Journal of Associated Medical Sciences 2023; 56 (1): 159-166

JAMS
Journal of Associated Medical Sciences

Scopus indexed & Thai-Journal Citation Index Centre (TCI)

Journal of Associated Medical Sciences

Journal homepage: https://www.tci-thaijo.org/index.php/bulletinAMS/index

Developing a PET normal brain template using diffusion tensor imaging images: A proof of concept

Paramest Wongsa[1,2*] **Witaya Sungkarat**[1] **Supatana Auethavekiat**[2,3]

[1]*Radiological Technology School, Faculty of Health Science Technology, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand.*
[2]*Department of Biomedical Engineering, Faculty of Engineering, Chulalongkorn University, Bangkok, Thailand.*
[3]*Department of Electrical Engineering, Faculty of Engineering, Chulalongkorn University, Bangkok, Thailand.*

ARTICLE INFO

Article history:
Received 4 September 2022
Accepted as revised 11 November 2022
Available online 17 November 2022

Keywords:
Brain template, image registration, probabilistic tractography

ABSTRACT

Background: Registered Positron emission tomography (PET) brain images to the standard normal PET brain templates can be performed to diagnosis dementia by using a vendor software, in which the brain template is based on T1-Weighted (T1W) images. However, the imperfection of an overlap between PET images and the PET-T1W based brain template could be observed.

Objectives: This pilot study aimed to develop a new PET brain template and compare the accuracy of image registration between a conventional PET-T1W based brain template and our proposed PET-DTI based brain template.

Materials and methods: The new PET-DTI based brain template was developed from twenty-four normal volunteers (age ranged 42-79 years old) who underwent 11C-Pittsburgh compound B PET scans and both T1W and diffusion tensor image (DTI) magnetic resonance imaging brain scans. The correction of Eddy-Current distortions and related artifact removing in DTI images were performed using the open-source FMRIB Software Library (FSL) to generate whole-brain probabilistic tractography maps (MRI-Probtract). MRI-Probtract map was then deformably registered and normalized to PET images, which were used for brain boundary guidance. The accuracy of image registration was assessed by applying the newly developed PET-DTI brain template to PET images of four mild cognitive impairment patients who underwent the same brain-scanning protocols. The accuracy of image registrations using the conventional PET-T1 and PET-DTI templates was evaluated qualitatively by three nuclear medicine physicians. Wilcoxon Signed Ranks test was used to compare registration scores of the two methods. Additionally, the dice similarly coefficient was obtained to quantitatively evaluate the accuracy of image registration.

Results: The registration scores of the PET images registered with the PET-DTI template were significantly higher than the PET-T1 template at p-value < 0.05. This result is consistent with the dice similarly coefficient where the value of PET-DTI template was higher.

Conclusion: Result of this pilot study showed that new PET-DTI brain template provides higher registration quality, suggesting the feasibility of using PET-DTI template in a clinical PET study of the brain.

* **Corresponding author.**
Author's Address: *Department of Biomedical Engineering, Faculty of Engineering, Chulalongkorn University, Bangkok, Thailand.*
** **E-mail address:** paramest.w@student.chula.ac.th
doi: 10.12982/JAMS.2023.031
E-ISSN: 2539-6056

Introduction

Positron Emission Tomography (PET) is an imaging device in nuclear medicine to detect lesions inside the human body. After a small injection of sufficient amounts of radiopharmaceuticals into a patient's body, the radiation compounds bind with the target organ. Images can then be taken by imaging devices, such as PET-Computed Tomography (PET-CT).[1,2] Clinically, nuclear medicine radiologists interpret visual PET images qualitatively by abnormal uptake or non-uptake of radiopharmaceutical substances in the area of interest. Besides, quantitative analysis is performed by calculating numerical values from such area. The standard uptake value (SUV) indicates the ratio of radioactivity concentration in tissues by patient's body weight. Normally, the SUV value is high at the area of high uptake of radiopharmaceuticals.[3-5]

Development of qualitative analysis is especially important for patients with specific pathologies, including brain atrophy. It helps to reduce visual errors at the brain region in which radiopharmaceutical uptakes. Therefore, qualitative analysis is widely used to interpret patient's lesions. For example, to diagnose brain function in particular dementia using PET images, a standard PET brain template is required for referencing radiopharmaceutical uptake values at a voxel level of normal brain. It is typically developed from a group of subjects with intact memory. The normal pattern of radiopharmaceutical uptake at different brain regions was used as a reference for diagnosing brain function abnormality. This standard template is overlaid on PET images to detect an increase or a decrease of radiopharmaceutical uptake at any brain regions.[6-8]

Currently, registering PET images to the standard PET brain templates can be performed using a vendor software, in which the brain template is based on T1-weighted magnetic resonance imaging (MRI). However, the imperfection of an overlap between PET images and the PET-T1W based brain template could be observed. The image of cerebral cortex from an aging person especially in brain atrophy or hydrocephalus has less details than the image from a healthy person. These anatomical changes in brain cortex on T1W images can cause discrepancies between PET brain image and PET-T1W based brain template, leading to wrong interpretation.[9,10] Therefore, PET-T1W based brain template requires an improvement. The T1W image of the brain could be replaced by diffusion tensor imaging (DTI) MRI. The DTI map represents fiber tract orientation of white matter of the brain, which is profoundly less affected by brain atrophy than gray matter.[11] In this study, we hypothesis that utilizing DTI map to develop brain template could improve the accuracy of image overlay between PET image and brain template in the case of diagnosing spatial brain function abnormality compared with the vendor's standard template. The potential use of DTI based brain template in solving miss-interpretation around the edge of the cerebral cortex in animal's brain model and human brain model has also been reported. [12,13]

In this study, we aimed to (1) develop a new PET-DTI based brain template, and (2) validate our method by comparingour brain template with the standard template derived from normal brain volunteers and comparing the accuracy of image registration between PET images and both templates in dementia patients with deteriorated pathology of brain tissue.

Materials and methods

This was a retrospective study. We collected PET/CT and MRI images from a group of volunteers enrolled in the "Assessment of the Accumulation of Amyloid and Tau proteins in Thai People without Degenerative Brain Disease" project, National Cyclotron and PET Centre, Chulabhorn Hospital, Thailand. The method consists of two parts. First, two types of brain templates: PET-DTI and PET-T1W were created as a part of method development. Second, registration accuracy of two different templates was evaluated and compared after registering each template with four dementia participants, which were part of method validation. This study was approved by the Human Research Ethics Committee of Chulabhorn Research Institute.

Participants

PET/CT and MRI images of twenty-four normal healthy participants during 2016-2017 (age ranged 42-79 years old) were collected. All were participated in the "Assessment of the Accumulation of Amyloid and Tau proteins in Thai People without Degenerative Brain Disease" project, National Cyclotron and PET Scan Centre, Chulabhorn Hospital. Also, PET/CT and MRI images of four dementia participants who met our inclusion criteria were retrospectively to validate a new PET template. The inclusion criteria included male and female patient being diagnosed of dementia and being able to participate in MRI scan. Healthy volunteers and patient were scanned using identical PET/CT and MRI protocol. Patients who could not finish both PET/CT and MRI scan were excluded.

MRI imaging procedure

MRI imaging was performed on the Siemens/Trio 3.0 Tesla MRI scanner (Siemens Healthcare, Erlangen, Germany). A 3D sagittal T1-wieghted sequence was first obtained (slice thickness =1.0 mm with 50% overlap, Repetition Time (TR) =1600 msec, Time to Echo (TE) =2 msec, flip angle =90°, and matrix size =256x256 pixels). Then a whole-brain single shot echo planar imaging (EPI) pulse sequence was applied for DTI image data using following parameters: slice thickness =2.0 mm, TR =6508 msec, TE =90 msec, flip angle =90°, number of averages =1, voxel size =1.95x1.95x2 mm, matrix size =128x128 pixels, and direction =64.

PET imaging procedure

PET imaging was conducted on the Siemens/Biograph16 PET/CT scanner (Siemens Healthcare, Erlangen, Germany) with 3D mode. A radioactive rod source of 68Ge was used for daily quality control. CT brain images for localization and attenuation correction was performed. The PET dynamics protocol was done immediately after

intravenous injection of 555 MBq 11C-PiB (PET scan time: 70 mins, matrix size: 168, zoom: 1, and a Gaussian filter with a full width at half-maximum: 5.0). The images were reconstructed using a fully 3D ordered subset expectation maximization (3D-OSEM) algorithm for all corrections (scatter, random, dead time, attenuation, and normalization) with 4 iterations, 8 subsets, and a 4 mm pixel size. The scan time ranged from 50 to 70 mins.[14-16]

Developing of PET brain template

The template using the same method as Chotipanich *et al* was created.[17] PET-DTI brain templates were constructed using the scan of twenty-four normal participants. All participants completed three scans: PET, MRI-T1W, and MRI-DTI. The PET-DTI brain template was generated by averaging individual PET images of normal brains, which had their DTI images coregistered to the template and spatial normalized. This template represents the sampled-basedspatial pharmaceuticals uptake in normal brain. The details of data processing were elaborated as follows:

[I.] All PET and MRI images in DICOM format (Digital Imaging and Communications in Medicine) were converted to NifTI format (Neuroimaging Informatics Technology Initiative) using MRI Convert software.[18]

[II.] The prepared DTI images was imported to FMRIB Software Library (FSL) for preprocessing and modeling processes. Firstly, Brain Extraction Tool (BET) was used for removing the skull while retaining only brain tissue (line estimate: 0.15 and intensity: 0.10). Secondly, FMRIB's diffusion toolbox (FDT) was used for Eddy current correction, local modelling of diffusion parameters, tractography and connectivity-based segmentation, and local fitting of diffusion tensors. Finally, a whole-brain probabilistic DTI tractography map (MRI-Probtract) was obtained.[19]

[III.] For PET images, SPM 99 software (distributed under General Public License as published by the Free Software Foundation) was used for the entire construction process. Anterior commissure (AC) area was set as a reference anatomical landmark to reorient PET and MRI-Probtract images to the same position. After this process, the reoriented slices of PET and MRI-Probtract images were arranged for image registration (rPET images).

[IV.] SPM 2 software (distributed under General Public License as published by the Free Software Foundation) was used for co-registration of the group (twenty-four participants) data. Each individual B0 image obtained during the DTI image processing was co-registered to rPET image data. The output was subsequently normalized with MRI-Probtract. Finally, the new PET-DTI brain template was obtained.

For the development of PET-T1W brain templates, the same data processing technique was performed as mentioned above, except that we replaced the DTI with T1W in each step to obtain another PET-T1W brain template (Figure 1).

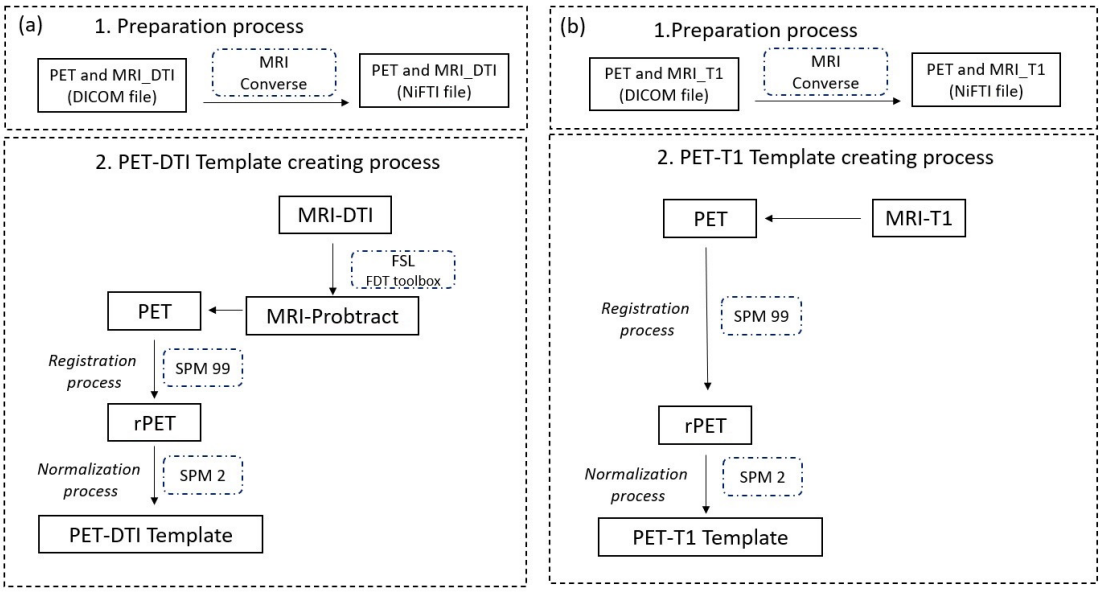

Figure 1 *Comparison between development process of proposed PET-DTI brain template (a) and the standard PET-T1 brain template (b) of normal brain.*

Image registration quality assessment in four dementia patients

The newly developed PET-DTI brain template and the conventional PET-T1W brain templates were registered to PET images of four dementia patients. The dice similarity coefficient score (DSC) was assessed to measure the quality of image registration for both methods. The lateral ventricle area in templates and PET brain contouring were drawn by using ImageJ software to calculate dice score as shown in Figure 2. The value of a DSC ranges from 0, no spatial overlap between two images, to 1, perfect overlap. The DSC score was defined as follow:

$$DSC = 2 \times |X \cap Y| / (|X| + |Y|)$$

Where X and Y are the region of interest in two PET template and PET images, respectively. ∩ represents the intersection operator. |X| is the area of X, and |Y| is the area of Y.

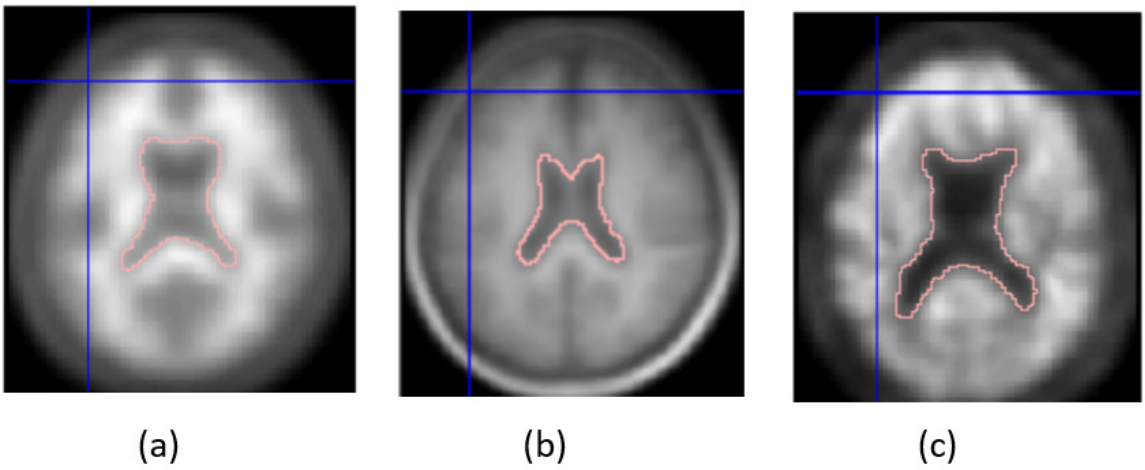

Figure 2 *Comparison of lateral ventricle segmentation between proposed PET-DTI brain template (a), standard PET-T1 brain template (b), and PET image(C) of normal brain in the same patient. This segmented area was used to calculate the DSC score for comparison between methods.*

Accuracy scores of image registration measurement by nuclear medicine radiologists

Although DSC is among the widely used methods for assessing image registration quality, it does not provide the accuracy of spatial information inside the image area. Therefore, the accuracy of PET image and templates registration using human visual inspection was assessed by slice-by-slice approach. The accuracy scores of images overlay between the developed method (PET image/PET-DTI based template registration) and the standard method (PET image/PET-T1W based template registration) were assessed by three nuclear medicine radiologists with more than five years of experience in the PET-CT interpretation. Blind observations were performed. The radiologists scrolled through all slices of PET image and examined each slice to evaluate the overlap between the PET images and the brain template and provides the overlapping scores between PET image and PET brain template at eight areas: four at the outer edge and four at the inner edge of cerebral cortex as shown the example of evaluation in Figure 3. Four areas at the outer edge of the cerebral cortex are right inferior frontal gyrus (A), left inferior frontal gyrus (B), right Lateral cerebral sulcus (C), and left Lateral cerebral sulcus (D). Four areas at the inner edge of the cerebral cortex are right anterior horn of lateral ventricle (E), left anterior horn of lateral ventricle (F), right posterior horn of lateral ventricle (G), and left posterior horn of lateral ventricle (H) as shown in Figure 4. The given registration scores are based on how PET image was overlapped with brain template using the assessment criteria as follow: 3 for perfect overlapped, 2 score for partially overlapped, and 1 for non-overlapped.

The scores from all nuclear medicine radiologist were used to compare between our developed and the standard template.

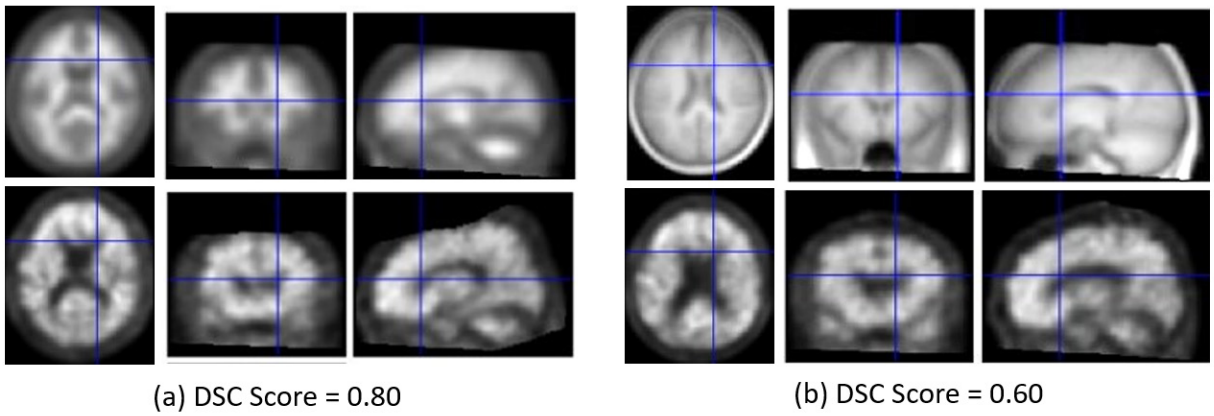

Figure 3 *Shows an example of brain-region localization at a reference point F (crosshair) and the accuracy of lateral ventricle overlapping using DSC score in patient 1. (a): proposed PET-MRI brain template in upper row and PET image in lower row, (b): standard PET-T1 brain template in upper row and PET image in lower row (b). Accuracy of lateral-ventricle area overlapping (DSC score =0.8) in proposed PET-MRI showed more improvement compared to the standard method (DSC score =0.60).*

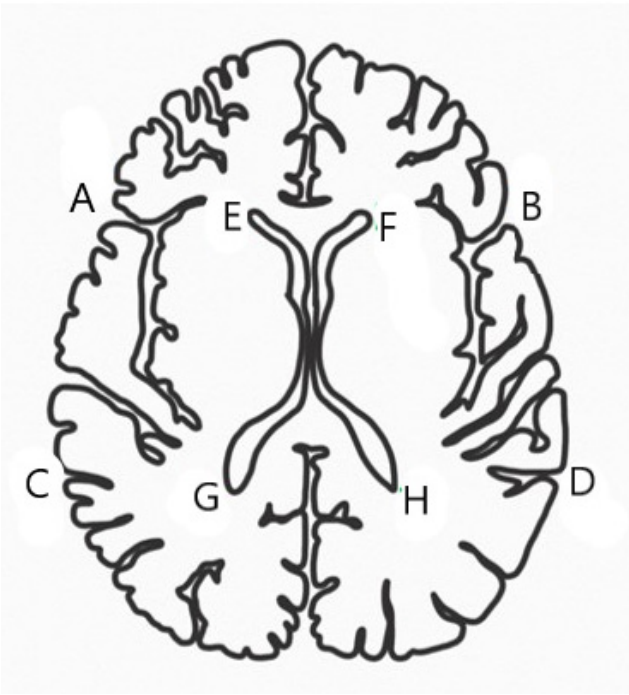

Figure 4 *Reference brain regions, including four areas at the outer edge of the cerebral cortex (A-D), four areas at the inner edge of cerebral cortex (E-F-G-H), were used to evaluate the image registration scores.*

Statistics and data analysis

The similarity between PET images and both brain templates in four patients were reported as average DSC scores. Wilcoxon Signed Ranks Test at 95% confidence interval was applied to compare the accuracy of image registration scores of newly developed PET-DTI and the conventional PET-T1 templates using SPSS software.

Results

1. Image registration quality assessment in four dementia patients

The DSC score was calculated based on the lateral ventricle area in the whole brain images. The results showed that the DSC score of PET-DTI normal brain template was higher than PET-T1 normal brain template and it has a DSC value closest to 1 (Table 1 and 2).

2. Accuracy scores of image registration measurement by Nuclear Medicine Radiologists

The applications of PET-DTI and PET-T1 templates provided the perfect registration for the edge area. However, the application of PET-DTI template gave better registration for the inner edge area. The registration score was 2.89, compared to 2.31 for the conventional PET-T1W templates (Table 3). The averaged registration scores of the PET-DTI template were significantly higher than the PET-T1 template (p=0.001).

Table 1 DSC score of PET-DTI normal brain template registration with four patients.

Patient	Lateral ventricle area (pixel)		DSC Score
	PET-DTI template	PET brain image	
1	1081±20.76	1634±23.28	0.80
2	1046±16.38	1073±17.14	0.99
3	1031±17.63	1022±24.87	1.00
4	1180±21.16	1055±27.50	0.94

Table 2 The DSC score of PET-T1 normal brain template registration with four patients.

Patient	The lateral ventricle area (pixel)		DSC Score
	PET-DTI template	PET brain image	
1	788 ± 10.32	1824 ± 23.61	0.60
2	744 ± 9.77	945 ± 14.67	0.88
3	810 ± 9.07	998 ± 19.15	0.90
4	1031 ± 19.84	1207 ± 29.68	0.92

Table 3 The accuracy scores of images overlay between the developed method (PET-DTI template) and the standard method (PET-T1 template).

	Registration score			
	PET-DTI template		PET-T1 template	
	Outer edge [a]	Inner edge [a]	Outer edge [a]	Inner edge [a]
Radiologist No.1	3.00 ± 0.00	2.92 ± 0.17	3.00 ± 0.00	2.63 ± 0.14
Radiologist No.2	3.00 ± 0.00	2.75 ± 0.29	3.00 ± 0.00	1.81 ± 0.13
Radiologist No.3	3.00 ± 0.00	3.00 ± 0.13	3.00 ± 0.00	2.50 ± 0.20
Average score	3.00 ± 0.00	2.89 ± 0.19	3.00 ± 0.00	2.31 ± 0.16

[a] *Averaged across 4 reference areas.*

Discussion

This study demonstrated the feasibility of using PET-DTI brain template to cope with the miss-registration due to brain scans using DTI. The construction of PET-DTI based template was similar to the standard template derived from T1W images. When validated our proposed template in a small number of dementia patients, we found that the application of PET-DTI template improved the registration accuracy both qualitatively and quantitatively.

The structure and shape of the skull and cerebral cortex might be different among different ethnic groups.[20,21] The standard PET brain template was developed from Caucasian brains, so we constructed the PET-T1W brain template from Thai patients to reduce the bias on physiological differences among ethnics group. We followed the work of Chotipanich *et al*.[17] In that work, the normal PET brain template of Thai individuals for ^{11}C-PiB and ^{18}F-THK 5351 was constructed using statistical parametric mapping (SPM) software. It was found that the new PET brain template was better than the standard template in distinguish patients with dementia from those with normal brain conditions.

There was no difference in the registration quality observed at the outer edge of the cerebral cortex where the pathological deformation was rare in an early stage of dementia. Both MRI-T1 or MRI-DTI templates provided perfect registration. However, the registration quality at the inner edge of the cerebral cortex was significantly different between the two templates. The findings in this study indicated that the DTI registration provided more accurate results and could be applied to dementia patients with altered brain pathology. Since the brain atrophy let to an incomplete and less details in the MRI image, it increased a mismatch and reduced the quality of image registration between the PET image and the PET brain template. Moreover, a smaller reference point on the brain atrophy image resulted in the wrong referencing of radiopharmaceutical substance value on the standard template. Thus, using the MRI-DTI template with white matter track as a core reference could fix this problem. It improved the image registration quality and might provide more accurate radiopharmaceutical substance value referencing.

This study found that our method could improve the accuracy of spatial information (inner edge) of image registration between PET image and PET-DTI template evaluated by nuclear medicine radiologists, which corresponds to the previous study by Sungkarat et al.12 They reported that dog's probabilistic diffusion tensor imaging tractography map generated from DTI images could reduce overlapping problems and artifacts found around the edge of the cerebral cortex.

Additionally, the result from this current study corresponds to the study by Tritanon *et al*.[13] They reported that whole-brain probabilistic tractography normalization technique could improve interpretation of Alzheimer disease in human brain in particular around the edge of the cerebral cortex.

The limitation of our study is the small number of dementia patients. MRI scanning takes a long time and MRI-DTI is not a standard protocol, so only few patients completed all three imaging protocols (PET, MRI-T1W and MRI-DTI). However, the preliminary result of this pilot study indicated that the application of PET-DTI was more robust against brain atrophy than the conventional PET-T1W template. The template could be constructed for other PET radiopharmaceuticals.

Conclusion

This pilot study investigated the application of a new brain template for dementia diagnosis using DTI images. The experiment on four dementia patients revealed that PET-DTI based template yielded more accurate image registration than the standard PET-T1W brain template. Although intensive investigation is required for further studies, this current study had showed that the PET-DTI template had the potential to solve the limitation of the standard brain template in diagnosing dementia with brain atrophy using PET images.

Conflicting Interests

The authors declare that they have no conflicts of interest.

Ethics Approval

The study was granted ethics approval by the Human Research Ethics Committee of Chulabhorn Research Institute (Project code 050/2562).

References

[1] Fletcher JW, Djulbegovic B, Soares HP, Siegel BA, Lowe VJ, Lyman GH, et al. Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med. 2008; 49: 480-508. doi: 10.2967/jnumed.107.047787.

[2] Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2010; 37: 181-200. doi: 10.1007/s00259-009-1297-4.

[3] Hofman MS, Hicks RJ. How we read oncologic FDG PET/CT. Cancer Imaging. 2016; 16: 1-4. doi.org/10.1186/s40644-016-0091-3.

[4] Papathanassiou D, Bruna-Muraille C, Liehn JC, Nguyen TD, Curé H. Positron emission tomography in oncology: present and future of PET and PET/CT. Crit Rev Oncol Hematol. 2009; 72: 239-54. doi: 10.1016/j.critrevonc.2008.10.006.

[5] Burdette JH, Minoshima S, Vander Borght T, Tran DD, Kuhl DE. Alzheimer disease: improved visual interpretation of PET images by using three-dimensional stereotaxic surface projections. Radiology. 1996; 198: 837-43. doi: 10.1148/radiology.198.3.8628880.

[6] Xiong KL, Yang QW, Gong SG, Zhang WG. The role of positron emission tomography imaging of β-amyloid in patients with Alzheimer's disease. Nucl Med Commun. 2010; 31: 4-11. doi: 10.1097/mnm.0b013e32833019f3.

[7] Patterson JC, Lilien DL, Takalkar A, Pinkston JB. Early detection of brain pathology suggestive of early AD using objective evaluation of FDG-PET scans. Int J Alzheimer Dis. 2010; 2011: 946590. doi: 10.4061/2011/946590D.

[8] Daniela P, Orazio S, Alessandro P, Mariano NF, Leonardo I, Pasquale Anthony DR, et al. A survey of FDG and amyloid-PET imaging in dementia and GRADE analysis. Biomed Res Int. 2014; 785039. doi.org/10.1155/2014/785039.

[9] Chotipanich C, Nivorn M, Kunawudhi A, Promteangtrong C, Boonkawin N, Jantarato A. Evaluation of imaging windows for Tau PET imaging using 18F-PI2620 in cognitively normal individuals, mild cognitive impairment, and Alzheimer's disease patients. Mol Imaging. 2020; 19: 1-8. doi: 10.1177/1536012120947582.

[10] Jantarato A, Vachatimanont S, Boonkawin N, Yaset S, Kunawudhi A, Promteangtrong C, et al. The Evaluation of Tau Deposition with [18F] PI-2620 by Using a Semiquantitative Method in Cognitively Normal Subjects and Patients with Mild Cognitive Impairment and Alzheimer's Disease. Mol Imaging. 2021; 2021: doi: 10.1155/2021/6640054.

[11] Jankovic J, Mazziotta JC, Newman NJ, Pomeroy SL. Diagnosis of Neurological Disease. Bradley and Daroff's Neurology in Clinical Practice. 8th Ed. Philadelphia, PA: Elsevier. 2022.

[12] Sungkarat W, Laothamatas J, Lumlertdacha B, Wacharapluesadee S, Hemachudha T.Dog's Whole Brain Probabilistic Diffusion Tensor Imaging Tractography Normalization: A Solution for Brain Image Normalization Difficulty Problems. Proc. Intl. Soc. Mag. Reson. Med. 2012; 20: 3394.

[13] Tritanon O, Laothamatas J, Wirojtananugoon C, Sungkarat W, Sukying C, Chansirikarnjana S. White Matter Involvement in Mild Cognitive Impairment and Mild Alzheimer's Disease Using Whole-Brain Probabilistic Tractography Normalization. Proc. Intl. Soc. Mag. Reson. Med. 2012; 20: 979.

[14] Kemppainen NM, Aalto S, Wilson IA, Någren K, Helin S, Brück A, et al. PET amyloid ligand [11C] PIB uptake is increased in mild cognitive impairment. Neurology. 2007; 68: 1603-6. doi: 10.1212/01.wnl.0000260969.94695.56.

[15] Rinne JO, Brooks DJ, Rossor MN, Fox NC, Bullock R, Klunk WE, et al. 11C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. Lancet Neurol. 2010; 9: 363-72. doi: 10.1016/S1474-4422(10)70043-0.

[16] Zhang S, Smailagic N, Hyde C, Noel-Storr AH, Takwoingi Y, McShane R, et al. 11C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev. 2014; 7. doi: 10.1002/14651858.CD0 10386.pub2.

[17] Chotipanich C, Kongthai S, Kunawudhi A, Promteangtrong C, Jantarato A. 18F-THK 5351 and 11C-PiB PET of the Thai normal brain template. Asia Ocean J Nucl Med Biol. 2021; 9: 21. doi: 10.22038/AOJNMB.2020.49623.1338.

[18] Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, Beckmann C, et al. Bayesian analysis of neuroimaging data in FSL. Neuroimage. 2009; 45: S173-86. doi: 10.1016/j.neuroimage.2008.10.055.

[19] Jbabdi S, Sotiropoulos SN, Savio AM, Graña M, Behrens TE. Model-based analysis of multishell diffusion MR data for tractography: How to get over fitting problems. Magn Reson Med. 2012; 68(6): 1846–1855. doi: 10.1002/mrm.24204.

[20] Rao NP, Jeelani H, Achalia R, Achalia G, Jacob A, dawn Bharath R, et al. Population differences in brain morphology: need for population specific brain template. Psychiatry Res. 2017; 265: 1-8. doi: 10.1016/j.pscychresns.2017.03.018.