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THE EFFECT OF 18F-FDG-PET IMAGE RECONSTRUCTION ALGORITHMS ON THE EXPRESSION OF CHARACTERISTIC METABOLIC BRAIN NETWORK IN PARKINSON'S DISEASE

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Abstract

PURPOSE—To evaluate the reproducibility of the expression of Parkinson's Disease Related Pattern (PDRP) across multiple sets of 18F-FDG-PET brain images reconstructed with different reconstruction algorithms.

METHODS—18F-FDG-PET brain imaging was performed in two independent cohorts of Parkinson's disease (PD) patients and normal controls (NC). Slovenian cohort (20 PD patients, 20 NC) was scanned with Siemens Biograph mCT camera and reconstructed using FBP, FBP+TOF, OSEM, OSEM+TOF, OSEM+PSF and OSEM+PSF+TOF. American Cohort (20 PD patients, 7 NC) was scanned with GE Advance camera and reconstructed using 3DRP, FORE-FBP and FORE-Iterative. Expressions of two previously-validated PDRP patterns (PDRP-Slovenia and PDRP-USA) were calculated. We compared the ability of PDRP to discriminate PD patients from NC, differences and correlation between the corresponding subject scores and ROC analysis results across the different reconstruction algorithms.

RESULTS—The expression of PDRP-Slovenia and PDRP-USA networks was significantly elevated in PD patients compared to NC ($p < 0.0001$), regardless of reconstruction algorithms. PDRP expression strongly correlated between all studied algorithms and the reference algorithm

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CONFLICT OF INTEREST: none.

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($r = 0.993$, $p < 0.0001$). Average differences in the PDRP expression among different algorithms varied within 0.73 and 0.08 of the reference value for PDRP-Slovenia and PDRP-USA, respectively. ROC analysis confirmed high similarity in sensitivity, specificity and AUC among all studied reconstruction algorithms.

CONCLUSIONS—These results show that the expression of PDRP is reproducible across a variety of reconstruction algorithms of 18F-FDG-PET brain images. PDRP is capable of providing a robust metabolic biomarker of PD for multicenter 18F-FDG-PET images acquired in the context of differential diagnosis or clinical trials.

Keywords

Parkinson's disease; FDG-PET; reconstruction algorithms; specific metabolic brain networks

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative brain disorder. Its diagnosis is made by clinical examination and may be challenging in the early phases [1,2], particularly the differential diagnosis of PD in relation to less common parkinsonian syndromes. Parkinson's disease related pattern (PDRP) is a specific functional network, which displays covarying metabolic changes in spatially distributed brain regions that are functionally interconnected. PDRP was initially identified in a group of PD patients and healthy controls in the USA [3] using 18F-FDG-PET imaging and network analysis – a multivariate spatial covariance technique based on scaled subprofile model/principal component analysis (SSM/PCA) [4]. Later it was replicated in additional independent PD patient populations [5–7] including the Slovenian one by our research group [8].

PDRP is characterized by increased metabolic activity in pallidum, putamen, thalamus, brain stem and cerebellum, along with reduced metabolic activity in posterior parietal/occipital regions and frontal cortex (Figure 1). These metabolic changes may not be fully accounted for in purely visual evaluation of 18F-FDG-PET images or in voxel-by-voxel image comparison using univariate methods such as Statistical Parametric Mapping (SPM). PDRP expression can be measured prospectively in individual subject's 18F-FDG-PET brain images as a PDRP subject score [5,9,10]. It is calculated using Topographic Profile Rating (TPR) technique [4]. PDRP expression or subject score correlates with a variety of clinical measures and can be used for improving early and differential diagnosis of parkinsonian syndromes in conjunction with analogous metabolic brain networks associated with atypical parkinsonian syndromes as already being used in clinical practice in few centers worldwide [11,12].

The aim of this study was to evaluate the reproducibility of PDRP expression across different image reconstruction algorithms. The reproducibility was tested on two patterns: PDRP-Slovenia, which was identified recently [8] and the original PDRP identified by Eidelberg's group (PDRP-USA) [3]. Both patterns have already been validated in the independent patient groups using the same protocols of image acquisition and reconstruction as used for their identification. The effect of reconstruction algorithms on PDRP expression

has only been studied empirically by now, using independent patient data from different scanners [6,13,14].

In this study, PDRP expression was compared across 18F-FDG-PET brain images reconstructed by different image reconstruction algorithms in each of the two studied patient cohorts (i.e. Slovenian and American), each scanned by the same PET scanners. This has never been systematically examined before.

Reconstruction algorithms used in clinical practice in the corresponding institutions/scanners were evaluated. For the analysis of PDRP-Slovenia we studied common reconstruction methods available in Siemens Biograph mCT scanner: analytic 3D filtered-backprojection (FBP) algorithm, iterative ordered-subsets expectation-maximization (OSEM) algorithm, OSEM combined with point spread function (PSF) [15] modeling (OSEM+PSF), all three with and without time of flight (TOF) [16]. PDRP-USA was examined with analytic 3D reprojection (3DRP) algorithm [17] and with Fourier rebinning (FORE) technique [18] combined with FBP (FORE-FBP) and iterative (FORE-Iterative) [19] reconstruction, all available with GE Advance PET scanner. We assessed the reproducibility of each pattern's ability to discriminate PD patients from healthy controls based on PDRP subject score calculations. Additionally, we evaluated the differences between subject scores calculated from different reconstruction algorithms and performed correlation among corresponding subject scores. The receiver operating characteristic (ROC) analysis was performed and its results were compared across different reconstruction algorithms. Finally, we examined the effect of the preprocessing Gaussian filter width as well as the effect of number of iterations, on one additional test PD patient.

MATERIALS AND METHODS

IMAGE ACQUISITION AND PROCESSING

We studied two cohorts of PD and healthy control subjects whose demographic and clinical characteristics are given in Table 1. One additional PD patient (male, age 64.9 yrs, disease duration 4.9 yrs) was recruited for the study of reconstruction parameter variation.

All PD patients were diagnosed by movement disorders specialists based on the UK brain bank criteria [20]. Study participants were fasting overnight prior to 18F-FDG-PET scanning and were placed to rest in a quiet dimly-lit room with eyes closed during radiotracer uptake and imaging.

20 PD patients from University Medical Centre Ljubljana (UMCL) and 20 age-matched normal controls (NC) who comprised Slovenian Cohort as well as the additional PD patient underwent 18F-FDG-PET brain scanning between 30–40 min post-injection with Siemens Biograph mCT PET/CT. Slovenian Cohort brain scans were reconstructed into a 400×400×110 matrix with a voxel size 1.02×1.02×3mm³ and Gaussian postprocessing filter of FWHM 4 mm, using six different reconstruction algorithms: FBP, FBP+TOF, OSEM (6 iterations, 24 subsets), OSEM+TOF (6 iterations, 21 subsets), OSEM+PSF (6 iterations, 24 subsets) and OSEM+PSF+TOF (6 iterations, 21 subsets). Brain scan of the one test PD patient was reconstructed with all six reconstruction algorithms using different Gaussian

filter FWHMs (from 1 to 10 mm) and the four iterative algorithms with different number of iterations (from 1 to 12).

Brain images of Slovenian Cohort and test patient were used for further validating PDRP-Slovenia which has been identified at this institution previously [8] in an independent cohort of PD patients and healthy controls using the same scanning protocol and OSEM+PSF+TOF image reconstruction algorithm.

American Cohort comprised of 20 PD patients and 7 NC who underwent 18F-FDG-PET brain scanning between 35–45 min post-injection with GE Advance tomograph at North Shore University Hospital, Manhasset, New York[21]. American Cohort brain scans were reconstructed into 128×128 matrix with a voxel size 2.34×2.34×4.25mm³ using three different reconstruction algorithms: 3DRP algorithm with transaxial Hanning filter with cutoff 6.0 mm and axial Ramp filter with cutoff 8.5 mm, FORE-FBP algorithm with transaxial Hanning filter with cutoff 6.0 mm and FORE-Iterative (4 iterations, 16 subsets) with postprocessing filter of 6.0 mm FWHM and loop filter of 4.3 mm FWHM. Attenuation correction was performed using PET transmission scan acquired after radiotracer injection.

Brain images of American Cohort were used for validating PDRP-USA which was identified at that center from scans acquired using the same imaging protocol and 3DRP image reconstruction algorithm [3].

All images were preprocessed using SPM5 software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London; <http://www.fil.ion.ucl.ac.uk/spm/software/SPM5/>) running in Matlab 7.0 (MathWorks Inc.). They were spatially normalized into a standard Montreal Neurological Institute (MNI) based PET template and smoothed using a Gaussian kernel of 10×10×10mm³ FWHM. Examples of reconstructed images for one PD patient from each Cohort are shown in Supplemental_file_1.

CALCULATION OF PDRP EXPRESSION

Voxel-based TPR algorithm in scanvp software (Center for Neurosciences at The Feinstein Institute for Medical Research, NY, USA; <http://www.feinsteinneuroscience.org>) was used to calculate subject scores of metabolic network expression of PDRP-Slovenia and PDRP-USA in images from Slovenian Cohort and test PD patient, and American Cohort respectively. Subject scores were Z-transformed using mean and standard deviation of the corresponding NC group for PDRP network identification. Therefore the unit (1.00) subject score equals to one standard deviation of the subject scores of the NC group in the identification of PDRP.

COMPARISON OF SUBJECT SCORES ACROSS RECONSTRUCTION ALGORITHMS

In the analysis of both Slovenian and American PDRP patterns we compared corresponding subject scores for PD and NC subjects across reconstruction algorithms. As a reference method we chose the reconstruction algorithm which was used in generating 18F-FDG-PET images for the original PDRP network identification procedures; OSEM+PSF+TOF in the case of PDRP-Slovenia and 3DRP in PDRP-USA.

STATISTICAL ANALYSIS

For each reconstruction algorithm we (i) assessed the ability of PDRP expression to differentiate between PD and NC groups using Student's independent-sample t-test; (ii) compared PDRP subject scores to PDRP subject score from the reference reconstruction algorithm by measuring differences using Student's paired t-test and independent sample t-test and by calculating Pearson correlation coefficients between corresponding subject scores; (iii) evaluated the diagnostic power for discrimination of PD patients from NC subjects by performing ROC analysis and applying the network specific optimal cut-off value for the diagnosis of PD to determine sensitivity and specificity and area under curve (AUC).

Additionally, we compared changes in PDRP-Slovenia expression for different numbers of iterations and different postprocessing Gaussian filter FWHMs in one test PD patient.

All statistical analysis was performed using Origin software (OriginLab, Northampton, MA, USA) and considered significant for $p < 0.0001$.

RESULTS

Subject scores of both PDRP-Slovenia and PDRP-USA expression were significantly higher in PD patients compared to NC subjects in both Slovenian and American Cohort, for all the reconstruction algorithms ($p < 0.0001$, Figure 1, Tables 2 and 3).

Average differences between subject scores from the studied reconstruction algorithms and the reference reconstruction algorithm were between 0.61/0.73 (FBP) and 0.26/0.17 (OSEM +PSF) in the case of PD/NC group of Slovenian Cohort and PDRP-Slovenia; and between -0.02/-0.03 (FORE-FBP) and -0.08/-0.07 (FORE-Iterative) in the case of PD/NC group of American Cohort and PDRP-USA (Tables 2 and 3). Lower average PDRP-Slovenia subject scores are observed when incorporating TOF and PSF information (Table 2). Different reconstruction methods introduced a systematic shift in network scores which were highly significant in the case of Slovenian Cohort and PDRP-Slovenia ($p < 0.0001$, paired t-test) but less so in American Cohort and PDRP-USA ($p = 0.06$, paired t-test). Nonetheless the changes in these subject scores relative to those of the reference methods did not differ significantly between any two corresponding PD or NC groups ($p > 0.05$, independent-sample-t-test).

Corresponding subject scores for the reference reconstruction algorithm and the other reconstruction algorithms highly correlated in the individual groups of PD and NC subjects, for Slovenian Cohort and PDRP-Slovenia; and for American Cohort and PDRP-USA ($r = 0.993$, $p < 0.0001$, Tables 2 and 3, Figure 2).

ROC analysis confirmed that the expressions of PDRP-Slovenia as well as PDRP-USA significantly discriminate between PD and NC subjects for all reconstruction algorithms ($p < 0.001$; Tables 2 and 3). It can be observed that AUC varies from 0.945 for FBP and FBP +TOF to 0.950 for OSEM+PSF and OSEM+PSF+TOF in the case of PDRP-Slovenia, and is constant at 0.979 for all three reconstruction methods in the case of PDRP-USA. The network specific cut-off value for the diagnosis of PD was determined from PDRP

identification images and reference reconstruction algorithm, as the subject score with the optimal value of sensitivity and specificity. For PDRP-Slovenia the cut-off value was 1.00, when it was applied to different reconstruction algorithms, the values of sensitivity are 0.90 for FBP and 0.85 for other five studied algorithms; and specificity is from 0.79 for FBP to 0.90 for OSEM+PSF+TOF. For PDRP-USA the cut-off value was 1.34 and it yielded sensitivity 0.82 for 3DRP and 0.81 for FORE-FBP and FORE-Iterative; whereas specificity was constant at 1.00 for all studied reconstruction algorithms.

Effects of the Gaussian filter width variation and iteration number variation in the reconstruction of a test PET brain scan on PDRP-Slovenia subject score is presented in Supplemental_file_2.

DISCUSSION

In clinical practice it is often necessary to measure subject scores of a previously-validated PDRP network prospectively in new subjects with 18F-FDG-PET images reconstructed by different reconstruction algorithms even on the same scanner. It is thus important to carefully analyze this issue for further implementation of PDRP network as a metabolic brain biomarker across different populations and different PET scanners worldwide. Since SSM/PCA network analysis is a small-signal based algorithm [22], subtle effects of different 18F-FDG-PET image reconstruction processes can alter the spatial profiles of these signals and affect PDRP expression in individual subjects.

In this study we evaluated the effect of 18F-FDG-PET image reconstruction algorithms on the expression of Parkinson's disease specific metabolic brain pattern. To do so, we reconstructed 18F-FDG-PET images of Slovenian and American Cohorts of PD patients and NC with various commonly used reconstruction algorithms. Then we calculated the expression of PDRP-Slovenia and PDRP-USA in each of the corresponding images and compared the PDRP subject scores across the reconstruction algorithms. PDRP expression was studied in images reconstructed with analytical and iterative algorithms which are widely used in clinical brain PET studies. Since PDRP-Slovenia was evaluated in a new generation PET/CT scanner, it also allowed us to observe the effect of advanced PSF and TOF image reconstruction modeling. Postprocessing filter width and number of iterations in examining reconstruction methods in the group of subjects were fixed as commonly used in clinical practice; therefore we further investigated the stability of PDRP expression on variation of these two parameters in one additional subject.

The results of this study demonstrated that PDRP expression was significantly elevated in PD patients compared to NC regardless of the reconstruction algorithm. Subject scores of both, Slovenian and American PDRP networks strongly correlated among all studied reconstruction algorithms at $p < 0.0001$. Average differences from the reference algorithm subject scores were within 0.73 for PDRP-Slovenia and within 0.08 for PDRP-USA. The differences are mostly significant when measured with paired-t-test within each subject group but not significant when they are compared with unpaired-t-test between the subject groups. These results suggest that different reconstruction methods may introduce a systematic shift in network scores but they do not alter the ability of disease discrimination.

The ROC analysis further confirmed good diagnostic accuracy for the differentiation of PD patients from NC with specificity and sensitivity of 79–100 %. The AUC values as well as values of sensitivity and specificity were highly similar across the reconstruction algorithms.

In iteration number variation PDRP subject scores reached plateau very fast. Subject scores were increasing with smoothing but they were kept within 0.2 for usual Gaussian filter widths. This confirms good stability of PDRP expression in variation of iteration number and filter width. This result implies that although the parameters were fixed in our detailed study of reconstruction algorithms effect, the findings are valid for a wider range of parameter values.

To the best of our knowledge this is the first study to systematically investigate the effect of using a wide range of reconstruction algorithms to reconstruct the same 18F-FDG-PET data on the PDRP expression. Although this topic was not systematically studied previously, our results are in line with findings of some similar prior studies. Moeller et al. [13] computed PDRP subject scores for PD patients and healthy volunteers in four populations (22/20, 18/10, 25/15, 14/10 PD/NC subjects) each scanned with different tomographs (SuperPETT3000, GE Advance, ECAT 933-16, PC4600 respectively) and showed that the resulting PDRP scores discriminated PD patients from healthy volunteers in all four populations with comparable accuracy. Furthermore, PDRP subject scores correlated significantly with the corresponding subject scores for the disease-related patterns identified from each individual population's data. Analogous approach was used by Wu et al. [6] to study PDRP subject scores for two populations each comprised of 33 PD and 33 NC subjects and scanned with two PET cameras (Siemens Biograph 64 with FBP, GE Advance with 3DRP) as well as by our group [8] studying two populations of 20/20 and 33/33 PD/NC subjects with two PET cameras (Siemens Biograph mCT with OSEM+PSF+TOF, GE Advance with 3DRP). Results of both these studies confirmed the discrimination between PD and NC groups regardless of reconstruction algorithm and scanner type and an excellent correlation between corresponding subject scores. Peng et al. [14] used FDG PET scans from 23 PD patients in comparable disease stages from five medical centers in the USA scanned with five different PET cameras operating in 3D mode (GE Advance, Siemens HR +, Siemens HR, GE Advance Nxi, GE Discovery LS) and reconstructed with the reconstruction algorithm commonly used at each site (3DRP, Iterative, FBP, 3DRP, FORE-Iterative). They showed that there was no difference between PDRP scores for the ten patients from first site and the 13 patients from other sites despite the use of multiple scanner and image reconstruction methods.

The results published so far have appeared to indicate that PDRP developed and cross-validated in one cohort of patients and control subjects scanned at a single imaging center could be applied prospectively to quantify network activity for 18F-FDG-PET images acquired in other PET scanners with different reconstruction algorithms. For a complete understanding of reconstruction algorithms effect on PDRP, further exploration of this topic may be needed by evaluating the influence of different image reconstruction algorithms on the PDRP topography itself. To do so we aim to generate and compare various versions of PDRP from one set of raw 18F-FDG-PET scans of PD patient and NC subjects reconstructed by different reconstruction algorithms. The different versions of PDRP can be

compared and cross-validated using the same strategy as described in this article. Ultimately, this kind of effort is going to establish PDRP activity as a reliable biomarker for PD-related clinical and research applications across multiple medical centers worldwide.

CONCLUSION

We confirmed that the expression of characteristic metabolic brain network associated with PD is reproducible across different types of PET reconstruction algorithms. Our results, together with previous validations that showed the independence of this specific network expression from differences in PET imaging systems and image preprocessing tools, further confirm the robustness of PDRP as a specific metabolic biomarker suitable for its widest clinical and research applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1. Parkinson's Disease Related Pattern (PDRP) is a robust metabolic biomarker of PD
2. PDRP expression is reproducible across FDG-PET reconstruction algorithms (RA)
3. Different RA may shift PDRP expression but do not affect disease discrimination

Figure 1.

(A) PDRP-Slovenia; (B) Subject scores of PDRP-Slovenia for the PD patients (filled circles) and NC subjects (empty circles) in Slovenian Cohort for six reconstruction algorithms; (C) PDRP-USA; (D) Subject scores of PDRP-USA for the PD patients (filled circles) and NC subjects (empty circles) in American Cohort for three reconstruction algorithms. Pattern expression significantly differentiated PD and NC subjects in all cases. Group mean values and standard deviations are plotted besides individual values. Horizontal dash line marks the optimal cut-off value based on ROC analysis in identification cohort of each pattern.

Figure 2.

Correlations between corresponding subject scores of (A) OSEM and reference OSEM+PSF+TOF reconstruction algorithm for PDRP-Slovenia in Slovenian Cohort; and (B) FORE-Iterative and reference 3DRP reconstruction algorithm for PDRP-USA in American Cohort. Filled symbols represent PD patients and empty symbols represent NC subjects. Correlations for other algorithms are represented by correlation coefficients and p- values in Tables 2 and 3.

Figure 3. ROC curves for (A) PDRP-Slovenia and (B) PDRP-USA are shown for all studied image reconstruction algorithms. Corresponding ROC curves are highly similar among each other and confirm significant discrimination between PD and NC subjects

Table 1

Demographic characteristics of study participants

	Slovenian Cohort		American Cohort	
	PD patients	NC	PD patients	NC
N	20	20	20	7
Age [yrs]	71.8 ± 7.3	63.4 ± 10.6	66.0 ± 9.5	65.0 ± 12.0
Gender [M/F]	11/9	8/12	14/6	4/3
Disease duration [yrs]	4.5 ± 3.7	-	4.9 ± 4.0	-

Values are given as mean ± standard deviation.

Table 2

Comparison of PDRP-Slovenia subject scores for images reconstructed using different reconstruction algorithms

	OSEM+PSF+TOF	FBP	FBP+TOF	OSEM	OSEM+TOF	OSEM+PSF
PD subject score ^a	3.22 ± 2.18	3.83 ± 2.14	3.71 ± 2.15	3.71 ± 2.14	3.52 ± 2.12	3.47 ± 2.22
NC subject score	-0.67 ± 1.200	0.06 ± 1.15	-0.04 ± 1.14	-0.12 ± 1.17	-0.23 ± 1.16	-0.50 ± 1.20
<i>PD/NC Subject Scores compared to those of the reference reconstruction algorithm¹</i>						
PD score difference <i>b,c</i>	-	0.61 ± 0.17	0.50 ± 0.12	0.50 ± 0.16	0.30 ± 0.08	0.26 ± 0.17
PD - correlation coefficient	-	0.997	0.999	0.997	1.000	0.997
NC score difference <i>b,c</i>	-	0.73 ± 0.15	0.65 ± 0.14	0.55 ± 0.13	0.44 ± 0.07	0.17 ± 0.11
NC - correlation coefficient	-	0.993	0.995	0.995	0.999	0.996
<i>Receiver operating characteristic analysis</i>						
AUC ² (CI ³)	0.950 (0.831, 0.994)	0.945 (0.824, 0.992)	0.945 (0.824, 0.992)	0.948 (0.827, 0.993)	0.948 (0.827, 0.993)	0.950 (0.831, 0.994)
Sensitivity ⁴	0.85	0.90	0.85	0.85	0.85	0.85
Specificity ⁴	0.90	0.79	0.80	0.84	0.85	0.89

Values are given as mean ± standard deviation.

¹ OSEM+PSF+TOF algorithm² AUC = area under curve in the receiver operating characteristic analysis³ CI = 95% confidence interval (lower bound, upper bound)⁴ Sensitivity and specificity at the optimal cut-off value determined at pattern identification^a p < 0.0001; compared to the NC subject score (independent sample t-test).^b p < 0.0001; method-difference within-group compared to the reference reconstruction algorithm (paired t-test).^c p > 0.05; method-difference between-groups compared to the reference reconstruction algorithm (independent sample t-test).

Table 3

Comparison of PDRP-USA subject scores for images reconstructed using different reconstruction algorithms

	3DRP	FORE-FBP	FORE-Iterative
PD subject score ^a	2.82 ± 1.33	2.79 ± 1.35	2.74 ± 1.34
NC subject score	0.12 ± 0.76	0.09 ± 0.76	0.05 ± 0.71
<i>PD/NC Subject Score comparison to reference reconstruction algorithm¹</i>			
PD score difference ^{b,c}	-	-0.02 ± 0.04	-0.08 ± 0.11
PD - correlation coefficient	-	1.000	0.996
NC score difference ^{b,c}	-	-0.03 ± 0.02	-0.07 ± 0.08
NC - correlation coefficient	-	1.000	0.996
<i>Receiver operating characteristic analysis</i>			
AUC ² (CI ³)	0.979 (0.835, 1.000)	0.979 (0.835, 1.000)	0.979 (0.835, 1.000)
Sensitivity ⁴	0.82	0.81	0.81
Specificity ⁴	1.00	1.00	1.00

Values are given as mean ± standard deviation.

¹ 3DRP algorithm² AUC = area under curve in the receiver operating characteristic analysis³ CI = 95% confidence interval (lower bound, upper bound)⁴ Sensitivity and specificity at the optimal cut-off value^a p < 0.0001; compared to the NC subject score (independent sample t-test).^b p < 0.06; method-difference within-group compared to the reference reconstruction algorithm (paired t-test).^c p > 0.05; method-difference between-groups compared to the reference reconstruction algorithm (independent sample t-test).