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FDG PET Parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease

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ABSTRACT

Background: The development of therapeutic interventions for Parkinson disease (PD) is challenged by disease complexity and subjectivity of symptom evaluation. A Parkinson's Disease Related Pattern (PDRP) of glucose metabolism via fluorodeoxyglucose positron emission tomography (FDG-PET) has been reported to correlate with motor symptom scores and may aid the detection of disease-modifying therapeutic effects.

Objectives: We sought to independently evaluate the potential utility of the PDRP as a biomarker for clinical trials of early-stage PD.

Methods: Two machine learning approaches (Scaled Subprofile Model (SSM) and NPAIRS with Canonical Variates Analysis) were performed on FDG-PET scans from 17 healthy controls (HC) and 23 PD patients. The approaches were compared regarding discrimination of HC from PD and relationship to motor symptoms.

Results: Both classifiers discriminated HC from PD ($p < 0.01$, $p < 0.03$), and classifier scores for age- and gender- matched HC and PD correlated with Hoehn & Yahr stage ($R^2 = 0.24$, $p < 0.015$) and UPDRS ($R^2 = 0.23$, $p < 0.018$). Metabolic patterns were highly similar, with hypometabolism in parieto-occipital and prefrontal regions and hypermetabolism in cerebellum, pons, thalamus, paracentral gyrus, and lentiform nucleus relative to whole brain, consistent with the PDRP. An additional classifier was developed using only PD subjects, resulting in scores that correlated with UPDRS ($R^2 = 0.25$, $p < 0.02$) and Hoehn & Yahr stage ($R^2 = 0.16$, $p < 0.06$).

Conclusions: Two independent analyses performed in a cohort of mild PD patients replicated key features of the PDRP, confirming that FDG-PET and multivariate classification can provide an objective, sensitive biomarker of disease stage with the potential to detect treatment effects on PD progression.

1. Introduction

The complex effects of Parkinson disease (PD), which include multi-faceted motor symptoms, cognitive effects, and non-motor symptoms, pose challenges in measuring treatment effect upon disease progression. Although the Unified Parkinson's Disease Rating Scale III (UPDRS-III) (Goetz et al., 2008) provides a broadly used measure of motor deterioration, more sensitive, objective measures of decline are needed (Heldman et al., 2011). Several published reports have explored the potential of glucose metabolism measurement using 2-deoxy-flor-oglucose positron emission tomography (FDG-PET) as a biomarker of PD progression for clinical trials. The present study sought to determine whether the Parkinson's Disease Related Pattern (PDRP) (Eidelberg et al., 1994; Ma et al., 2007) observed in previously published FDG-PET studies could be independently replicated in early stage PD subjects.

Regional cerebral glucose metabolism, the primary energy source for neuronal activity (Dienel and Hertz, 2001), reflects changes in neuronal function due to disease, therapeutic intervention, and

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cognitive or physical activity. Using FDG-PET and multivariate machine learning techniques, a Parkinson's Disease Related Pattern (PDRP) has been identified, characterized by hypometabolism in parieto-occipital and premotor cortices concomitant with metabolic preservation or hypermetabolism in cerebellum, pons, thalamus and lentiform nucleus (Eidelberg et al., 1994; Ma et al., 2007; Tomše et al., 2017a). The pattern is consistent with regional findings in other studies in PD patients (Kuhl et al., 1984; Bohnen et al., 1999; Bohnen et al., 2011). The PDRP has been demonstrated to correlate with cross-sectional disease severity and UPDRS motor scores (Eidelberg et al., 1994; Ma et al., 2007; Huang et al., 2013; Wu et al., 2013), longitudinal disease progression (Huang et al., 2007), and therapeutic response (Feigin et al., 2001; Feigin et al., 2007). Subjects with Parkinson's symptoms but without dopaminergic deficit have been found not to express the PDRP in contrast to PD patients with dopaminergic deficit (Eckert et al., 2007). It has also been applied to evaluate scans in comparison to other similarly derived disease related patterns to discriminate between idiopathic PD, multiple system atrophy, and progressive supranuclear palsy (Teune et al., 2013; Mudali et al., 2015; Tripathi et al., 2016). The pattern has been demonstrated using several different data sets from a variety of countries and ethnic populations (Eidelberg et al., 1994; Ma et al., 2007; Teune et al., 2013; Wu et al., 2013; Tomše et al., 2017a), PET scanners (Moeller et al., 1999), and reconstruction algorithms (Tomše et al., 2017b). The published PDRP studies to-date share a common analytic approach and all but one of these studies share at least one common author/co-author despite evaluating several unique data sets. The PDRP has yet to be confirmed in a unique data set by an independent group of authors using different analytic techniques.

The primary objective of our work was to confirm that the PDRP could be detected in a mild PD patient population using two different machine learning approaches by an independent research group. The second objective was to evaluate the relationship between metabolic pattern expression and motor scores. The first machine learning approach used the Standard Subscale Profile (SSP) Method (Moeller and Strother, 1991) that has identified the PDRP in multiple PD populations as described above. The second approach used a different image preprocessing sequence and applied Canonical Variates Analysis within the Non-parametric Activation and Influence Reproducibility Resampling (NPAIRS) framework (Strother et al., 2002; Strother et al., 2010). NPAIRS was previously developed to address the common problem of overfitting in machine learning, and uses intensive, iterative split half resampling of the data set to generate metrics of reproducibility (correlation between models derived for each half of the data set) and prediction (correct classification of test half based upon training half) for selection of model parameters that optimize classifier stability and generalizability.

2. Methods

2.1. Study participants

FDG-PET data were acquired in 17 Healthy Controls (HC) and 25 PD patients at the Tel-Aviv Sourasky Medical Center, between the years 2011 and 2015. The data were collected under Institutional Review Board approval with informed consent by participants. Subjects were characterized (in the on medication state) with the Hoehn & Yahr (H & Y), Unified Parkinson's Disease Rating Scale (UPDRS) and Montreal Cognitive Assessment (MoCA) scales (Nasreddine et al., 2005). PD patients were of both sporadic and autosomal dominant genetic origin (G2019S-LRRK2 mutation).

2.2. Image acquistion

All FDG-PET scans were acquired in the morning at approximately 11 am. Patients were asked to stop anti-Parkinson medication on the day of the PET scan. Blood glucose levels were measured prior to the injection of fluorodeoxyglucose and verified to be < 160 mg/ml in all study patients. 3D brain PET acquisition was performed using a GE Discovery 690 PET-CT scanner 30 min after the IV administration of 5-7 mCi (185-259 MBq) fluorodeoxyglucose over a period of 15 min. Subjects remained with eyes open at rest in a dimly lit room during the tracer uptake period. Images were attenuation corrected using a CT scan of 120 kV and automated mA, and reconstructed using a 2.5 mm slice thickness and the standard PET-CT reconstruction algorithms on the GE 690 Discovery system.

2.3. Data quality control and processing

Reconstructed images, produced in static form (a single timeframe), were visually inspected for anatomical completeness and to ensure suitability for processing. Images were spatially transformed to a common PET template using a PET to PET transformation in the Statistical Parametric Mapping software SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Images were smoothed for group analysis using an 8 mm Gaussian filter kernel, full width at half maximum.

2.4. Multivariate pattern analysis

As noted above, the classifier development was implemented using two approaches: (1) Scaled Subprofile Model (SSM) analysis (Moeller and Strother, 1991; Eidelberg et al., 1994; Spetsieris and Eidelberg, 2011) and (2) Canonical Variates Analysis (CVA, a form of linear discriminant analysis) as implemented within NPAIRS (Strother et al., 2002; Strother et al., 2010). The two approaches are similar in their use of supervised learning with defined training classes, Principal Component Analysis (PCA) to identify differentiating features between groups, and linear discriminant analysis to combine selected Principal Components (PCs) into a final model (set of patterns). The approaches differed in the intensity normalization methods applied to the images that were input to the machine learning model (SSM vs. z-scoring), the algorithm applied to mathematically combine selected Principal Components, and the method of using iterative data resampling to create a consensus classifier (NPAIRS).

When applying the SSM approach, the logarithm of each voxel value was calculated for each scan, the mean of the scan volume was removed from the voxels within the scan, and the mean of each voxel across all scans was additionally removed from that voxel (Moeller and Strother, 1991; Spetsieris and Eidelberg, 2011). The pre-processed scans, designated into training groups, were input to PCA, which identified uncorrelated patterns discriminating groups. Principal Components (PCs) were chosen and combined using logistic regression. To verify agreement between our implementation of SSM/PCA and that used in other published studies, analyses were performed using both published software (http://www.fil.ion.ucl.ac.uk/spm/ext) (Peng et al., 2014) and in-house software (www.admdx.com). In the initial analysis, the number of PCs was selected to include those that accounted for > 5% of variance.

In the NPAIRS CVA approach, PCA was applied for feature reduction to images that had been intensity normalized by z-scoring to whole brain, grouped into pre-specified training classes (defined as in the SSM approach), and mean centered. CVA was then performed to combine selected PCs into a set of intensity patterns that best accounted for variance across the classes. For comparison to SSM, the same number of PCs was selected as the basis for CVA as was selected for the SSM approach. A consensus pattern was produced based upon the multiple split-half resampling iterations. A numeric canonical variates score (CV score) was calculated for each scan, reflecting the degree to which the scan expressed the associated pattern of intensities.

For each classification model, results were tested using a Leave-One-Out algorithm that allows testing of each data point without incorporating that data into model development. For the set of N subjects, the classifier was developed N times, each time leaving out a different