Amyloid PET Quantification Using Low-dose CT-guided Anatomic Standardization

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Abstract

Background

Centiloid (CL) scaling has become a standardized quantitative measure in amyloid PET because it facilitates the direct comparison of results across institutions, even when different analytical methods or tracers are used. Standard volumes of interest must be used to calculate the CL scale after the anatomic standardization of amyloid PET images using coregistered MRI; if the MRI is unavailable, the CL scale cannot be accurately calculated. This study sought to determine the substitutability of low-dose CT, which is used to correct PET attenuation in PET/CT equipment, by evaluating the measurement accuracy when low-dose CT is used as an alternative to MRI in the calculation of the CL scale. Amyloid PET images obtained using ^{18}F-flutemetamol from 24 patients with possible or probable Alzheimer's disease were processed to calculate the CL scale using 3D T1-weighted MRI and low-dose CT of PET/CT. CL_{MRI} and CL_{CT} were respectively defined as the use of MRI and CT for anatomic standardization and compared. Trial registration: Japan Registry of Clinical Trials, jRCTs031180321. Registered 18 March 2019, https://jrct.niph.go.jp/latest-detail/jRCTs031180321.

Results

A Bland–Altman plot showed that CL_{CT} was slightly but significantly underestimated (mean ± standard deviation, −1.7 ± 2.4; $p < 0.002$) compared with CL_{MRI}. The 95% limits of agreement ranged from −2.8 to −0.7. Pearson correlation analysis showed a highly significant correlation of $r = 0.998$ between CL_{CT} and CL_{MRI} ($p < 0.001$). The linear regression equation was $CL_{MRI} = 1.027 \times CL_{CT} + 0.762$. In a Bland-Altman plot, Spearman correlation analysis did not identify a significant association between the CL_{MRI} versus CL_{CT} difference and the CL load ($\rho = -0.389$, $p = 0.060$). This slight underestimation of CL_{CT} may derive from slightly higher uptake when the cerebellum is used as a reference area in CT-based anatomically standardized PET images versus MRI-based images.

Conclusions

Low-dose CT of PET/CT can substitute for MRI in the anatomic standardization used to calculate the CL scale from amyloid PET, although a slight underestimation occurs.

Background

In clinical practice for dementia, amyloid PET increases the certainty of Alzheimer's disease (AD) and non-AD diagnosis. The binary classification of positive and negative amyloid PET findings is based on visual interpretation. Equivocal findings are thus inevitable and lead to interrater variability in visual interpretation [1] because raters have their own experience and potential internal criteria. In addition, in our previous multicenter study using ^{18}F-flutemetamol [2], disagreement between two raters was observed in 9% of cases. Equivocal findings should be avoided when determining the indication for the

disease-modifying drugs currently in development. Accordingly, quantitative analysis has been proposed as an adjunct to visual interpretation [3].

The quantitative analysis of amyloid PET has widely applied the standardized uptake value ratio (SUVR). However, SUVR values vary not only according to the target and reference regions used, but also according to the particular amyloid tracer used. This variability can be resolved through a Centiloid (CL) scaling process that standardizes the quantitative amyloid imaging measures by standardizing the outcome of each analytical method or PET ligand to a scale from 0 to 100 [4]. The CL scaling method can facilitate the direct comparison of results across institutions, even when different analytical methods or tracers are used, and may enable cutoffs for amyloid positivity to be clearly defined. A positive relationship of the CL scale cutoff with pathological findings has been found [5-8], and it is expected that the clinical value of the CL scale will continue to increase. When determining the CL scale, it is necessary to follow the method advocated by the Global Alzheimer's Association Interactive Network (GAAIN, http://www.gaain.org/centiloid-project). Because highly accurate anatomic standardization to standard Montreal Neurological Institute (MNI) space is required to use standard volumes of interest (VOIs) supplied from GAAIN to calculate the CL scale converted from the SUVR, anatomic standardization of amyloid PET images should be performed using coregistered MRI obtained around the same period. For this MRI, it is recommended to use a three-dimensional (3D) T1-weighted image that covers the whole brain. However, if a 3D T1-weighted image is not available, the CL scale cannot be accurately calculated. As an alternative, Pressoto et al. [9] reported that anatomic standardization of amyloid PET can be performed with low-dose CT, which is used to correct PET attenuation in PET/CT equipment. According to their report, the difference between the SUVR values measured by anatomic standardization using MRI and low-dose CT is only 0.01 ± 0.03 (mean ± standard deviation) and is thus negligible. The purpose of the present study was to establish the substitutability of low-dose CT of PET/CT proposed by Pressoto et al. by verifying the measurement accuracy when low-dose CT is used as an alternative to MRI in the calculation of the SUVR and CL scale in amyloid PET.

Materials And Methods

Participants

The study participants comprised 24 patients (15 men and 9 women; age range, 48–90 years) enrolled in a previous multicenter study [2]. They were recruited from an outpatient memory clinic of the National Center of Neurology and Psychiatry, Japan. The participants had a Mini-Mental State Examination score of 19.7 ± 4.6 and a global Clinical Dementia Rating of 0.8 ± 0.4. According to National Institute on Aging and the Alzheimer's Association criteria [10], 10 and 14 patients were diagnosed as having possible and probable AD, respectively.

Image acquisition

^{18}F-flutemetamol PET/CT

Each subject received an intravenous injection of 215 ± 33 MBq of ^{18}F-flutemetamol (Vizamyl, Nihon Medi-Physics). All PET acquisitions were performed using a hybrid PET/CT Biograph 16 True-point scanner (Siemens Healthineers, Erlangen, Germany). After positioning, a low-dose CT scan (kVp, 130KeV; current, 40 mA; rotation time, 1.0 s; table feed per rotation, 7.2 mm; spiral pitch factor, 0.75) was acquired to be used for the attenuation correction of the PET data. Images were reconstructed using the "H10s very smooth" kernel, a 30.0-cm reconstruction field of view, and a 2.0-mm slice interval for a resulting voxel size of 0.59 × 0.59 × 2.0 mm^3. A 3D-PET acquisition (list mode) was started 61.2 ± 0.8 min after the injection of the tracer and lasted for 20 min. Image reconstruction was performed using a 3D ordered subsets expectation maximization algorithm with the following parameters: image matrix, 168; field of view, 300 mm; subsets, 21; iterations, 4; post-filter (Gaussian), 4-mm FWHM; attenuation correction, CT-based. The resulting voxel size was 2.02 × 2.06 × 2.03 mm^3.

MRI

The MRI for all patients was performed on an Achieva 3.0-T MR scanner (Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel coil within 42 ± 21 days before the amyloid PET. A volumetric turbo field echo T1-weighted structural sequence (300 sagittal slices; TR, 7.0 ms; TE, 3.4 ms; field of view, 260 × 240 mm; voxel size, 0.7 × 0.7 × 0.6 mm^3; flip angle, 10°) was acquired for each subject.

Quantitative analysis

Figure 1 shows the processing pipeline applied to quantitative analysis using the SUVR and the 100-point CL scale [4]. This MRI-based pipeline has already been validated [2] using a GAAIN dataset of ^{11}C-PiB PET images for 34 young control individuals and 45 typical AD patients downloaded from the GAAIN website. In the present study, low-dose CT instead of MRI was also used for anatomic standardization. The CL scale assigns an average value of 0 to high-certainty amyloid-negative subjects and an average of 100 to typical AD patients. First, in this pipeline, the subject MRI or CT was manually oriented and coregistered to the MNI template (avg152T1.nii) provided with Statistical Parametric Mapping (SPM) 12 software (https://www.fil.ion.ucl.ac.uk/spm). The subject PET was then manually oriented and coregistered to the coregistered subject MRI or CT. Then, the coregistered subject MRI or CT was warped into MNI space using unified segmentation in SPM12. The parameters of the deformation field in this warping were applied to the coregistered subject PET for anatomic standardization into MNI space. Using the standard VOI in GAAIN, the SUVR was calculated from ^{18}F-flutemetamol PET counts in the global cortical target area (GAAIN, CTX VOI) and in the whole cerebellum (GAAIN, WhlCbl VOI) as the reference area. Then, a direct conversion equation (CL = 121.42 × SUVR − 121.16) was applied to convert the SUVR to the CL value, as described previously [11]. We respectively defined the $SUVR_{MRI}$ and $SUVR_{CT}$ and CL_{MRI} and CL_{CT} as the use of MRI and CT for anatomic standardization.

Endpoints

The endpoint of this study was the measurement accuracy of the $SUVR_{CT}$ and CL_{CT} when the $SUVR_{MRI}$ and CL_{MRI} were respectively regarded as the gold standard.

Statistical analysis

Concordances between the $SUVR_{MRI}$ and $SUVR_{CT}$ and between the CL_{MRI} and CL_{CT} were assessed using Bland–Altman plots and Pearson correlation estimates. In the Bland–Altman plot of the SUVR and CL, we performed a Spearman correlation to test whether there were associations between the difference in $SUVR_{MRI}$ versus $SUVR_{CT}$ and the SUVR load and between the difference in CL_{MRI} versus CL_{CT} and the CL load. The SUVR and CL and their standard deviations were computed with mean absolute differences and limits of agreement. These statistical tests were performed using JMP ver. 16 (SAS Institute). In addition, to investigate regional differences in the CT-based and MRI-based standardized amyloid PET images, a paired t-test was applied to these images on a voxel basis after smoothing with an 8mm FWHM Gaussian kernel using SPM12. Results were considered significant at $p < 0.001$ with an extent threshold of 300 voxels without multiple comparisons.

Results

Figure 2 shows the standardized MRI, CT, and amyloid PET images in MNI space in a subject, along with the three corresponding images in native space. When compared with $SUVR_{MRI}$ and CL_{MRI} using a Bland–Altman plot (Fig. 3a, b), the $SUVR_{CT}$ and CL_{CT} were slightly but significantly underestimated (−0.01 ± 0.02 and −1.7 ± 2.4, respectively; $p < 0.002$). The 95% limits of agreement ranged from −0.02 to −0.01 for the SUVR and from −2.8 to −0.7 for CL. Pearson correlation analysis (Fig. 3c, d) showed a highly significant correlation of $r = 0.998$ between the $SUVR_{CT}$ and $SUVR_{MRI}$ ($p < 0.001$). The linear regression equation was $SUVR_{MRI} = 1.027 \times SUVR_{CT} - 0.020$. CL_{CT} also showed a highly significant correlation of $r = 0.998$ with CL_{MRI} ($p < 0.001$). The linear regression equation was $CL_{MRI} = 1.027 \times CL_{CT} + 0.762$.

In a Bland–Altman plot, Spearman correlation analysis failed to identify a significant association between the difference in $SUVR_{MRI}$ versus $SUVR_{CT}$ and the SUVR load ($\rho = -0.379$, $p = 0.051$) or between the difference in CL_{MRI} versus CL_{CT} and the CL load ($\rho = -0.389$, $p = 0.060$).

Paired t-tests performed using SPM12 (Fig. 4 and Table 1) found that the brainstem exhibited the biggest differences in uptake between the CT-based and MRI-based standardized PET images. Higher uptake of CT-based standardized PET images than MRI-based PET images was observed within the whole cerebellar VOI. In the supratentorial area, most of the statistically significant differences in uptake between the CT-based and MRI-based standardized PET images were found outside of the global cortical target region VOI.

Discussion

This study confirmed that low-dose CT of PET/CT can substitute for MRI in the anatomic standardization performed to calculate the CL scale from amyloid PET. The average difference between the $SUVR_{CT}$ and SUV_{MRI} was only 0.01, which was the same as in a previous study [9]. The difference in the CL scale between CL_{CT} and CL_{MRI} was also only 1.7 on average. CT acquired at exactly the same time as amyloid PET enables accurate coregistration of CT and PET. When MRI is unavailable, simultaneously obtained low-dose CT of PET/CT can provide accuracy nearly equal to that of MRI for CL scale calculation. This simultaneity can avoid the misregistration of MRI and PET when there is a substantial delay between modalities during which brain atrophy progresses in AD patients.

Several studies have reported anatomic standardization using the amyloid PET template alone without MRI. However, the single-atlas PET template-based method provides a less accurate definition of cortical gray matter regions compared with the MRI-based method [12]. This inaccuracy may result from intensity-based standardization using a PET template. The high white matter and low gray matter uptake in amyloid-negative individuals tends to slightly shift the target's white matter toward the single-atlas gray matter, leading to increased sampling of the white matter and an overestimation of the neocortical uptake. Similarly, the low white matter and high gray matter uptake in amyloid-positive individuals tends to slightly shift the target's gray matter toward the single-atlas white matter, leading to decreased sampling of the gray matter and an underestimation of the neocortical uptake. Consequently, the single-atlas PET template-based method gives a lower discrimination performance between cognitively normal individuals and AD patients compared with the MRI-based method [13]. To overcome the drawback of the single-atlas PET template-based method, the application of a multi-atlas PET template to the anatomic standardization has been proposed [14,15]. Computation of similarities between the anatomically standardized image of a patient and the multi-atlas templates automatically chooses the appropriate PET template. This multi-atlas approach reduces the overall error from 5.6% using single-atlas to 2.7% in neocortical SUVR estimation compared with the MRI-based method [14]. Although this multi-atlas approach may improve the accuracy of anatomic standardization, it might not be able to cope with amyloid PET images with asymmetrical accumulation between the left and right hemispheres. This asymmetry causes interhemispheric differences in the accuracy of the registration to the PET template. From this point of view, structural images may be necessary for precise anatomic standardization.

CT-based standardization showed a slightly but significantly lower SUVR and CL scale compared with MRI-based standardization. Direct comparison indicates that CT evaluation exhibits increased uptake in bilateral cerebellar hemispheres compared with MRI. This slightly increased uptake of the cerebellar hemisphere in a reference area may lead to a slight decrease in the SUVR and CL in a target area of the cerebral cortex in CT-based standardization.

There are some limitations in this study. We did not study the influence of the CT image quality on the anatomic standardization. Future studies will need to assess both the lower dose limit at which the algorithm still performs correctly and whether the use of diagnostic-quality CT provides improvements. The SPM results showed a remarkable difference in brain stem uptake between MRI-based and CT-based

standardized images. Accordingly, the reference region should not be located in the brain stem, including the pons, in a CT-based method.

Conclusion

This study proposes the use of low-dose CT of PET/CT for calculating the CL scale from amyloid PET. CL scales based on low-dose CT show a highly significant positive correlation with those based on MRI, regardless of the degree of amyloid accumulation. The strongest advantage of the use of low-dose CT is the simultaneous acquisition of PET and CT. This simultaneity can avoid misregistration resulting from atrophy progression in AD when there is a substantial delay between MRI and PET acquisition.

Declarations

Acknowledgements

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Author's contribution

All authors contributed significantly to the analysis and interpretation of the data (HM, TY, MS, YS), to the writing of the manuscript (HM, TY), or to the revision of the manuscript (KO, NS). HM, KO, and NS managed the study. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was reviewed and approved by the Certified Clinical Research Review Board at the National Center of Neurology and Psychiatry. This study was registered in the Japan Registry of Clinical Trials (jRCTs, 031180321). The participants provided their written informed consent to participate in this study.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Competing interests

H. Matsuda has received a research grant from Nihon Medi-Physics Co., Ltd. All other authors declare that they have no competing interests.

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Table

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

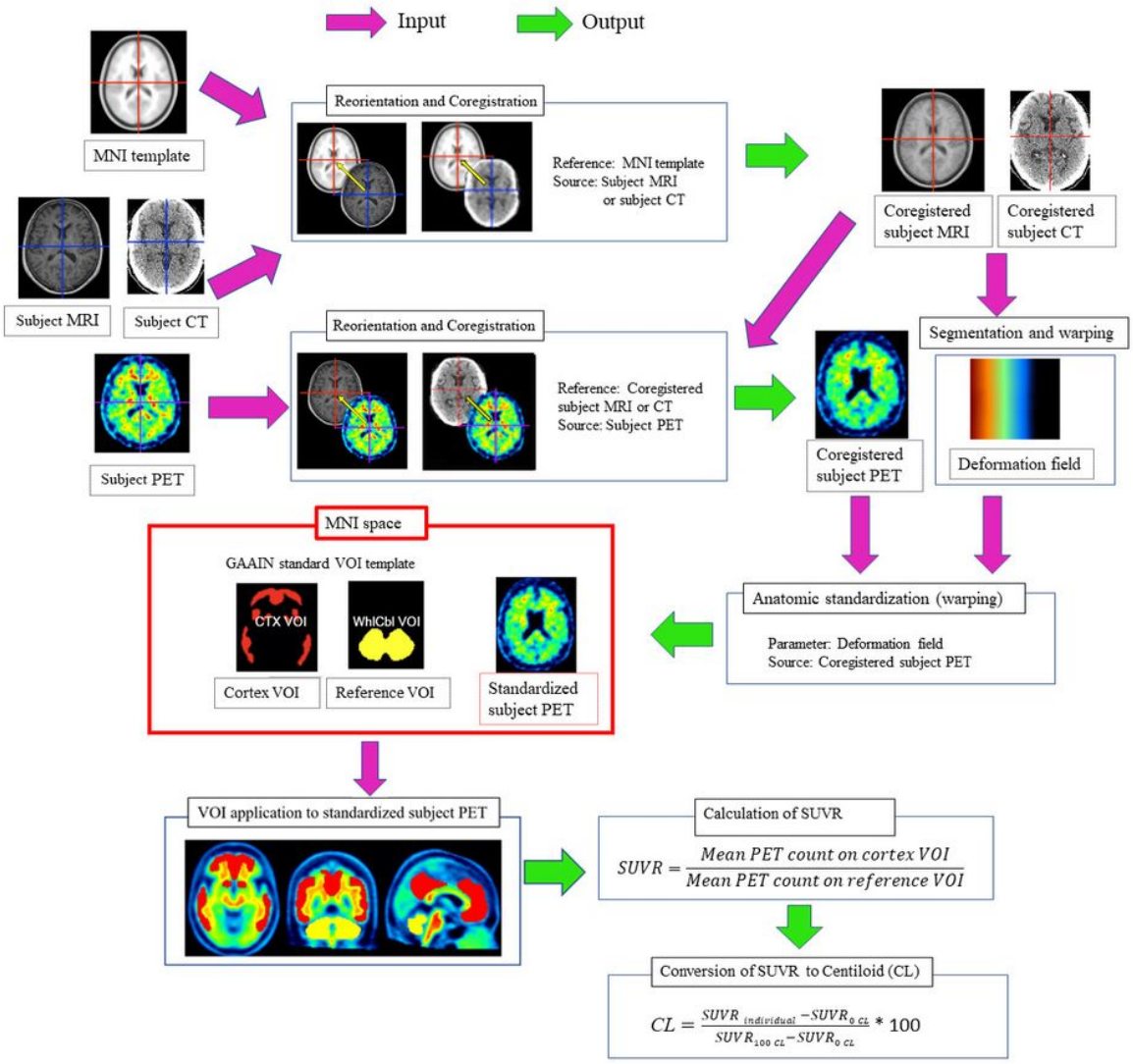

Figure 1

Processing pipeline for quantitative measurements of 18F-flutemetamol accumulation in the cerebral cortex. The subject MRI or CT was manually oriented and coregistered to the MNI template. The subject PET was manually oriented and coregistered to the coregistered subject MRI or subject CT. Then, the coregistered subject MRI or subject CT was warped into MNI space using unified segmentation in SPM12. The parameters of the deformation field in this warping were applied to the coregistered subject PET for anatomical standardization into MNI space. The SUVR was calculated from the 18F-flutemetamol PET counts in the cerebral cortical areas (Cortex VOI, CTX VOI) and in the whole cerebellum as a reference area (Reference VOI, WhlCbl VOI) using the GAAIN standard VOI template. Then, the SUVR was converted to CL using a direct conversion equation.

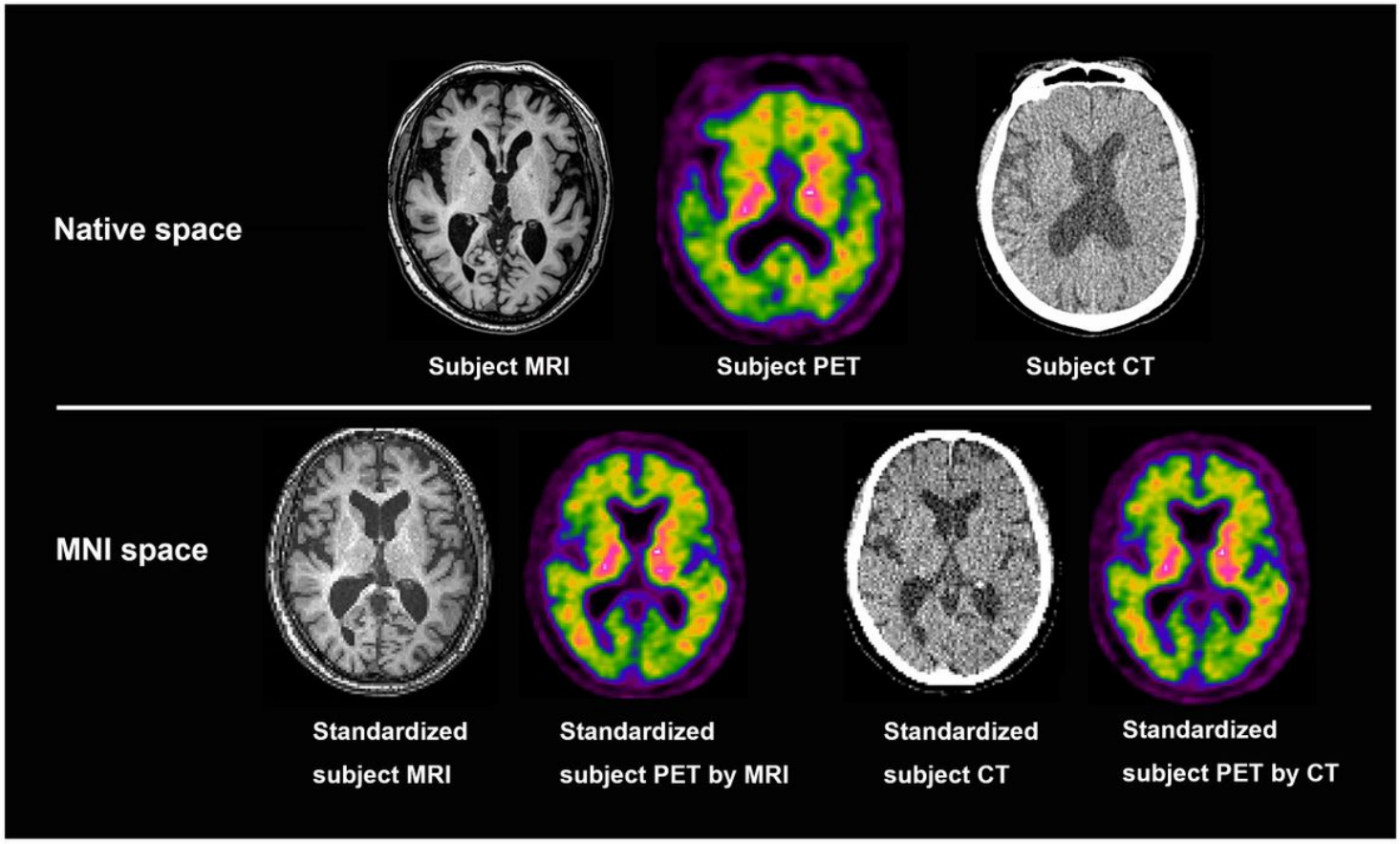

Figure 2

Coregistered (upper row, native space) and anatomically standardized (lower row, MNI space) MRI, PET, and CT images. Almost identical PET images were obtained after anatomic standardization between the MRI-based and CT-based approaches.

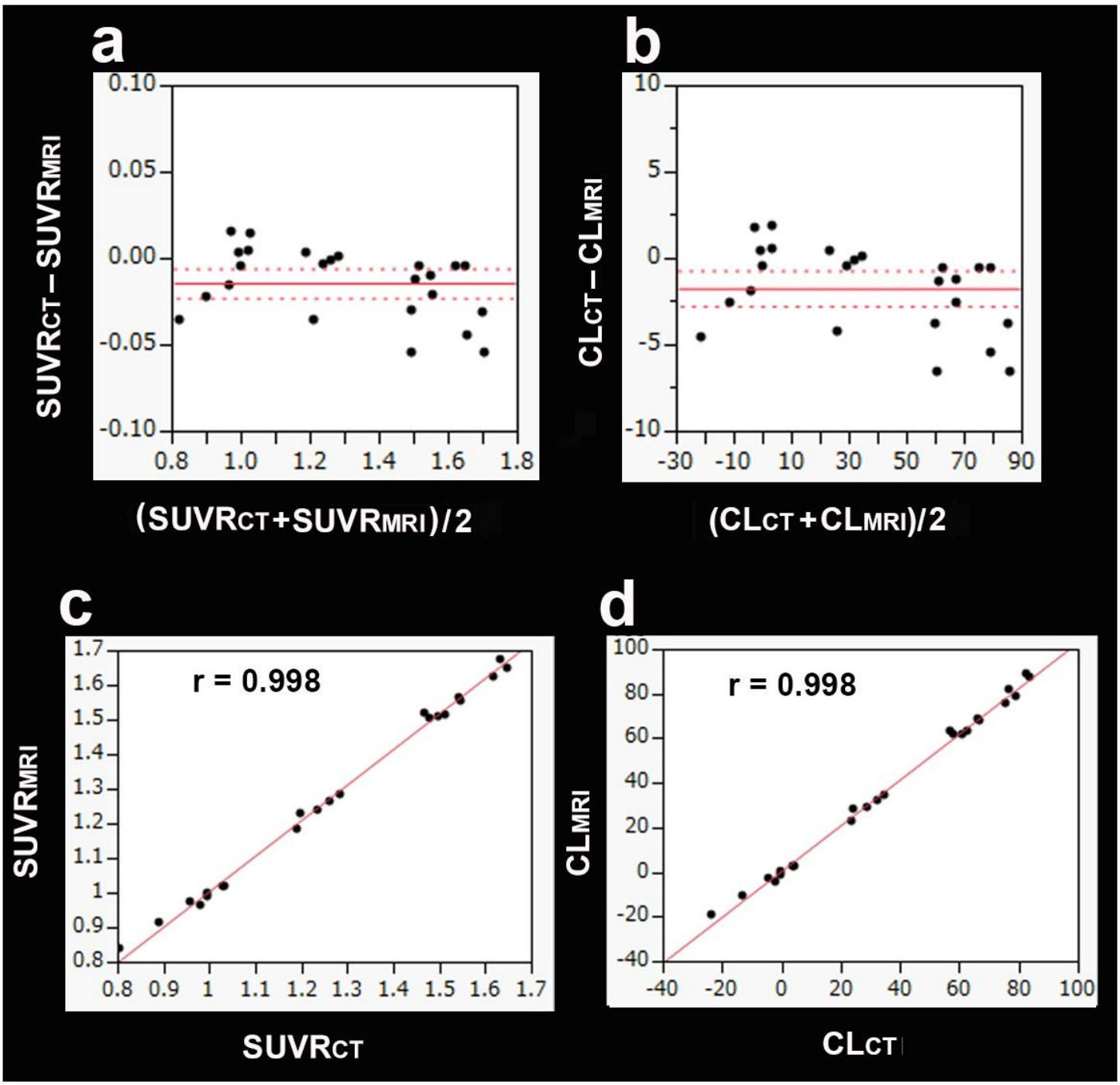

Figure 3

Comparison of the SUVR and CL values obtained from the MRI-based and CT-based approaches. Bland-Altman plots (a,b) showed slight but significant underestimation of the SUVRCT and CLCT compared with the SUVRMRI and CLMRI, respectively ($p<0.002$). Spearman correlation analysis did not show a significant association between the SUVRMRI versus SUVRCT difference and the SUVR load ($\rho=-0.379$, $p=0.051$) and between the CLMRI versus CLCT difference and the CL load ($\rho=-0.389$, $p=0.060$). Pearson correlation analysis (c,d) showed highly significant correlations of $r=0.998$ between the SUVRCT and SUVRMRI and between the CLCT and CLMRI ($p<0.001$).

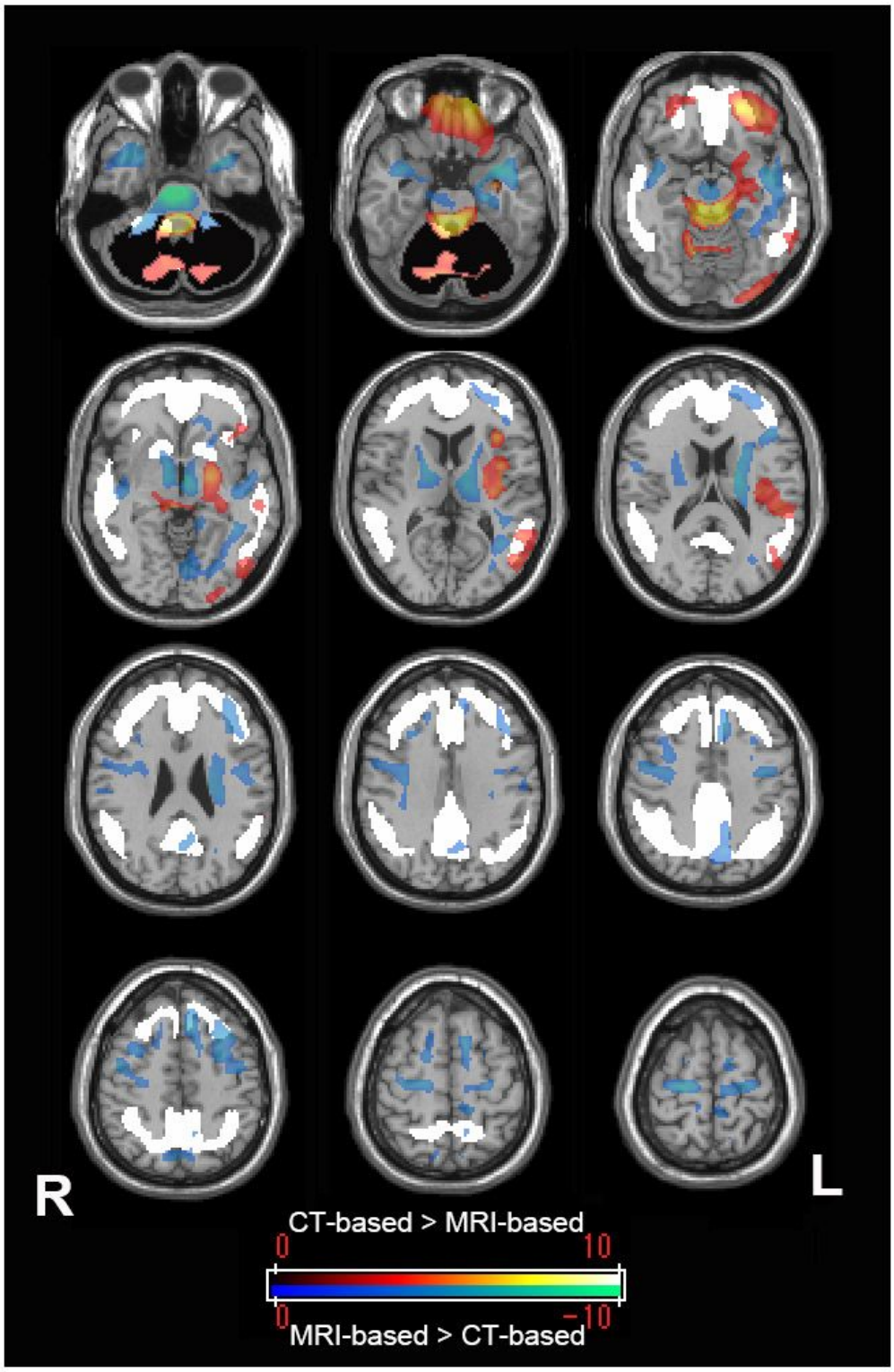

Figure 4

Direct comparison of anatomically standardized amyloid PET images using CT and MRI. SPM analysis showed significantly ($p<0.001$) higher and lower uptake of CT-based standardized PET images than MRI-based standardized PET images presented in a warm color scale and a cool color scale, respectively. The largest differences in the accumulation are visible in the brain stem. Higher uptake of CT-based standardized PET images was observed within the whole cerebellar VOI as a reference area (solid black

area). In the supratentorial area, most of the significant differences in uptake were found outside the cortical target VOI (solid white area).

Supplementary Files

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- Table1.xlsx