

Feasibility study of amyloid PET-only quantification; a comparison with visual interpretation.

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Abstract

Objective Visual evaluation is the standard for amyloid positron emission tomography (PET) examination, though the result depends upon the physician's subjective review of the images. Therefore, objective quantitative evaluation is expected to be useful for image interpretation. In this study, we examined the usefulness of the quantitative evaluation of amyloid PET using a PET-only quantification method in comparison with visual evaluation.

Methods A total of 166 individuals, including 58 cognitively normal controls, 62 individuals with mild cognitive impairment, and 46 individuals with early Alzheimer's disease, were retrospectively investigated. They underwent ¹¹C-Pittsburgh compound-B (PiB) PET examination through the Japanese-Alzheimer's disease neuroimaging initiative (J-ADNI). Amyloid accumulation in cerebral cortices was assessed using visual and quantitative methods. The quantitative evaluation was performed using the adaptive template method and empirically PiB-prone region of interest, and the standardized uptake value ratio (SUVR) in each area was obtained.

Results Visual evaluation and SUVR were significantly correlated in the cerebral cortices ($\rho = 0.85-0.87$; $p < 0.05$). In visual evaluation, the sensitivity, specificity, and accuracy were 78%, 76%, and 77%, respectively. Meanwhile, for quantitative evaluation, the sensitivity, specificity, and accuracy were 78%, 76%, and 77%, in mean cortical SUVR (mcSUVR) and 79%, 79%, and 79% in maximum SUVR (maxSUVR), respectively.

Conclusion The PET-only quantification method resulted in a concordant result with visual evaluation and was considered to be useful for amyloid PET.

Introduction

The number of people with dementia in Japan was about 4.62 million in 2012 [1, 2] and is expected to increase to about seven million by 2025. Overall, researchers estimated that one-fifth of elderly people aged 65 years or older will develop dementia. Alzheimer's disease (AD) is the most common form of dementia, with an incidence estimated to reach about five million people in 2025 [1, 3]. This growth in the number of patients with AD is expected to lead to huge medical costs and social burdens. Although there are no fundamental therapeutic agents for AD available, cholinesterase inhibitors that inhibit the decompose of acetylcholine temporarily improve cognitive function and suppress the progression of symptoms [4]. Thus, early diagnosis and early intervention are expected to decrease the social burden.

In the pathological process of AD, various abnormalities occur with the progression of the illness. Amyloid- β (A β) plaque accumulation, which forms senile plaque, is believed to begin before more than 10 years before the clinical manifestations develop [5]. The amyloid PET examination estimates the density of senile plaques in the brain, facilitating the visibility of A β plaque accumulation in the brain noninvasively [6-9]. ¹¹C-Pittsburgh compound-B (¹¹C-PiB) is a widely used amyloid PET radiopharmaceutical developed at the University of Pittsburgh [10]. Qualitative interpretation regarding

whether accumulation is visually positive or negative in amyloid PET is standard for clinical practice [6–12]. However, visual evaluation is subjective and causes both inter- and intrainterpretation variability [13]. Although the usefulness of quantitative evaluation in clinical practice has not been established, quantitative evaluation using standardized uptake value ratio (SUVR) has been used in clinical research and clinical trials [6–11].

Amyloid PET quantification typically requires spatial normalization. Although MRI is often used for spatial normalization, high-resolution three-dimensional MRI is not always available in clinical practice. Further, MRI-based quantification sometimes results in errors in the process of gray matter segmentation and coregistration between MRI and PET images [12]. Therefore, we developed an adaptive template method requiring the use of PET images only for spatial normalization by using amyloid-positive and -negative PET templates [12]. Some previous studies adopted either manually defined region-s of- interest (ROIs), automatic- anatomical- labeling ROIs or FreeSurfer-based ROIs [14–17]. However, these anatomical ROIs are not necessarily suitable for amyloid quantification because they are not restricted to the regions that are apt to accumulate amyloid PET drugs in pathological conditions. To solve this issue, we also developed empirically PiB-prone ROI (EPP-ROI), which is specialized for A β deposition in PiB-PET images [12]. A pilot study to examine PET-only amyloid quantification with adaptive templates and EPP-ROI suggested a degree of usefulness for quantitative evaluation [12].

The purpose of this study was to examine the usefulness of PET-only amyloid quantification and to compare outcomes of the visual and quantitative evaluations of amyloid PET scans using subjects registered in a multicenter study.

Methods

Subjects

The subjects of this study are a part of the study cohort of the Japanese-Alzheimer's disease neuroimaging initiative (J-ADNI) study [18]. The J-ADNI study is a multi-institutional joint research project on the subject of AD in Japan. A total of 537 subjects are registered, and imaging examinations and laboratory tests were performed. Amyloid PET examinations were conducted in 203 cases. The National Bioscience Database Center provided the registered data [18]. Separately, in this study, we examined 166 subjects who underwent ¹¹C-PiB PET in the J-ADNI study. Subjects consisted of 58 normal controls (NC), 62 patients with mild cognitive impairment (MCI), and 46 patients with AD (Table 1). This study is retrospective and was approved by the appropriate ethics committee. Subjects were willing to participate in JADNI and agreed that the study would be long-term.

Table 1
Characteristics of subjects

Clinical diagnosis	NC	MCI	AD
The number of subjects (M/F)	58 (30/28)	62 (30/32)	46 (21/25)
Age (years)	66.4 ± 4.51 (60–80)	71.4 ± 5.45 (60–82)	74.4 ± 6.31 (62–84)
Diagnosis criteria			
NINCDS-ADRDA	-	-	Probable AD
MMSE-J	24–30	24–30	20–26
CDR-J	0	0.5	0.5 or 1.0
WMS-R	-	Below cutoff	-
NC, Normal control; MCI, Mild cognitive impairment; AD, Alzheimer’s disease, NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and the Alzheimer’s Disease And Related Disorders Association; MMSE-J, Mini Mental State Examination-J; CDR-J, Clinical Dementia Rating Scale-J; WMS-R, Wechsler Memory Scale-Revised Logical Memory II.			

Data acquisition and image reconstruction

The subjects received intravenous injection of 555 ± 185 MBq of ^{11}C -PiB and PET dynamic scan for 70 minutes immediately after injection. Data were acquired using nine PET scanners and seven PET/CT scanners. The PET images were reconstructed using 20-minute data at 50-minutes postinjection. The attenuation correction of PET camera was performed by transmission scan using the segmentation method for six minutes, while that of the PET/CT camera was performed by CT scan. Regarding image reconstruction conditions for amyloid PET in the J-ADNI study, the phantom examination was performed in advance, and the reconstruction condition was optimized for brain PET imaging. All the PET images acquired in each PET site went through the J-ADNI PET quality control process [18].

Image interpretation

Visual interpretation was performed by three board-certified nuclear medicine physicians well-trained in amyloid PET image interpretation. The regional uptake for four cortical areas on each side, including the frontal lobe, lateral temporal lobe, lateral parietal lobe, and precuneus/posterior cingulate, was awarded two points (positive), one point (equivocal), or zero points (negative) regional uptake. The visual interpretation criteria are described in the article by Yamane et al. [13].

Quantitative evaluation of ^{11}C -PiB

Quantitative evaluation was performed using SUVR, which is the uptake ratio of each region to the reference region. The reference region was the cerebellar cortex. Mean cortical SUVR (mcSUVR) is the mean SUVR in the entire ROI, while maximum SUVR (maxSUVR) is the maximum SUVR of the four

regional SUVRs including that from the precuneus/posterior cingulate, frontal lobe, temporal lobe lateral side and parietal lobe lateral side, respectively, as well as visual interpretation.

Figure 1 shows the PET-only amyloid quantification method for ^{11}C -PiB PET [12]. The PET images were spatially normalized by using the adaptive template method. The images were normalized to both the positive and negative templates generated by averaging 11 and eight typical images, respectively. The transformation vector for a template that most resembles the image was adopted. The EPP-ROI developed based on the ^{11}C -PiB accumulated area in patients with AD patients was inversely transformed by using a transformation vector and placed on the individual PET [12] in native space. Image processing was performed with PMOD version 3.7 (PMOD Technologies, Zürich, Switzerland).

Statistical analysis

JMP Pro 13 (SAS Institute Inc, Cary, USA) was used for statistical analyses. Correlation between visual and quantitative evaluation was analyzed using Spearman's rank correlation coefficient. The significant level was $p < 0.05$. The SUVR cut-off value for differentiating normal and diseased subjects was calculated using receiver operating characteristic curve (ROC) analysis.

Results

Figure 2 shows the results of the visual evaluation in relation to clinical diagnosis. Among subjects with NC, 44 subjects (75.9%) were amyloid PET-negative and 14 subjects (24.1%) showed either positive or equivocal result. Among patients with MCI, 21 patients (33.9%) were negative, and 41 patients (66.1%) were either positive or equivocal. finally, in patients with AD, three patients (6.5%) were negative and 43 patients (93.5%) were either positive or equivocal. When MCI and AD were considered to be a disease, the sensitivity was 78%, the specificity was 76%, and the accuracy was 77% (Table 2).

Table 2
Comparison of the diagnostic accuracy for differentiation

	Sensitivity	Specificity	Accuracy
Visual evaluation	78% (84/108)	76% (44/58)	77% (128/166)
mcSUVR	77% (83/108)	79% (46/58)	78% (129/166)
maxSUVR	79% (85/108)	79% (46/58)	79% (131/166)
Not significant			
mcSUVR, Mean cortical standardized uptake value ratio; maxSUVR, maximum SUVR.			

Figure 3 shows the relationship between regional visual interpretation and regional SUVR in each region. When the visual point of regional uptake was high, the SUVR was also high. Spearman's rank correlation coefficient was significant ($\rho = 0.86$; $p < 0.05$). Significant correlations were also observed in the

precuneus/posterior cingulate ($\rho = 0.87$; $p < 0.05$), the frontal lobe ($\rho = 0.87$; $p < 0.05$), the lateral temporal lobe ($\rho = 0.86$; $p < 0.05$), and the lateral parietal lobe ($\rho = 0.85$; $p < 0.05$).

The relationship between visual and quantitative evaluation by patient group is shown in Fig. 4. The cut-off value for differentiating between visually negative and both positive and equivocal results was calculated by ROC analysis. Cutoff values were 1.41 for mcSUVR and 1.59 for maxSUVR. Concordant results between visual and quantitative evaluation were obtained as 157 of 166 cases (94.6%) for mcSUVR and 158 of 166 cases (95.2%) for maxSUVR. In 98 subjects with visually positive or equivocal findings, seven subjects were negative using mcSUVR, and six subjects were negative using maxSUVR. Among 68 subjects with visually negative results, one subject was positive using mcSUVR, and no subjects were positive using maxSUVR. The mcSUVR values of negative, equivocal, and positive outcomes were 1.25 ± 0.11 , 1.39 ± 0.20 , and 2.17 ± 0.34 , respectively. The difference in mcSUVR among visual classifications was significant ($p < 0.05$). Separately, the maxSUVR values of negative, equivocal, and positive results were 1.35 ± 0.13 , 1.56 ± 0.21 , and 2.48 ± 0.41 , respectively ($p < 0.05$).

The comparison of diagnostic accuracy between visual and quantitative evaluation is shown in Table 2. The sensitivity, specificity, and accuracy when using visual evaluation were 78%, 76%, and 77%, respectively. Additionally, they were 77%, 79%, and 78% using mcSUVR and were 79%, 79%, and 79% using maxSUVR, respectively. In comparison with visual evaluation, one true-positive subject decreased, and two true negative subjects increased using mcSUVR. Further, by using maxSUVR, one true-positive subject increased and two true negative subjects increased. Ultimately, the diagnostic accuracy of quantitative evaluation was almost equal to that of visual evaluation. The clinical diagnosis by maxSUVR tended to be a little higher than that when using visual evaluation and mcSUVR, though the difference was not statistically significant.

Discussion

In this study, we examined the usefulness of amyloid-PET only quantification and compared it with the visual evaluations. This method adopted the adaptive template method and EPP-ROI. In the area specialized for A β deposition, visual evaluation and SUVR were highly correlated. The PET-only quantification method was almost equivalent to visual evaluation. Relatively with visual evaluation, the diagnostic accuracy for differentiation in PET-only quantification was almost equivalent.

In the precuneus/posterior cingulate, the frontal lobe, temporal lobe lateral side, parietal lobe lateral side, visual interpretation, and SUVR were highly correlated ($\rho = 0.85-0.87$). Further, the concordance rates between quantitative evaluation and visual evaluation were 94.6% in mcSUVR and 95.2% in maxSUVR. Thurfjell et al. reported that the concordance rate between quantitative value (SUVR) and the visual evaluation of ^{18}F -flutemetamol PET images was 97.1–99.4% [19]. Our results are consistent with this report. Thus, quantitative evaluation was considered almost equivalent to visual evaluation by using the threshold.

The sensitivity, specificity, and accuracy were about 75–80% in both visual evaluation and quantitative evaluation. Jack et al. reported that 30% of NC, 60% of MCI, and 85–90% of AD subjects were positive using amyloid PET [20]. The diagnostic accuracy of our study was almost the same as that reported by Jack et al. In quantitative evaluation by maxSUVR, the sensitivity, specificity, and accuracy tended to be slightly higher than those of visual evaluation. A subject with MCI whom was visually negative became positive when assessed by maxSUVR. Conversely, two subjects with NC who were visually equivocal became negative when assessed by maxSUVR. Elsewhere, Yamane et al. also compared visual and quantitative evaluations using the J-ADNI data [13] and reported that some amyloid-negative cases with low mcSUVR were interpreted as positive by visual evaluation. These authors concluded that quantitative evaluation was useful, especially for subjects with mild amyloid accumulation with an SUVR of around 1.5. In our study, quantitative evaluation showed slightly higher diagnostic accuracy than that of visual evaluation when the SUVR was around the threshold. These results suggest that quantitative evaluation using amyloid PET is useful to a similar degree as with visual evaluation for diagnosing AD and may even show an advantage in the differentiation of subjects with borderline accumulation. Furthermore, Vandenberghe et al. reported that test–retest variabilities of regional SUVRs were 1–4% [21], so quantitative evaluation can be expected to yield high reproducibility. Further examination with more subjects of subject is required.

In this study, the diagnostic accuracy of maxSUVR was concordant with both the visual evaluation and mcSUVR. Relative to mcSUVR, one more subject was found to be true–positive using maxSUVR. The mcSUVR was the average of SUVR in five regions, while the maxSUVR was the highest SUVR among the regions. In cases with PiB accumulation in a small limited area, using mcSUVR, which is an average of a wider area, was considered to lead to an underestimation. Because the visual classification results were positive with PiB accumulation in only two gyri, maxSUVR is considered to provide similar results relative to visual classification. Thurfjell et al. reported that the concordance with visual classification was slightly higher in SUVR calculated by small and narrow composite regions as compared with larger ones [19]. Large regions are considered to be more affected by partial-volume effects. The maxSUVR may improve sensitivity for the evaluation of amyloid PET.

Some limitations in the present study exist. First, the diagnostic accuracy was not significantly different between the modalities; therefore, increasing the number of cases is necessary. Also, the examination of subjects with more advanced AD may provide different results. Furthermore, ^{18}F –labeled pharmaceuticals received regulatory approval only recently. In the future, we should examine the usefulness of our method for ^{18}F –labeled amyloid PET.

Conclusion

PET-only amyloid PET quantification is comparably useful to visual evaluation for diagnosing AD. The concordance rates between visual interpretation and quantitative evaluation were 94.6% in mcSUVR and 95.2% in maxSUVR. The quantification of amyloid PET would be useful, especially among for subjects with mild A β plaque accumulation in the brain.

Abbreviations

PET

Positron emission tomography; AD:Alzheimer's disease; Amyloid β :A β ; ^{11}C -PiB: ^{11}C -Pittsburgh Compound-B; SUVR:Standardised uptake value ratio; ROI:Region of interest; AAL:Automatic-anatomical-labeling; EPP:Empirically PiB-prone; J-ADNI:Japanese-Alzheimer's disease neuroimaging initiative; NC:Normal control; MCI:Mild cognitive impairment; mcSUVR:Mean cortical SUVR; maxSUVR:Maximum SUVR;

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by Kyushu University Institutional Review Board for Clinical Research (29-83).

Consent for publication

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

Availability of data and material

The clinical datasets analyzed in this article are available from the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) database deposited in the National Bioscience Database Center Human Database, Japan (Research ID: hum0043.v1, 2016).

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

NS wrote the manuscript and performed the image analysis. MK contributed to perform the data analysis. GA and MS made substantial contributions to the conception and design of the study. All authors read and approved the final manuscript.

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Figures

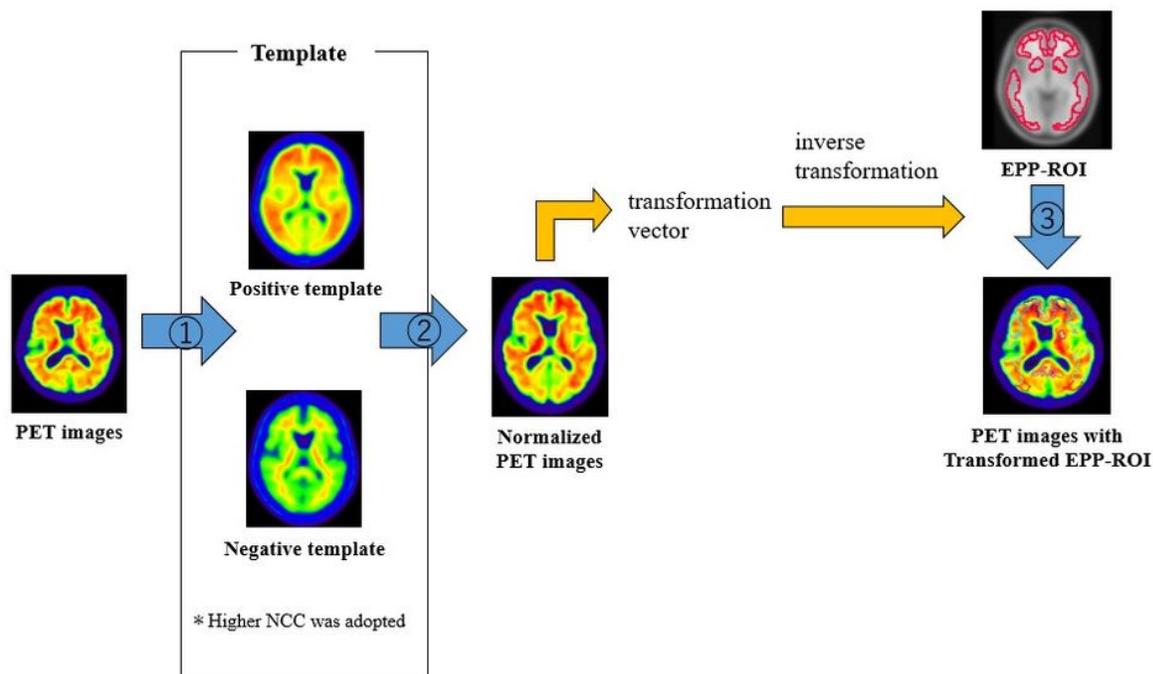


Figure 1

Scheme of the PET-only amyloid quantification method [10]. Transformation vectors for templates that more closely resemble the images were adopted. EPP-ROI was inversely transformed by using a transformation vector and placed on the individual PET scans. (NCC, normalized cross-correlation; EPP-ROI, empirically PiB-prone region of interest).

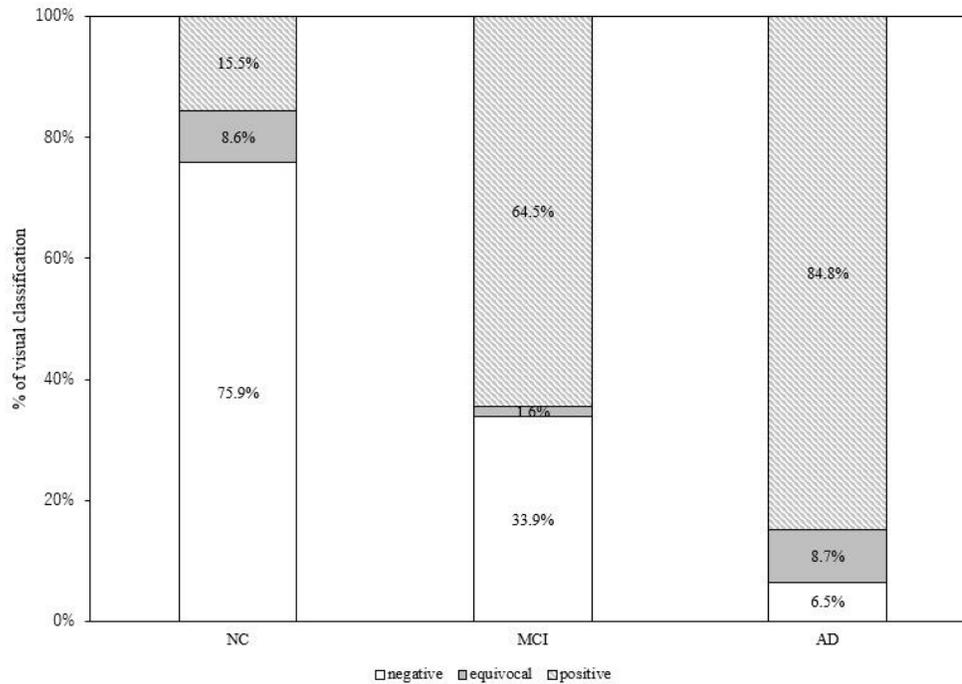


Figure 2

Visual evaluation of subjects in relation to clinical diagnosis. Most of the subjects with NC were PET – negative, while most with MCI and AD were PET–positive.

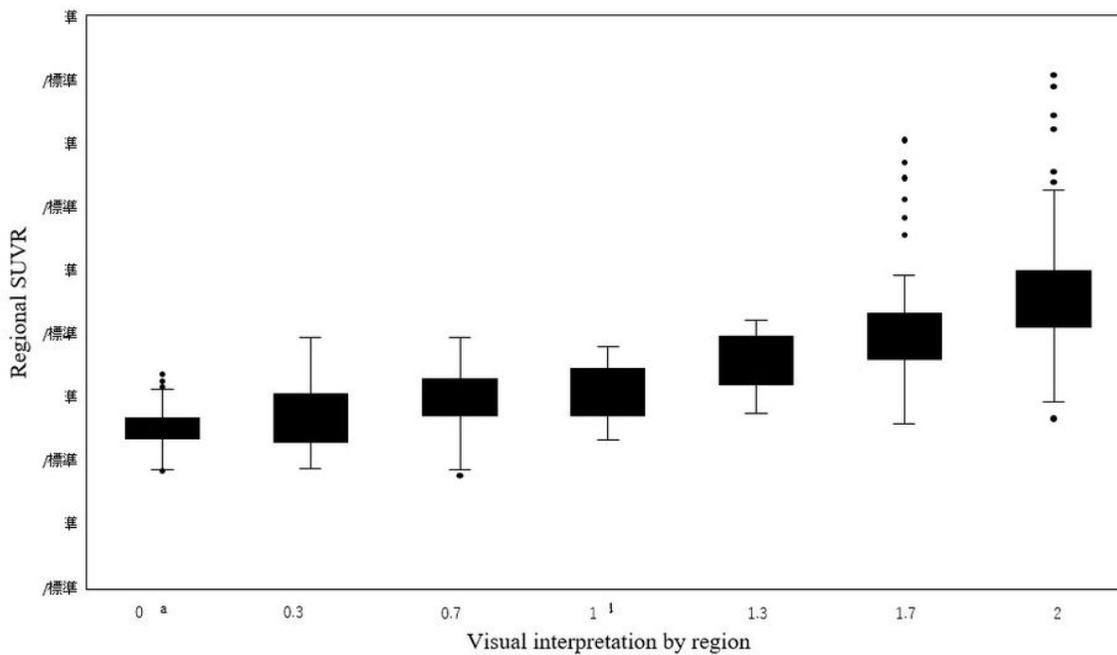


Figure 3

Relationship between visual interpretation by region and regional SUVR. Spearman's rank correlation coefficient for each region was $\rho = 0.87$ for the precuneus/posterior cingulate ($p < 0.05$), $\rho = 0.87$ for the frontal lobe ($p < 0.05$), $\rho = 0.86$ for the lateral temporal lobe ($p < 0.05$), and $\rho = 0.85$ for the lateral parietal lobe ($p < 0.05$).

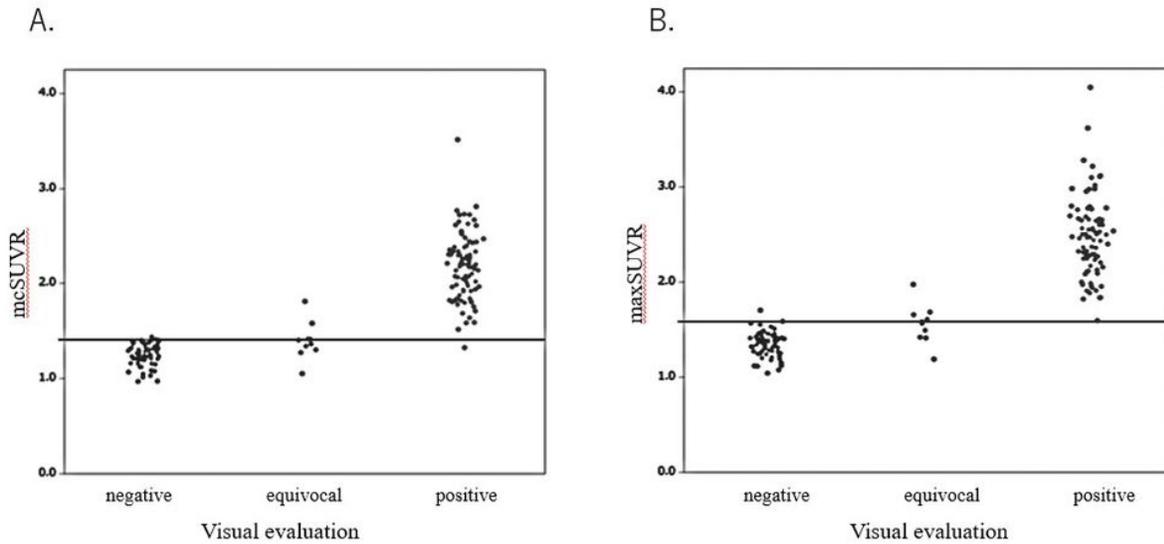


Figure 4

Relationship between visual evaluation and SUVR (A: mcSUVR, B: maxSUVR). Solid lines indicated cutoff values. The difference among visual classification was significant ($p < 0.05$).