems) and which is spatially co-registered to the MPRAGE scan of the individual patient using SPM (Filss et al., 2014; Herzog et al., 2011; Kops et al., 2014). Sixty-six

Table 1
Characteristics of subjects.

	Women n = 40	Men n = 67	p-Value*
Age	44.1 ± 13.9	46.2 ± 17.9	0.51
Hybrid PET/MR scans	19 (48%)	22 (33%)	0.13
Injected dose [MBq/kg]	2.8 ± 0.3	2.7 ± 0.3	0.10
Weight [kg]	78.9 ± 17.8	87.2 ± 12.7	0.01*
Height [cm]	167.5 ± 6.9	179.4 ± 7.2	0.01*
BMI [kg/m^2]	28.2 ± 6.4	27.1 ± 3.6	0.33
BSA [m^2]	1.9 ± 0.2	2.1 ± 0.2	0.01*

BMI: body mass index.
BSA: body surface area.
* p-Value for comparison between women and men.

[redacted] the resulting deformation field was applied to the PET scans. The final template was built by averaging these normalized PET images and applying a 3-dimensional Gaussian filter (FWHM 8 mm^3). The dimensions of the resulting voxels were 2 mm^3. This original adaptive ^{18}F-FET PET template is available in Fig. 1A and in Supplementary materials. Then, initial PET images were normalized to this in-house adaptive template, using the algorithm provided by SPM8 and thereafter, normalized PET images were smoothed with a 3-dimensional Gaussian filter (FWHM 8 mm^3).

In order to obtain parametric SUV PET images, normalized PET images were divided by the value of the injected dose for each subject [MBq/g] according to the definition of SUV value:

$$"SUV = \frac{r}{(a'/w)}"$$

where r is the radioactivity concentration [MBq/ml] within a volume of [redacted] that 1 ml of tissue is equivalent to 1 g of body weight (W. A. Weber et al., 2008). Finally, a correction for the voxel size was applied by dividing each image by 8 (voxel size of resulting images is 8 mm^3) in order to obtain a radioactivity concentration in 1 ml.

Statistical analysis was performed with a linear model of regression analysis for age, BMI, and BSA effects, with gender, and type of PET as nuisance covariates. Analysis of variance (ANOVA)-test comparisons were performed for: i) gender with age, BMI, BSA, and type of PET as covariates, and ii) type of PET with age, gender, BMI, and BSA as covariates. SPM (T) maps were obtained at a threshold (voxel-level significance) of $p < 0.001$ uncorrected, but corrected for cluster volume as recommended to avoid type II errors (Lieberman and Cunningham, 2009). The anatomical localization of the most significant voxels was then identified using MNI coordinates.

In order to extract the quantitative values of SUV_{mean} of ^{18}F-FET, several Volumes of Interest (VOIs) were applied at individual level using Marsbar® (Marseille, France), including a large crescent shape fronto-parietal area placed on the semi-oval centre as recommended (Unterrainer et al., 2017), but also in the temporal, occipital, and cerebellar areas. Afterwards, it was evaluated whether the SUV_{mean} of ^{18}F-FET in these brain areas is differently influenced by various factors. These VOIs are illustrated in Fig. 1B, C, D, and E.

2.4. Statistical analysis

Quantitative variables are expressed as mean ± standard deviation, and categorical variables as percentage. *t*-Tests were performed for the comparison of means between two quantitative variables with normal distribution and Chi-square tests for comparison between two categorical variables. Pearson coefficients were used for correlation analysis. A linear regression model was applied for multivariate

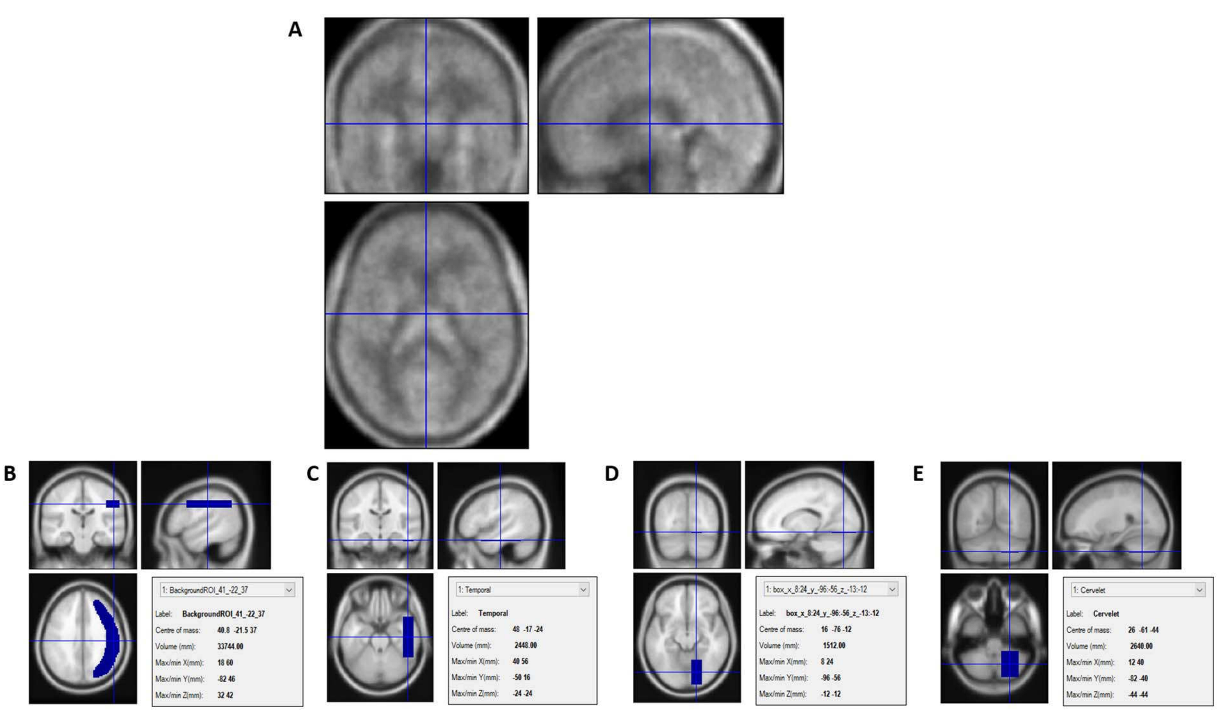

Fig. 1. Slice sections of A, original ^{18}F-FET PET template calculated from images of ^{18}F-FET PET negative scans of 14 patients (39.8 ± 15.6 years old, 12 women) and volumes of interest defined for the background uptake of ^{18}F-FET in the fronto-parietal (B), the temporal (C), the occipital (D), and the cerebellar (E) areas.

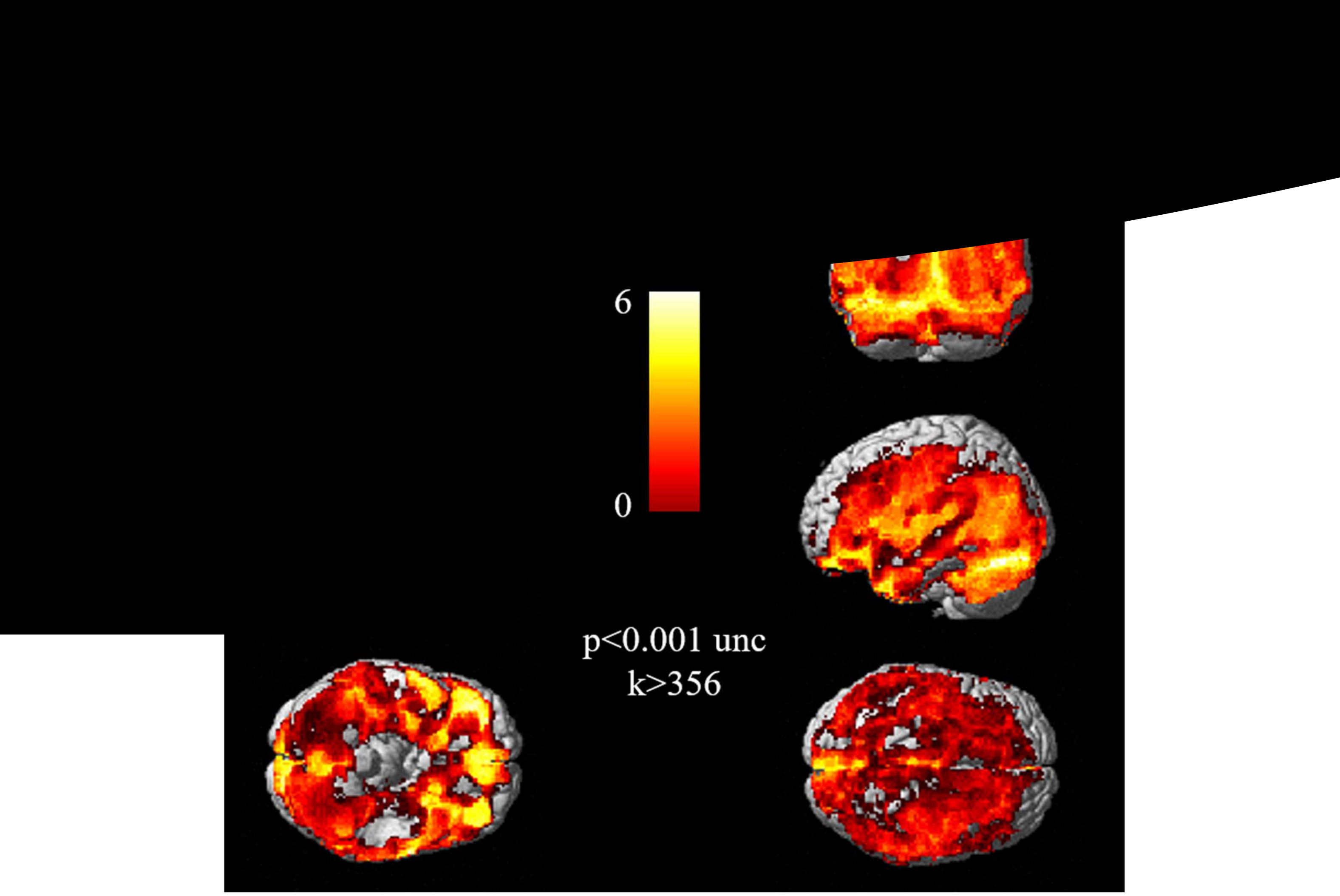

Fig. 2. Anatomical localization of areas of increased SUV of ^{18}F-FET in women in comparison with men, projected onto 3D volume rendering. SUV of ^{18}F-FET was higher in women than in men in diffuse cortical areas including frontal, parietal, temporal, and occipital lobes, as well as the cerebellum ($p < 0.001$ uncorrected, $k > 356$).

analysis. A $p < 0.05$ was determined as significant. Statistical analysis based upon SPM is mentioned above.

3. Results

3.1. SPM analysis

SUV of ^{18}F-FET was higher in women than in men in diffuse cortical areas involving frontal, parietal, temporal, occipital lobes, and cerebellum ($p < 0.001$ uncorrected, $k > 356$) (Fig. 2).

Moreover, BMI was positively correlated with higher SUV of ^{18}F-FET in diffuse cortical areas involving frontal, parietal, temporal, occipital lobes and cerebellum ($p < 0.001$ uncorrected, $k > 332$) (Fig. 3). However, the extent of findings was lower than for gender effects (277 vs. 818 cm^3).

No statistical significant finding was observed for the effects of age, BSA and type of PET.

3.2. Marsbar analysis and influence on SUV_{mean} VOI

An univariate analysis was calculated for effects of age, gender, type of PET, weight, height, injected activity, BMI, and BSA on SUV_{mean} VOI. Gender, height, and BMI significantly influenced SUV_{mean} of ^{18}F-FET in the fronto-parietal VOI. In detail, SUV_{mean} of ^{18}F-FET in women was 23% higher than in men ($p < 0.01$) as shown in box-plots in Fig. 4. Moreover, SUV_{mean} of ^{18}F-FET was weakly positively correlated with BMI, in overall population and for women ($r = 0.29$, 0.33 $p < 0.04$) but not in men ($p = 0.14$) as illustrated in Fig. 5, and negatively correlated with height, in overall population and in women ($r = -0.40$ and -0.32 respectively; $p < 0.05$) but not in men ($p = 0.95$). In addition, SUV_{mean} of ^{18}F-FET was 12% higher in obese subjects ($n = 25$, defined as BMI $\geq 30\ kg/m^2$, (Gorber et al., 2007)) than in subjects with normal weight (1.42 ± 0.31 vs. 1.27 ± 0.26, $p = 0.02$).

In multivariate analysis using a linear regression model with all factors mentioned above and taking into account inter-correlated parameters, only gender and BMI remained as significant parameters influencing SUV_{mean} of ^{18}F-FET in the brain tissue VOI ($SUV_{mean} = 0.257 \times$ female gender $+ 0.014 \times$ BMI $+ 1.080$; $p < 0.01$).

For the evaluation of regional ^{18}F-FET distribution, the previously defined VOIs (temporal, occipital, and cerebellar) were influenced by gender, height, and BMI in the same way as the fronto-parietal VOI (increase of 24% of SUV_{mean} of ^{18}F-FET in women in comparison to men, and a correlation coefficient with height and BMI of -0.40 and 0.31 for the temporal VOI, 22%, -0.41 and 0.37 for the occipital VOI, and 26%, -0.39 and 0.33 for the cerebellar VOI, $p < 0.01$). Thus, the influence of physiological factors on SUV of ^{18}F-FET was similar in all brain areas.

4. Discussion

This study shows that female gender and weakly high BMI are two independent factors leading to significantly increased SUV_{mean} of ^{18}F-FET in the entire brain.

These relationships have not been previously known and it seems important to discuss the influence of these parameters on the quantification of ^{18}F-FET uptake in brain tumours. An effect of gender has also been observed for other PET tracers such as ^{18}F-FDG showing diffusely higher cerebral glucose metabolism in females than in males (Willis

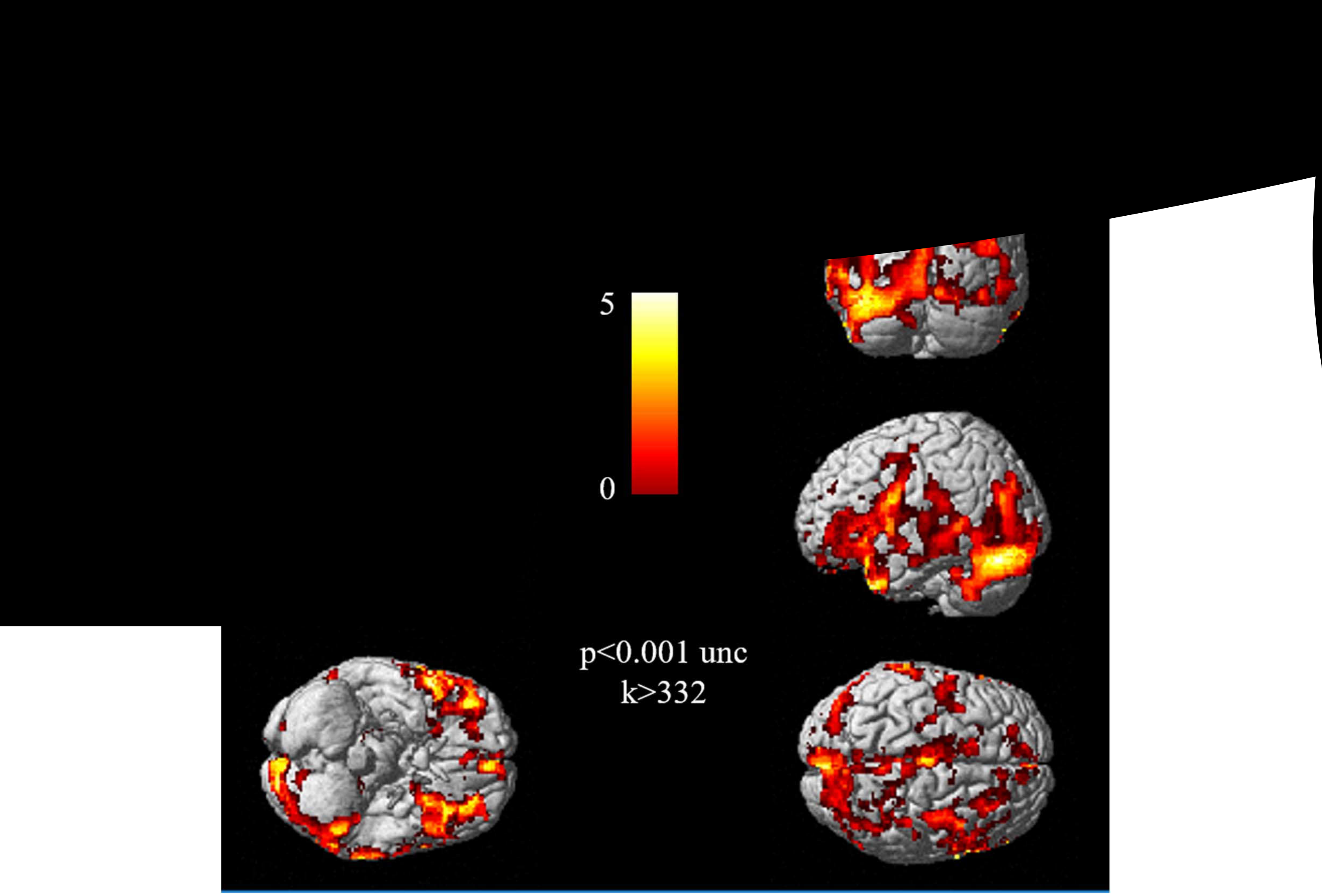

Fig. 3. Anatomical localization of areas of increased SUV of ^{18}F-FET related to Body Mass Index (BMI), projected onto 3D volume rendering. BMI was positively correlated with higher SUV of ^{18}F-FET in diffuse cortical areas including frontal, parietal, temporal, and occipital lobes, as well as the cerebellum ($p < 0.001$ uncorrected, $k > 332$).

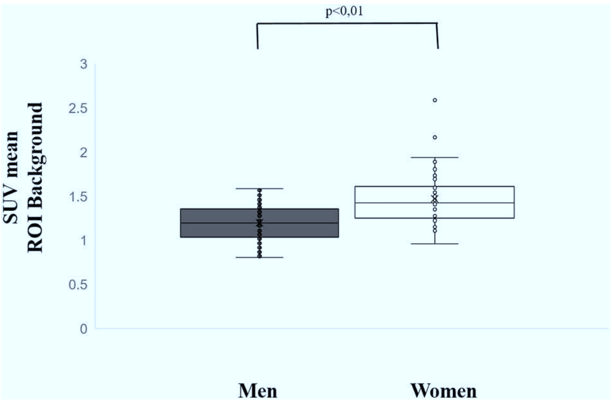

Fig. 4. Box-plots of SUV_{mean} of ^{18}F-FET in women and men within a fronto-parietal VOI, used as background region. Women had higher SUV_{mean} of ^{18}F-FET than men (1.47 ± 0.31 vs. 1.20 ± 0.20, $p < 0.01$).

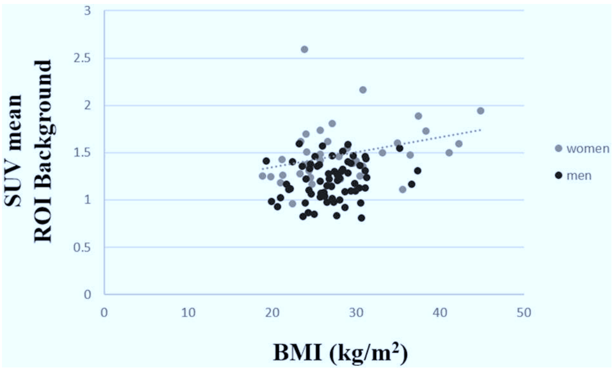

Fig. 5. Correlation curve between SUV_{mean} of ^{18}F-FET within a fronto-parietal VOI, used as background region, and Body Mass Index (kg/m^2). SUV_{mean} of ^{18}F-FET was positively correlated to BMI for women ($r = 0.33$ $p < 0.04$).

et al., 2002; Yoshizawa et al., 2014). Earlier studies have reported that cerebral glucose metabolism in women is 19 to 26% higher than in men which corresponds to the proportion of higher ^{18}F-FET uptake in the current study (Baxter et al., 1987; Yoshii et al., 1988). A possible explanation for this finding may be a higher cerebral blood flow in female patients (Yoshizawa et al., 2014) which could be linked to effect of hormones, especially estrogen, on cerebral metabolism (Reiman et al., 1996). It was speculated that these differences in gender are applicable to different PET tracers (Niven et al., 2001).

The second factor in the present study that influenced SUV_{mean} of ^{18}F-FET weakly is BMI. We assume that differences in BMI are associated with a differential whole-body distribution of ^{18}F-FET. Whole-body ^{18}F-FET PET scans have shown that there is noticeable tracer accumulation in the skeletal muscles and the heart with about 40% of the total injected dose activity accumulated in muscles (Pauleit et al., 2003). In contrast, low uptake was observed in adipose tissue. It is well known that obese patients have a greater loss of muscle mass compared to patients with BMI < 30 kg·m^{-2} (Dickerson, 2005; Port and Apovian, 2010). Moreover, there is a greater tendency to develop sarcopenia in these patients, which is related to increased age and intramuscular fat infiltration (Thornell, 2011), and overweight in elderly people induces impaired protection mechanisms of skeletal muscle, leading to a [redacted] background VOI without influencing tumour uptake, the TBR in brain tumours would be decreased in these patient groups.

Another major finding of this study is that the influence of physiological factors on SUV of ^{18}F-FET is similar in all brain areas. Thus, ^{18}F-FET distribution in the brain appears to be highly stable, which suggests that background regions in different brain areas are equally valid for the evaluation of TBR. Nevertheless, intra- and inter-reader variability regarding the assessment of the background reference remains an important issue. Recently, it has been shown that background activity assessment using a crescent-shaped volume of interest in the contralateral hemisphere including white and grey matter allows minimization of both intra- and inter-reader variability and might facilitate comprehensive methodological standardization of amino acid PET, which is of interest in the light of future technical guidelines (Unterrainer et al., 2017). Moreover, a standardization of the reference region is needed, while absolute values of SUV of ^{18}F-FET could differ between areas even if they are influenced in a similar way by external factors.

The following limitations need to be discussed. Firstly, subjects included in this study cannot be considered as healthy subjects since all showed brain abnormalities in MRI. For ethical reasons, however, it would be difficult to investigate such a large number of healthy subjects by ^{18}F-FET PET. In addition, each scan was carefully checked before inclusion to ascertain its negative state with regard to ^{18}F-FET uptake. Secondly, scans were performed on two different PET systems. However, the quantitative analysis did not show an effect of type of PET scanner on SUV of ^{18}F-FET uptake and this parameter was included as a covariate in our statistical model. Finally, a whole-brain quantitative analysis has been performed although the areas with suspicious brain lesions as identified on MRI have not been excluded from the VOI analyses. The brain lesions areas were nevertheless indistinguishable from that of the normal brain, as reported in the Materials and methods section and were differently located for each individual subjects, making it almost unlikely to influence overall results of group analysis.

5. Conclusion

In summary, SUV_{mean} of ^{18}F-FET in the normal brain is influenced by gender and weakly by BMI. We suggest that these findings are partly caused by different whole-body distribution of ^{18}F-FET depending on the muscle mass but other gender specific factors dominate. The influence of these factors on SUV of ^{18}F-FET is similar in all brain areas. However, although ^{18}F-FET distribution in the normal brain appears to be highly stable, a standardization of the reference region is necessary for comparison of data between different centres.

[redacted]

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2017.11.005.

References

Albert, N.L., Weller, M., Suchorska, B., Galldiks, N., Soffietti, R., Kim, M.M., la Fougère, C., Pope, W., Law, I., Arbizu, J., Chamberlain, M.C., Vogelbaum, M., Ellingson, B.M., Tonn, J.C., 2016. Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. Neuro-Oncol. 18, 1199–1208. http://dx.doi.org/10.1093/neuonc/now058.

Baxter, L.R., Mazziotta, J.C., Phelps, M.E., Selin, C.E., Guze, B.H., Fairbanks, L., 1987. Cerebral glucose metabolic rates in normal human females versus normal males. Psychiatry Res. 21, 237–245.

Calcagni, M.L., Galli, G., Giordano, A., Taralli, S., Anile, C., Niesen, A., Baum, R.P., 2011. Dynamic O-(2-[18F]fluoroethyl)-L-tyrosine (F-18 FET) PET for glioma grading: assessment of individual probability of malignancy. Clin. Nucl. Med. 36, 841–847. http://dx.doi.org/10.1097/RLU.0b013e3182291b40.

Dickerson, R.N., 2005. Hypocaloric feeding of obese patients in the intensive care unit. Curr. Opin. Clin. Nutr. Metab. Care 8, 189–196.

Filss, C.P., Galldiks, N., Stoffels, G., Sabel, M., Wittsack, H.J., Turowski, B., Antoch, G., Zhang, K., Fink, G.R., Coenen, H.H., Shah, N.J., Herzog, H., Langen, K.-J., 2014. Comparison of 18F-FET PET and perfusion-weighted MR imaging: a PET/MR imaging hybrid study in patients with brain tumors. J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 55, 540–545. http://dx.doi.org/10.2967/jnumed.113.129007.

Galldiks, N., Langen, K.-J., Holy, R., Pinkawa, M., Stoffels, G., Nolte, K.W., Kaiser, H.J., Filss, C.P., Fink, G.R., Coenen, H.H., Eble, M.J., Piroth, M.D., 2012. Assessment of treatment response in patients with glioblastoma using O-(2-18F-Fluoroethyl)-L-tyrosine PET in comparison to MRI. J. Nucl. Med. Off. Publ. Soc. Nucl. Med. http://dx.doi.org/10.2967/jnumed.111.098590.

Galldiks, N., Rapp, M., Stoffels, G., Fink, G.R., Shah, N.J., Coenen, H.H., Sabel, M., Langen, K.-J., 2013. Response assessment of bevacizumab in patients with recurrent malignant glioma using [18F]Fluoroethyl-L-tyrosine PET in comparison to MRI. Eur. J. Nucl. Med. Mol. Imaging 40, 22–33. http://dx.doi.org/10.1007/s00259-012-2251-4.

Gehan, E.A., George, S.L., 1970. Estimation of human body surface area from height and weight. Cancer Chemother. Rep. 54, 225–235.

Gispert, J.D., Pascau, J., Reig, S., Martínez-Lázaro, R., Molina, V., García-Barreno, P., Desco, M., 2003. Influence of the normalization template on the outcome of statistical parametric mapping of PET scans. NeuroImage 19, 601–612.

Gorber, S.C., Tremblay, M., Moher, D., Gorber, B., 2007. A comparison of direct vs. self-report measures for assessing height, weight and body mass index: a systematic review. Obes. Rev. 8, 307–326. http://dx.doi.org/10.1111/j.1467-789X.2007.00347.x.

Herzog, H., Langen, K.-J., Weirich, C., Rota Kops, E., Kaffanke, J., Tellmann, L., Scheins, J., Neuner, I., Stoffels, G., Fischer, K., Caldeira, L., Coenen, H.H., Shah, N.J., 2011. High resolution BrainPET combined with simultaneous MRI. Nukl. Nucl. Med. 50, 74–82. http://dx.doi.org/10.3413/Nukmed-0347-10-09.

Hsieh, T.-C., Lin, W.-Y., Ding, H.-J., Sun, S.-S., Wu, Y.-C., Yen, K.-Y., Kao, C.-H., 2012. Sex- and age-related differences in brain FDG metabolism of healthy adults: an SPM analysis. J. Neuroimaging Off. J. Am. Soc. Neuroimaging 22, 21–27. http://dx.doi.org/10.1111/j.1552-6569.2010.00543.x.

Hutterer, M., Ebner, Y., Riemenschneider, M.J., Willuweit, A., McCoy, M., Egger, B., Schröder, M., Wendl, C., Hellwig, D., Grosse, J., Menhart, K., Proescholdt, M., Fritsch, B., Urbach, H., Stockhammer, G., Roelcke, U., Galldiks, N., Meyer, P.T., Langen, K.-J., Hau, P., Trinka, E., 2017. Epileptic activity increases cerebral amino acid transport assessed by 18F-Fluoroethyl-L-tyrosine amino acid PET: a potential brain tumor mimic. J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 58, 129–137. http://dx.doi.org/10.2967/jnumed.116.176610.

Jansen, N.L., Graute, V., Armbruster, L., Suchorska, B., Lutz, J., Eigenbrod, S., Cumming, P., Bartenstein, P., Tonn, J.-C., Kreth, F.W., la Fougère, C., 2012. MRI-suspected low-grade glioma: is there a need to perform dynamic FET PET? Eur. J. Nucl. Med. Mol. Imaging 39, 1021–1029. http://dx.doi.org/10.1007/s00259-012-2109-9.

Jansen, N.L., Suchorska, B., Wenter, V., Schmid-Tannwald, C., Todica, A., Eigenbrod, S., Niyazi, M., Tonn, J.-C., Bartenstein, P., Kreth, F.-W., la Fougère, C., 2015. Prognostic significance of dynamic 18F-FET PET in newly diagnosed astrocytic high-grade glioma. J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 56, 9–15. http://dx.doi.org/10.2967/jnumed.114.144675.

Kakimoto, A., Ito, S., Okada, H., Nishizawa, S., Minoshima, S., Ouchi, Y., 2016. Age-related sex-specific changes in brain metabolism and morphology. J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 57, 221–225. http://dx.doi.org/10.2967/jnumed.115.166439.

Kops, E.R., Herzog, H., Shah, N.J., 2014. Comparison template-based with CT-based

[redacted]
org/10.1007/s00259-003-1118-0.

Pauleit, D., Floeth, F., Hamacher, K., Riemenschneider, M.J., Reifenberger, G., Müller, H.-W., Zilles, K., Coenen, H.H., Langen, K.-J., 2005. O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas. Brain J. Neurol. 128, 678–687. http://dx.doi.org/10.1093/brain/awh399.

Pöpperl, G., Götz, C., Rachinger, W., Gildehaus, F.-J., Tonn, J.-C., Tatsch, K., 2004. Value of O-(2-[18F]fluoroethyl)-L-tyrosine PET for the diagnosis of recurrent glioma. Eur. J. Nucl. Med. Mol. Imaging 31, 1464–1470. http://dx.doi.org/10.1007/s00259-004-1590-1.

Pöpperl, G., Kreth, F.W., Herms, J., Koch, W., Mehrkens, J.H., Gildehaus, F.J., Kretzschmar, H.A., Tonn, J.C., Tatsch, K., 2006. Analysis of 18F-FET PET for grading of recurrent gliomas: is evaluation of uptake kinetics superior to standard methods? J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 47, 393–403.

Pöpperl, G., Kreth, F.W., Mehrkens, J.H., Herms, J., Seelos, K., Koch, W., Gildehaus, F.J., Kretzschmar, H.A., Tonn, J.C., Tatsch, K., 2007. FET PET for the evaluation of untreated gliomas: correlation of FET uptake and uptake kinetics with tumour grading. Eur. J. Nucl. Med. Mol. Imaging 34, 1933–1942. http://dx.doi.org/10.1007/s00259-007-0534-y.

Port, A.M., Apovian, C., 2010. Metabolic support of the obese intensive care unit patient: a current perspective. Curr. Opin. Clin. Nutr. Metab. Care 13, 184–191. http://dx.doi.org/10.1097/MCO.0b013e328335f1e6.

Potes, Y., de Luxán-Delgado, B., Rodriguez-González, S., Guimarães, M.R.M., Solano, J.J., Fernández-Fernández, M., Bermúdez, M., Boga, J.A., Vega-Naredo, I., Coto-Montes, A., 2017. Overweight in elderly people induces impaired autophagy in skeletal muscle. Free Radic. Biol. Med. 110, 31–41. http://dx.doi.org/10.1016/j.freeradbiomed.2017.05.018.

Rapp, M., Heinzel, A., Galldiks, N., Stoffels, G., Felsberg, J., Ewelt, C., Sabel, M., Steiger, H.J., Reifenberger, G., Beez, T., Coenen, H.H., Floeth, F.W., Langen, K.-J., 2013. Diagnostic performance of 18F-FET PET in newly diagnosed cerebral lesions suggestive of glioma. J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 54, 229–235. http://dx.

[redacted]

Stegmayr, C., Schöneck, M., Oliveira, D., Willuweit, A., Filss, C., Galldiks, N., Shah, N.J., Coenen, H.H., Langen, K.-J., 2016. Reproducibility of O-(2-(18)F-fluoroethyl)-L-tyrosine uptake kinetics in brain tumors and influence of corticoid therapy: an experimental study in rat gliomas. Eur. J. Nucl. Med. Mol. Imaging 43, 1115–1123. http://dx.doi.org/10.1007/s00259-015-3274-4.

Stockhammer, F., Plotkin, M., Amthauer, H., van Landeghem, F.K.H., Woiciechowsky, C., 2008. Correlation of F-18-fluoro-ethyl-tyrosin uptake with vascular and cell density in non-contrast-enhancing gliomas. J. Neuro-Oncol. 88, 205–210. http://dx.doi.org/10.1007/s11060-008-9551-3.

Thornell, L.-E., 2011. Sarcopenic obesity: satellite cells in the aging muscle. Curr. Opin. Clin. Nutr. Metab. Care 14, 22–27. http://dx.doi.org/10.1097/MCO.0b013e3283412260.

Ulbrich, E.J., Nanz, D., Leinhard, O.D., Marcon, M., Fischer, M.A., 2017. Whole-body adipose tissue and lean muscle volumes and their distribution across gender and age: MR-derived normative values in a normal-weight Swiss population. Magn. Reson. Med. http://dx.doi.org/10.1002/mrm.26676.

Unterrainer, M., Vettermann, F., Brendel, M., Holzgreve, A., Lifschitz, M., Z?hringer, M., Suchorska, B., Wenter, V., Illigens, B.M., Bartenstein, P., Albert, N.L., 2017. Towards standardization of 18F-FET PET imaging: do we need a consistent method of background activity assessment? EJNMMI Res. 7. http://dx.doi.org/10.1186/s13550-017-0295-y.

Van Der Gucht, A., Verger, A., Guedj, E., Malandain, G., Hossu, G., Yagdigul, Y., Roch, V., Poussier, S., Maillard, L., Karcher, G., Marie, P.-Y., 2015. Age-related changes in FDG brain uptake are more accurately assessed when applying an adaptive template to the SPM method of voxel-based quantitative analysis. Ann. Nucl. Med. 29, 921–928. http://dx.doi.org/10.1007/s12149-015-1022-2.

Vees, H., Senthamizhchelvan, S., Miralbell, R., Weber, D.C., Ratib, O., Zaidi, H., 2009. Assessment of various strategies for 18F-FET PET-guided delineation of target volumes in high-grade glioma patients. Eur. J. Nucl. Med. Mol. Imaging 36, 182–193. http://dx.doi.org/10.1007/s00259-008-0943-6.

Weber, W.A., Grosu, A.L., Czernin, J., 2008. Technology insight: advances in molecular imaging and an appraisal of PET/CT scanning. Nat. Clin. Pract. Oncol. 5, 160–170. http://dx.doi.org/10.1038/ncponc1041.

Weber, D.C., Zilli, T., Buchegger, F., Casanova, N., Haller, G., Rouzaud, M., Nouet, P., Dipasquale, G., Ratib, O., Zaidi, H., Vees, H., Miralbell, R., 2008. [(18)F] Fluoroethyltyrosine-positron emission tomography-guided radiotherapy for high-grade glioma. Radiat. Oncol. Lond. Engl. 3, 44. http://dx.doi.org/10.1186/1748-717X-3-44.

Willis, M.W., Ketter, T.A., Kimbrell, T.A., George, M.S., Herscovitch, P., Danielson, A.L., Benson, B.E., Post, R.M., 2002. Age, sex and laterality effects on cerebral glucose metabolism in healthy adults. Psychiatry Res. 114, 23–37.

Yoshii, F., Barker, W.W., Chang, J.Y., Loewenstein, D., Apicella, A., Smith, D., Boothe, T., Ginsberg, M.D., Pascal, S., Duara, R., 1988. Sensitivity of cerebral glucose metabolism to age, gender, brain volume, brain atrophy, and cerebrovascular risk factors. J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 8, 654–661. http://dx.doi.org/10.1038/jcbfm.1988.112.

Yoshizawa, H., Gazes, Y., Stern, Y., Miyata, Y., Uchiyama, S., 2014. Characterizing the normative profile of 18F-FDG PET brain imaging: sex difference, aging effect, and cognitive reserve. Psychiatry Res. 221, 78–85. http://dx.doi.org/10.1016/j.pscychresns.2013.10.009.