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Comparison of perfusion ^{18}F-FP-CIT PET and ^{99m}Tc-ECD SPECT in parkinsonian disorders

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Abstract

Early and accurate identification of various conditions that can cause parkinsonian symptoms is important for determining treatment policies. Currently dopamine transporter (DAT) imaging using FP-CIT, glucose metabolism imaging using fluorodeoxyglucose, cerebral blood flow image using ethyl cysteinate dimer (ECD), and others are used for differentiation. However, the use of multiple modalities is inconvenient and costly. In the present retrospective study, we evaluated the correlation between regional brain uptake ratios (URs) in perfusion FP-CIT PET and ECD SPECT images.

Twenty patients with Parkinson's symptoms underwent perfusion DAT positron emission tomography (^{18}F-FP-CIT PET/CT) and cerebral blood flow tomography (^{99m}Tc-ECD SPECT) within a 2-week period. Perfusion ^{18}F-FP-CIT PET/CT and ^{99m}Tc-ECD SPECT URs of 19 brain regions (bilateral frontal, temporal, parietal and occipital lobes, bilateral caudate nucleus, bilateral putamen, bilateral insula, bilateral cingulate gyrus, bilateral thalamus, and brainstem) were directly compared and correlations were analyzed.

Average ^{18}F-FP-CIT PET/CT regional perfusion URs were higher than ^{99m}Tc-ECD SPECT URs. Uptake ratios were well correlated in all 19 regions (except right putamen), and especially in dopamine poor regions (cerebral cortex). In left putamen, URs were significantly correlated, but the correlation coefficient was lower than those of other regions.

A single tracer dual phase *N*-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane test seems to be helpful for differential diagnosis of parkinsonian disorders. Large-scale, longitudinal studies on complementary diseases with parkinsonian patterns are required to investigate differences in correlations between perfusion ^{18}F-FP-CIT PET/CT and ^{99m}Tc-ECD SPECT over time.

Abbreviations: APD = atypical parkinsonian disorders, DAT = dopamine transporter, ECD = ethyl cysteinate dimer, FDG = fluorodeoxyglucose, FP CIT = *N*-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane, IPD = idiopathic Parkinson's disease, MR = magnetic resonance, MSA = multiple system atrophy, PD = Parkinson disease, PET = positron emission tomography, PSP = progressive supranuclear palsy, SPECT = single-photon emission computed tomography, URs = uptake ratios.

Keywords: ECD SPECT, parkinsonian symptoms, perfusion FP-CIT PET

1. Introduction

Accurately identifying the various conditions that can cause parkinsonian symptoms, such as Parkinson disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), is challenging, but early identification is important for determining treatment strategies.[1] Typically, dopamine transporter (DAT) imaging is highly sensitive at detecting neurodegenerative parkinsonian disorders, but is poor at their differentiation.[2,3] Various methods such as DAT imaging by *N*-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl) nortropane (FP CIT), glucose metabolism imaging by fluorodeoxyglucose (FDG), or brain perfusion imaging by ethyl cysteinate dimer (ECD) are used for this purpose.[4–7] Van Laere et al[6] reported that dual-tracer DAT and perfusion single-photon emission computed tomography (SPECT) in combination with discrimination analysis allowed the automated, accurate differentiation of the most common forms of parkinsonism. ^{18}F-FDG positron emission tomography (PET) is helpful by showing preserved or raised lentiform nucleus glucose metabolism in in idiopathic Parkinson's disease (IPD), reduced metabolism in most cases of atypical parkinsonian disorders (APD),[8–10] and can be used for the differential diagnosis of parkinsonian disorders.[4,11]

Furthermore, many of the available tests are inconvenient and expensive, and thus, research continues to resolve these issues and devise simpler test methods. Previous studies have shown that glucose metabolism and cerebral perfusion are tightly coupled,[12,13] and thus, perfusion imaging can be used as an alternative to glucose imaging. ^{18}F-FP-CIT shows rapid tracer uptake increases in brain and a high extraction fraction rate after intravenous injection.[14] Images obtained within 10 minutes of intravenously injecting ^{18}F-FP-CIT well represent perfusion flow and glucose metabolism in brain.[1,15] In addition, early FP CIT imaging reflects perfusion, and thus, is helpful in Parkinson's disease and can be used as an alternative to glucose imaging.

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Several studies have evaluated the usefulness of perfusion imaging using ^{18}F-FP-CIT for the differential diagnosis of PD and Parkinson-plus syndrome.[1,16] Jin et al[16] reported that dual-phase ^{18}F-FP-CIT PET imaging might be useful for the differential diagnosis of atypical parkinsonism and for evaluating striatal DAT loss in neurodegenerative parkinsonism. However, no direct comparative study of ^{99m}Tc-ECD perfusion SPECT and early phase (perfusion) ^{18}F-FP-CIT PET has been performed, though they are considered to be well correlated because both reflect perfusion

In the present study, we compared uptake ratios (URs) determined by perfusion ^{18}F-FP-CIT PET and ^{99m}Tc-ECD perfusion SPECT in patients with parkinsonian symptoms.

2. Materials and methods

2.1. Subjects

This retrospective study included 20 patients (5 females and 15 males; mean age 69.1 ± 6.3 years) with parkinsonian symptoms such as tremor, bradykinesia and rigidity that underwent DAT positron emission tomography (^{18}F-FP-CIT PET) and cerebral blood perfusion tomography (^{99m}Tc-ECD SPECT) within a period of 2 weeks between January 1, 2018 and August 30, 2018. There was no cerebrovascular disease between ^{18}F-FP-CIT PET and ^{99m}Tc-ECD SPECT. The study was approved by the Institutional Review Board of Yeungnam University Hospital and the need for written informed consent was waived (IRB no. YUMC 2019-06-033).

2.2. Data acquisition

^{99m}Tc-ECD SPECT images were obtained 30 minutes after injecting ^{99m}Tc-ethyl cysteinate dimer (ECD, Neurolite, Dupont Pharma/Durham APS, Kastrup, Denmark) 925 MBq (25 mCi) using a SPECT camera (Discovery 630, GE Medical Systems, Milwaukee, WI). All patients were imaged in a standardized manner (supine, dimly lit room, low noise). Reconstruction was performed by filtered backprojection using a Butterworth filter (order, 10: cutoff, 0.3). Uniform Chang attenuation correction (AC) was used to compensate for photon attenuation.

Perfusion ^{18}F-FP-CIT PET images were obtained using a PET/CT unit (Discovery 710, GE Medical Systems, Milwaukee, WI). Antiparkinsonian drugs were stopped 12 hours before scans. All patients underwent an emission scan after injecting 185 MBq (5 mCi) of ^{18}F-FP-CIT. Perfusion PET/CT image acquisition was performed within 10 minutes of intravenously injecting ^{18}F-FP-CIT. Brain CT was performed in helical mode at auto mAs (50–200 mAs) and 120 kVp. ^{18}F-FP-CIT PET images were acquired in the 3-dimensional (3D) mode for 10 minutes. Reconstruction was performed by iterative reconstruction with 20 subsets/2 iterations. The matrix size for AC was 128 × 128, and a 2.57 mm Gaussian filter and a fully 3D iterative algorithm (VUE Point HD) were applied. Late ^{18}F-FP-CIT PET images were obtained using a PET/MR unit (Biograph mMR, Siemens Medical Solution, Hoffman Estates, Knoxville, TN) 3 hours after intravenous injection to assess striatal DAT binding patterns. The PET/MR imaging acquisition protocol was as follows; iterative reconstruction with 21 subsets/5 iterations, and a matrix size of 344 × 344 using a 4 mm Gaussian post reconstruction filter. All 20 patients underwent MR imaging with an ultrashort echo time sequence conducted with a repetition time of 11.94 ms, echo time 1 of 0.07 ms, echo time 2 of 2.46 ms, field of view 300 × 300 mm, matrix size 192 × 192, and flip angle 10°. PET data were acquired over a single bed position over 20 minutes and 30 cm, which covered the head and neck. PET/MR systems used segmentation-based AC based on attenuation maps derived from MR images.

2.3. Data analysis

The perfusion images of DAT positron tomography (PET) and cerebral blood flow tomography (SPECT) were interpreted by visual inspection and using quantitative regional uptake values for spatially normalized perfusion PET and SPECT images using Pmod Software Ver. 3.6 (Pmod Technologies Ltd, Adliswil, Switzerland). The T1-weighted MR brain images were loaded using Pmod in the HFS (Head First Supine) direction. Space normalization was performed after rigid matching on the MRI T1 brain template. After loading the PET/SPECT image in the HFS direction, the transformation matrix obtained during MR T1 image normalization was applied to PET/SPECT. After determining the ROI of cerebellum using Hammer's atlas, intensity normalization was performed by dividing the entire area by the average SUV value of the cerebellum area. URs were defined as 19 VOI counts (bilateral frontal, temporal, parietal and occipital lobes, bilateral caudate nucleus, bilateral putamen, bilateral insula, bilateral cingulate gyrus, bilateral thalamus, and brainstem) divided by whole cerebellar count. URs obtained by ^{18}F-FP-CIT PET/CT and ^{99m}Tc-ECD SPECT were directly compared and correlations were analyzed using Pearson's correlation analysis. URs in PET/CT and SPECT images were compared using the *T* test. Probability values of <.05 were considered statistically significant.

3. Results

Visual inspection of late ^{18}F-FP-CIT PET/MR scans showed 10 of the 20 patients exhibited IPD, 1 patient showed multiple system atrophy-C (MSA-C), and 1 showed PSP, criteria were based on subregional patterns of preferential striatal DAT loss.[17] PET images with PD showed preferential DAT loss in dorsal posterior putamen (PP), PSP showed preferential DAT loss in caudate nucleus and putamen. MSA showed preferential DAT loss in ventral putamen and dorsal PP. The other 8 patients had normal FP-CIT findings. Figure 1 shows a transaxial ^{99m}Tc-ECD SPECT image and corresponding perfusion ^{18}F-FP-CIT PET/CT and late ^{18}F-FP-CIT PET/MR images of an IPD patient. Clinical diagnosis based on cardinal symptoms, clinical features, neurologic examination, and diagnostic criteria (movement rating scale & neuropsychiatric inventory) such as UPDRS. In the case of PSP, mandatory exclusion and supportive criteria were used. Demographic features of 20 patients are reported in Table 1.

Average regional perfusion ^{18}F-FP-CIT PET URs were higher than ^{99m}Tc-ECD SPECT URs. Uptake ratios were significantly higher in bilateral frontal and right temporal lobes and in bilateral putamen and thalamus (Table 2).

^{18}F-FP-CIT PET/CT and ^{99m}Tc-ECD SPECT URs were well correlated for all regions (except right putamen), and were especially well correlated for cerebral cortex (correlation coefficients: right frontal 0.896, left frontal 0.891, right temporal 0.897, left temporal 0.885, right parietal 0.895, left parietal 0.901, right occipital 0.848, left occipital 0.862, right caudate nucleus 0.762, left caudate nucleus 0.764, right putamen 0.265,

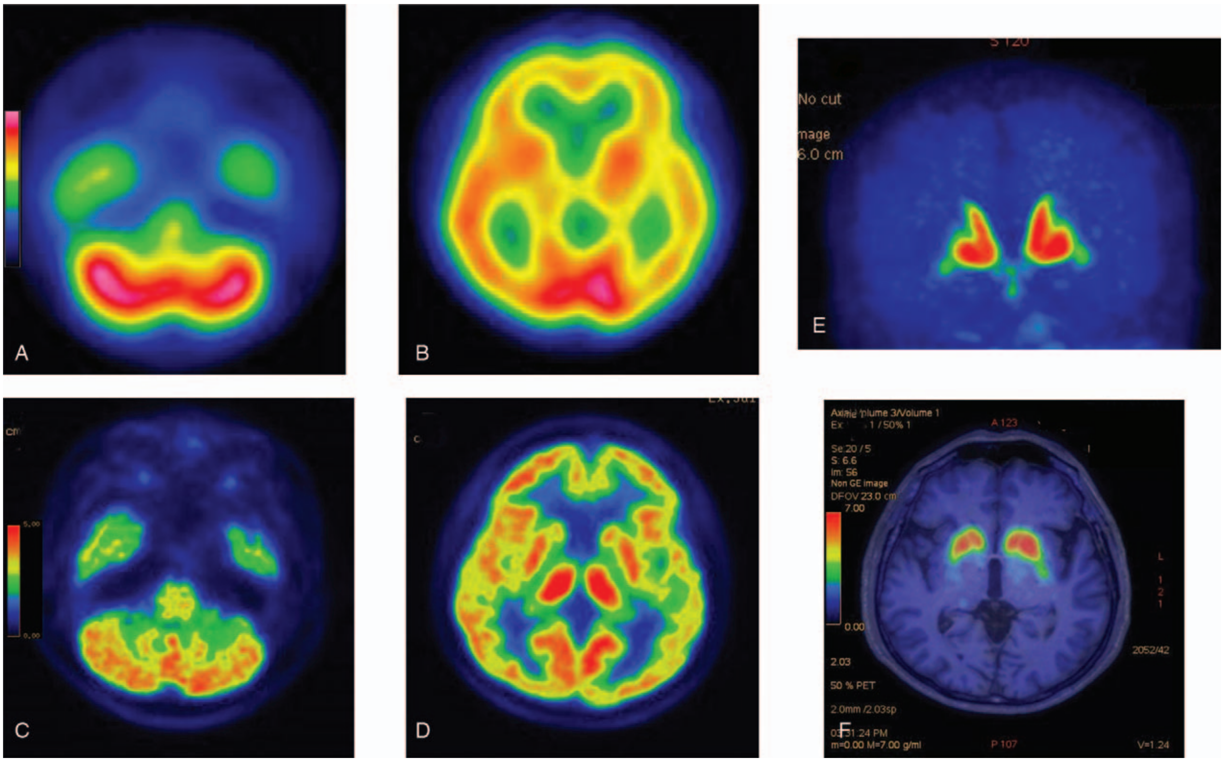

Figure 1. Parkinson disease patient (patient no. 4). (A, B) Transaxial perfusion SPECT images of ^{99m}Tc-ECD. (C, D) Transaxial perfusion PET images of ^{18}F-FP-CIT PET/CT. (E, F) Maximum intensity projection (MIP) and transaxial fusion images of late ^{18}F-FP-CIT PET/MR.

left putamen 0.487, right thalamus 0.787, left thalamus 0.818, right insula 0.8, left insula 0.656, right cingulate gyrus 0.832, left cingulate gyrus 0.821, and brainstem 0.619). For left putamen, the correlation coefficient was significant but lower than for other regions (Fig. 2).

4. Discussion

We investigated the correlation between regional URs obtained by perfusion ^{18}F-FP-CIT PET and ^{99m}Tc-ECD SPECT. We found that URs of all brain regions (except right putamen) were significantly correlated.

Table 1

Demographic features of 20 patients with parkinsonian symptoms.

Patient no.	Sex/age	Clinical diagnosis	Symptom duration (yr)	Late FP CIT finding	UPDRS III score
1	F/67	PD	2.5	PD	26
2	M/61	PD	5	PD	19
3	M/75	N	7	DLB	52
4	M/69	PD	1.5	PD	32
5	M/69	PD	3	PD	15
6	M/76	PD	0.7	PD	27
7	M/77	PD	1.6	PD	20
8	M/72	N	8	DLB	2
9	M/73	PD	4	PSP	45
10	M/78	N	7	MSA	29
11	F/74	N	10	ET	41
12	F/62	MSA	1	MSA	4
13	M/68	PSP	3	PSP	48
14	F/59	N	0.4	DIP	44
15	F/62	PD	0.4	PD	19
16	M/61	N	0.1	DIP	57
17	M/67	N	11	MSA	26
18	M/77	N	9	ET	32
19	M/75	PD	6	PD	39
20	M/60	PD	0.5	PD	14

DIP = drug induced parkinsonism, DLB = dementia with Lewy body, ET = essential tremor, MSA = multiple system atrophy, N = normal, PD = Parkinson disease, PSP = progressive supranuclear palsy.

Table 2

URs of 20 patients in perfusion ^{18}F-FP-CIT PET/CT and ^{99m}Tc-ECD SPECT images for all VOIs.

Anatomic region	Early FP CIT PET (mean ± SD)	ECD SPECT (mean ± SD)	*T* test (*P* value)
Right frontal	0.89 ± 0.09	0.8 ± 0.08	.004
Left frontal	0.88 ± 0.1	0.82 ± 0.07	.02
Right temporal	0.81 ± 0.1	0.74 ± 0.07	.013
Left temporal	0.79 ± 0.09	0.76 ± 0.08	.247
Right parietal	0.89 ± 0.1	0.83 ± 0.08	.057
Left parietal	0.87 ± 0.1	0.84 ± 0.08	.204
Right occipital	1.11 ± 0.12	1.05 ± 0.11	.168
Left occipital	1.07 ± 0.13	1.05 ± 0.1	.601
Right caudate nucleus	0.61 ± 0.23	0.49 ± 0.16	.084
Left caudate nucleus	0.62 ± 0.22	0.51 ± 0.16	.102
Right putamen	1.31 ± 0.13	0.98 ± 0.11	<.001
Left putamen	1.27 ± 0.13	1.00 ± 0.11	<.001
Right thalamus	1.03 ± 0.12	0.7 ± 0.13	<.001
Left thalamus	0.99 ± 0.13	0.69 ± 0.13	<.001
Right insula	0.94 ± 0.11	0.87 ± 0.1	.062
Left insula	0.91 ± 0.1	0.85 ± 0.09	.068
Right cingulate gyrus	0.89 ± 0.14	0.8 ± 0.1	.033
Left cingulate gyrus	0.87 ± 0.13	0.8 ± 0.09	.057
Brainstem	0.91 ± 0.06	0.74 ± 0.05	<.001

Precise and early discrimination of diseases such as IPD, MSA, and PSP, which can cause Parkinson's symptoms, is important for determining treatment policies, but it is difficult to differentiate them during early disease stages. Various methods are used to differentiate these conditions, such as FP-CIT DAT images, FDG PET glucose metabolism images, ECD or HMPAO brain perfusion SPECT images, or diffusion-weighted magnetic resonance (MR) images.[4,6,7]

DAT imaging with ^{18}F-FP-CIT PET is highly sensitive at detecting parkinsonian disorders, such as PD and APD, but poor at their differentiation,[1,14] although it is useful for excluding essential tremor, drug induced parkinsonism, vascular parkinsonism, and Alzheimer's disease.[16]^{18}F-FDG PET is a well-established modality for the differential diagnosis of parkinsonism and helpful for revealing preserved or raised glucose metabolism of the lentiform nucleus in IPD and reduced glucose metabolism in the majority of APD cases.[1,16] Perfusion imaging with ECD or HMPAO may also be helpful, because regional cerebral perfusion is usually coupled to cerebral metabolism.[1,16] Accurate diagnoses often require FDG PET or perfusion SPECT and DAT imaging, but there are inconveniences, such as the radiation exposures and high costs involved,[14] and thus, more cost-effective, simpler methods are required.

^{18}F-FP-CIT PET shows rapid tracer uptake increase in brain and early perfusion uptake of FP CIT in dopamine-poor regions (e.g., cerebral cortex and cerebellum) peaks around 10 minutes after injection.[14] Furthermore, early imaging within 10 minutes of injecting ^{18}F-FP-CIT well represents perfusion flow and mimics glucose metabolism in brain. In 1 study, early (perfusion) ^{18}F-FP-CIT PET and ^{18}F-FDG PET images were compared[1] and regional cerebral uptake of perfusion FP CIT correlated well to that of the FDG images. However, differences between perfusion and metabolism exist. They[1] reported that hyperperfusion is evident in putamen, midbrain, and cerebellum and hypoperfusion is observed in the superior frontal lobe.

Recent comparative studies on cerebral perfusion SPECT and FP CIT PET for the differentiation of patients with Parkinson's symptoms have compared delayed FP CIT PET images rather than perfusion FP CIT PET images, and no study has directly compared perfusion FP CIT PET and cerebral perfusion SPECT in this context. Accordingly, the present study was undertaken to determine whether perfusion FP CIT PET URs correlate well with cerebral perfusion ECD SPECT URs, because if the URs of perfusion dopamine PET images obtained by ^{18}F-FP-CIT PET and brain perfusion SPECT images obtained by ^{99m}Tc-ECD are similar, a single tracer dual phase FP CIT PET test might facilitate the differentiation of patients with parkinsonian symptoms.

Our results show good correlation between the URs of ^{18}F-FP-CIT PET and ^{99m}Tc-ECD SPECT for all regions except right putamen and a relatively low correlation, but significant correlation, for left putamen. Jin et al[1] reported that early ^{18}F-FP-CIT PET images correlated well with FDG, especially in dopamine-poor brain regions, such as the frontal cortex and cerebellum. In dopamine-rich brain regions, such as putamen and midbrain, the correlation was poor with time.

In the present study, an inconsistency between perfusion ^{18}F-FP-CIT PET images and ^{99m}Tc-ECD SPECT images was in right putamen, a dopamine-rich region. Even though images were taken within 10 minutes, it seems that wash out and DAT uptakes differed, probably due to kinetic differences between brain regions.[1] Therefore, it appears optimal timing of perfusion ^{18}F-FP-CIT PET plays a role in determining whether it reflects correct perfusion. Furthermore, the different drug kinetics and resolutions of PET and SPECT are also likely to influence results.

Even though our datasets are small, our study shows a single tracer dual phase FP CIT PET test maybe helpful for differential diagnosis of parkinsonian disorders. We recommend larger-scale studies be conducted on diseases with different parkinsonian patterns to examine correlations between ^{18}F-FP-CIT PET and ^{99m}Tc-ECD SPEC URs over time.

Author contributions

Data curation: KyungAh Chun, EunJung Kong, IhnHo Cho.
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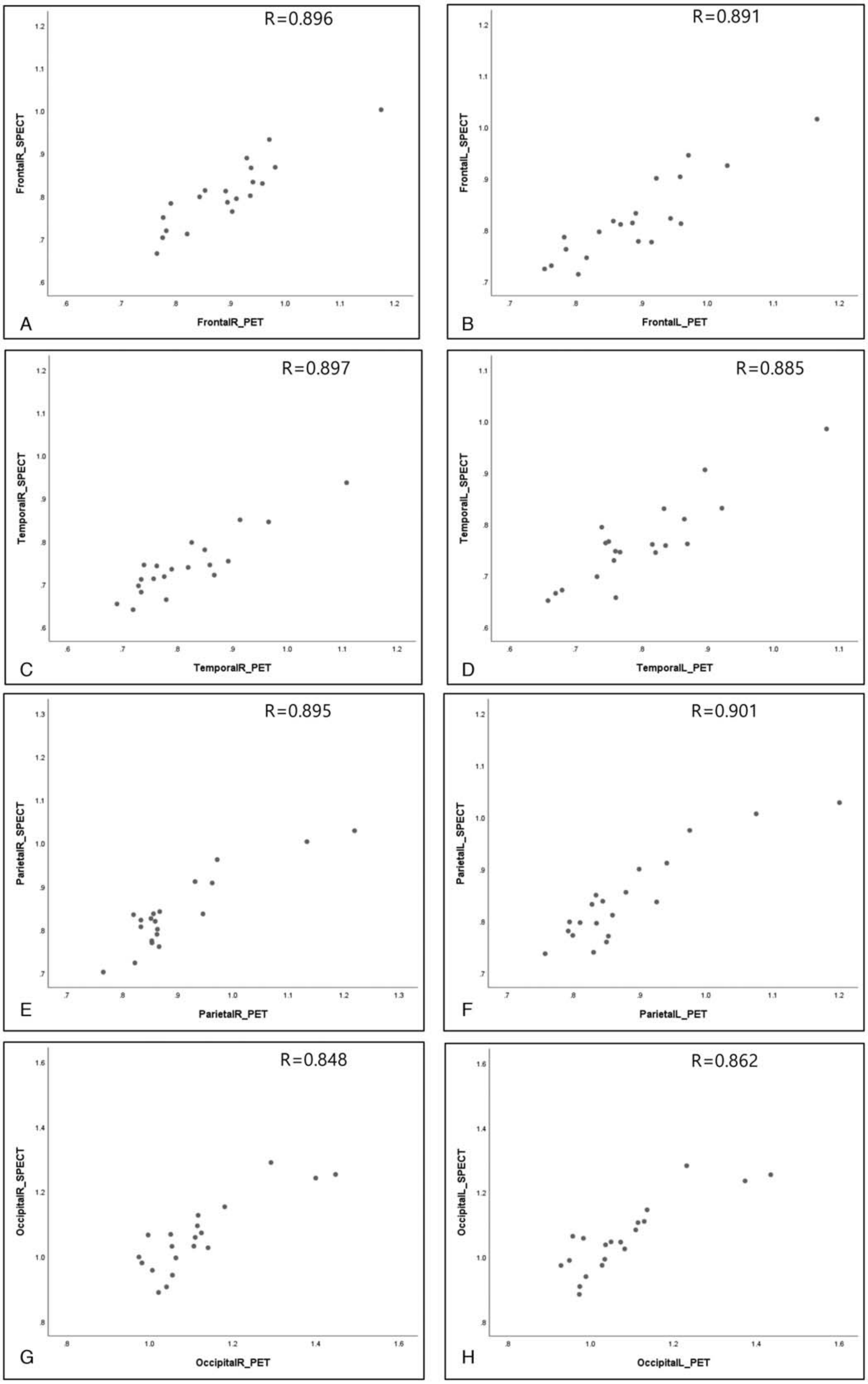
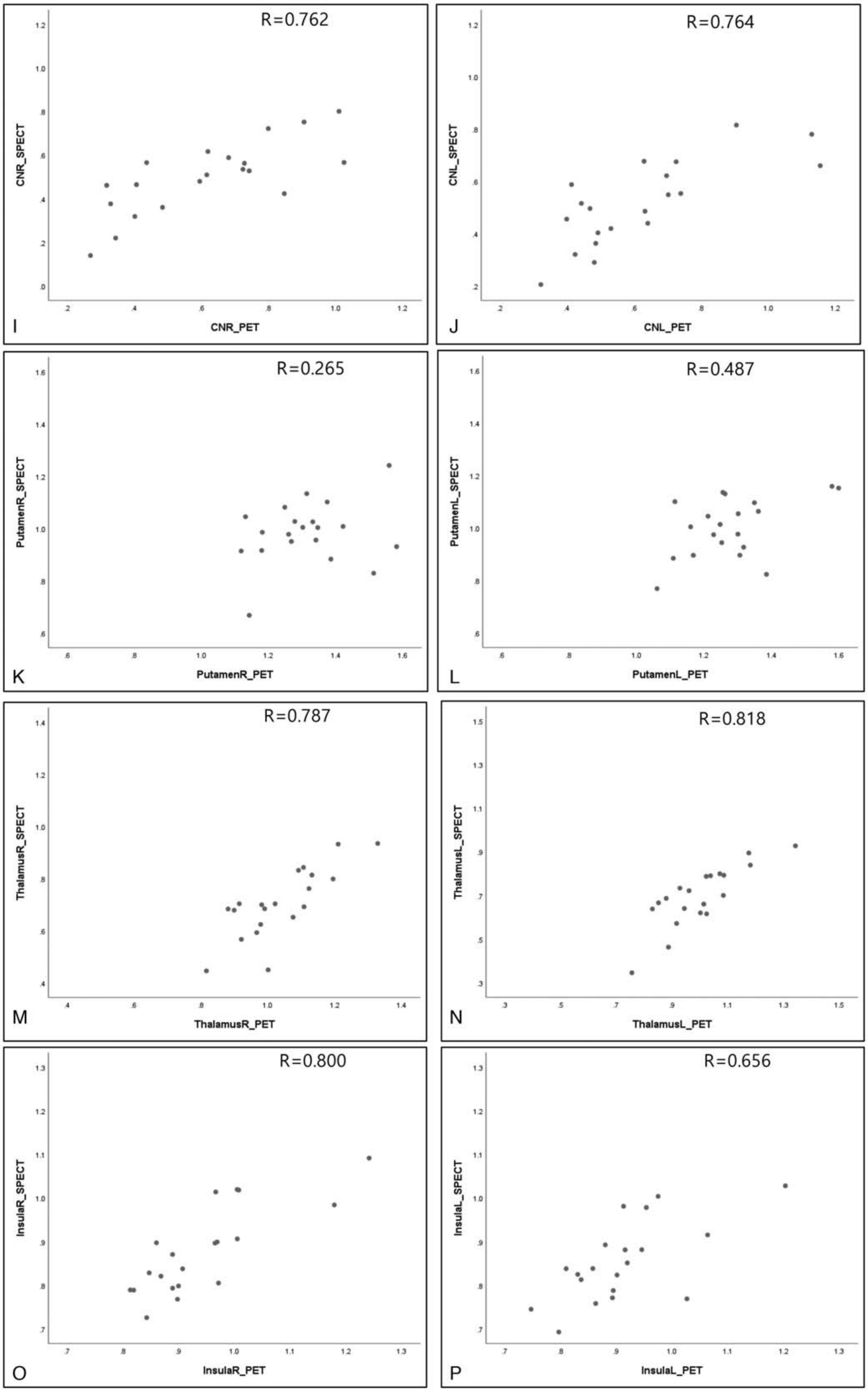


Figure 2. Correlations between regional uptake ratios (URs) as determined using perfusion ^{18}F-FP-CIT PET/CT and ^{99m}Tc-ECD SPECT images. Right frontal (A), left frontal (B), right temporal (C), left temporal (D), right parietal (E), left parietal (F), right occipital (G), left occipital (H), right caudate nucleus (I), left caudate nucleus (J), right putamen (K), left putamen (L), right thalamus (M), left thalamus (N), right insula (O), left insula (P), right cingulate gyrus (Q), left cingulate gyrus (R) and brainstem (S).



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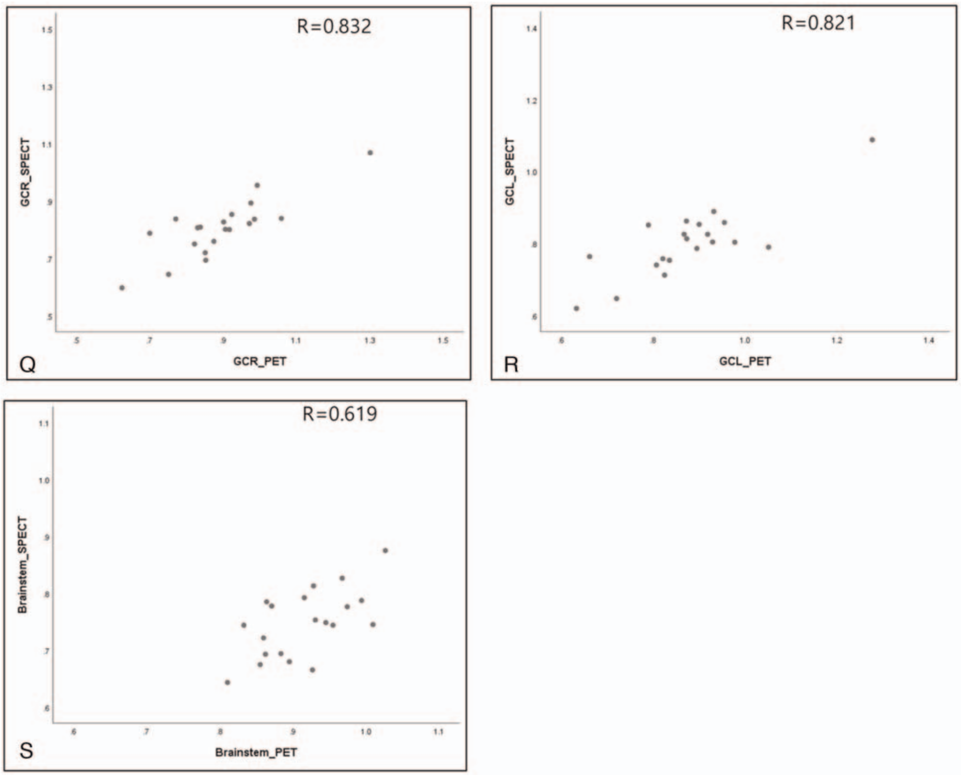

Figure 2. Continued.

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