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Original paper

The effects of image reconstruction algorithms on topographic characteristics, diagnostic performance and clinical correlation of metabolic brain networks in Parkinson's disease

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ABSTRACT

Purpose: The purpose of this study was to evaluate the effects of different image reconstruction algorithms on topographic characteristics and diagnostic performance of the Parkinson's disease related pattern (PDRP).
Methods: FDG-PET brain scans of 20 Parkinson's disease (PD) patients and 20 normal controls (NC) were reconstructed with six different algorithms in order to derive six versions of PDRP. Additional scans of 20 PD, 25 atypical parkinsonism (AP) patients and 20 NC subjects were used for validation. PDRP versions were compared by assessing differences in topographies, individual subject scores and correlations with patient's clinical ratings. Discrimination of PD from NC and AP subjects was evaluated across cohorts.
Results: The region weights of the six PDRPs highly correlated ($R \geq 0.991$; $p < 0.0001$). All PDRPs' expressions were significantly elevated in PD relative to NC and AP subjects ($p < 0.0001$) and correlated with clinical ratings ($R \geq 0.47$; $p < 0.05$). Subject scores of the six PDRPs highly correlated within each of individual healthy and parkinsonian groups ($R \geq 0.972$, $p < 0.0001$) and were consistent across the algorithms when using the same reconstruction methods in PDRP derivation and validation. However, when derivation and validation reconstruction algorithms differed, subject scores were notably lower compared to the reference PDRP, in all subject groups.
Conclusion: PDRP proves to be highly reproducible across FDG-PET image reconstruction algorithms in topography, ability to differentiate PD from NC and AP subjects and clinical correlation. When calculating PDRP scores in scans that have different reconstruction algorithms and imaging systems from those used for PDRP derivation, a calibration with NC subjects is advisable.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative brain disorder characterized by motor and non-motor symptoms. Diagnosis is made clinically and may be difficult in its early phases due to the overlapping clinical features with atypical parkinsonian syndromes (AP). As functional brain imaging with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is becoming more widely available, its ability to provide an objective basis for discriminating PD patients from normal controls (NC) as well as from AP patients is more commonly utilized [1–12]. For the clinical differential diagnostic purposes FDG-PET images can be evaluated by visual inspection of relative glucose metabolism in basal ganglia, however, mild changes in regional brain metabolism may be difficult to observe in early stages of parkinsonism.

Various statistical mapping approaches have been used to support the use of FDG-PET in early differential diagnosis. While statistical parametric mapping (SPM) provides a widely used method to delineate abnormal regional metabolism specific to a given illness, multivariate approaches based on spatial covariance mapping [e.g., scaled subprofile model/principal component analysis (SSM/PCA)] provide specific disease-related networks, which can be prospectively quantified in individual subjects [5,13–16]. Indeed, the SSM/PCA toolbox [17] allows

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automated voxelwise computations for generating abnormal covariance patterns from FDG-PET brain images that are characteristic for PD or other neurodegenerative disorders like multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration and Alzheimer's disease [5,6,15,18–23].

An algorithm called topographic profile rating (TPR) has also been devised to prospectively quantify expression of a given pattern for new subjects [5,13–17]. TPR method quantifies the magnitude of network expression in an individual FDG-PET brain image and reports it as a subject score. It has been shown that subject scores of Parkinson's disease related pattern (PDRP) strongly correlate with disease severity [22,24,25] and can be used for objective assessment of disease progression [26,27] as well as for the evaluation of treatment response [28–30]. Furthermore, an automated multivariate classification tool has been developed to accurately discriminate between parkinsonian patients by calculating probability of each parkinsonian syndrome based on the expressions of multiple disease-related abnormal networks obtained prospectively in individual subjects [16].

The derivation and expression of the disease related metabolic patterns could be affected by physiological variability of patient populations as well as differences in FDG-PET image preprocessing methods including reconstruction algorithms and other relevant procedures. For example, FDG-PET scanning protocols may change in individual institutions when imaging systems are being replaced or with the purpose of radiation dose reduction [31]. With the increasing numbers of multicenter clinical trials, it is also becoming a priority to establish inter-institution interchangeability of FDG-PET data, where centres involved may use different image preprocessing software [32,33]. The need for optimization and harmonization has been well recognized in imaging studies of various neurodegenerative disorders. It has already been confirmed that different scanners have no impact on SPM-based analysis of metabolic patterns using FDG-PET images in differential diagnostics of dementia [34]. Research in metabolic brain networks of PD has so far shown that spatial normalization by different versions of SPM software did not affect the networks and their clinical correlates [35].

To further validate the PDRP as a robust imaging biomarker of PD, we have previously identified a PDRP in a new European cohort of PD patients, validated its discrimination ability in an independent cohort of PD and AP patients, and its correlation with the patients' clinical scores [25]. That study was performed on the latest generation PET/CT scanner using the optimal image reconstruction algorithm employed in routine clinical practice. We also showed significant similarities in spatial topographies and network scores between this new pattern and the original PDRP in an American population [14]. Additionally, we confirmed the within-subject reproducibility in expression of this pattern across FDG-PET brain images, which were reconstructed with various image reconstruction algorithms on the same scanner [36].

The FDG-PET images that were so far used for the identification of various replications of PDRP pattern were acquired using different protocols and reconstruction algorithms [14,22–24]. It is not yet known precisely whether these differences have any effect on the PDRP topography or its ability to differentiate PD patients from NC subjects and other parkinsonian patients. In this study we wish to round up the analysis concerning the effects of image preprocessing methods on PDRP pattern and on its ability in differential diagnosis. Our goal was to investigate systematically in a within-subject design whether and how different image reconstruction algorithms may affect the performance of the SSM/PCA analysis and the characteristics and diagnostic performance of the PDRP network, which has not been performed previously.

2. Methods

2.1. Participants

We investigated the same cohorts of parkinsonian patients and normal control subjects who were originally used to derive and validate the PDRP-Slovenia [25]. There were a total of 105 parkinsonian and healthy control subjects acquired on a Siemens Biograph mCT PET/CT scanner, divided into three cohorts. Raw FDG-PET brain scans from twenty PD patients and twenty age-matched NC (Cohort A) were first reconstructed with six different algorithms in order to derive six versions of PDRP. For prospective validation of these PDRPs we used additional forty raw FDG-PET brain scans (twenty PD and twenty NC – Cohort B) and twenty-five scans from AP patients (fourteen MSA and eleven PSP – Cohort C). The demographic and clinical characteristics of these cohorts have been described previously [25] and are summarized in Supplementary Table 1 for easy access.

2.2. Image processing

FDG-PET brain scans were reconstructed into a 400 × 400 × 110 matrix with a voxel size 1.02 × 1.02 × 3 mm^3. For Cohort A and B scans, six different reconstruction algorithms were used: Filtered Backprojection (FBP), FBP including Time-Of-Flight (TOF) information (FBP + TOF), Ordered Subsets Expectation-Maximization (OSEM) (6 iterations, 24 subsets), OSEM + TOF (6 iterations, 21 subsets), OSEM incorporating Point-Spread-Function (PSF) correction (OSEM + PSF) (6 iterations, 24 subsets) and OSEM + PSF + TOF (6 iterations, 21 subsets). Brain scans from Cohort C were reconstructed only using OSEM + PSF + TOF (6 iterations, 21 subsets) algorithm at the time when raw data were available. FBP used a ramp filter with no cut-off at high frequencies. The time of flight kernel applied in the TOF reconstruction was 580 ps (FWHM). The parameters for iterative reconstruction algorithms were chosen according to the scanner manufacturer's recommendations. Gaussian postprocessing filter with 4 mm FWHM was applied in all cases.

All images were spatially normalized to PET template and smoothed using a Gaussian kernel of 10 × 10 × 10 mm FWHM using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm/software/SPM5/) running in Matlab 7.0 (MathWorks Inc.).

2.3. PDRP derivation and comparison across reconstruction algorithms

2.3.1. Derivation of PDRPs

The software for SSM/PCA analysis (freely available at www.feinsteinneuroscience.org) was used to rapidly analyse brain images from patients and healthy controls. The underlying algorithm and its assumptions were first introduced for use in regions-of-interest (ROI) data [13,37,38] and later upgraded for voxel-level whole brain analysis [14,18,29,39,40]. This SSM/PCA toolbox was developed to provide automated voxel-wise computations with an improved user-interface, and optimized efficiency for general applications.

For the derivation of six versions of PDRP, an automatic voxel-based SSM/PCA analysis was applied to the six datasets of FDG-PET brain images from patient and control groups in Cohort A and principal components were identified. Each PCA run produced images for a set of principal components (PCs) that contribute different fractions to the total voxel × subject variance in the data. The PC whose expression in individual subject images produced the most significant differentiation between PD and NC groups was determined as a PDRP. TPR analysis was then performed to calculate the expression for each of the six newly derived PDRP patterns in images of subjects from Cohorts A, B and C.

All subject scores were Z-transformed using mean and standard deviation of subject scores from NC in the derivation sample (i.e., Cohort A) for each version of PDRP. Therefore, for each pattern, an average Z-score of PDRP in NC subjects of Cohort A was 0.0 with