Accuracy to Differentiate Mild Cognitive Impairment in Parkinson's Disease Using Cortical Features

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Abstract. Mild cognitive impairment (MCI) is common in Parkinson's Disease (PD) patients and it is key to predict the development of dementia. There is not report of discriminant accuracy for MCI using based-surface cortical morphometry. This study used Cortical-Thickness (CT) combined to Local-Gyrification-Index (LGI) to assess discriminant accuracy for MCI stages in PD. Sixty-four patients with idiopathic PD and nineteen healthy controls (HC) were analyzed. CT and LGI were estimated using Freesurfer software. Principal Component Analysis and Lineal Discriminant Analysis (LDA) assuming a common diagonal covariance matrix (or Naive-Bayes classifier) was used with cross-validation leave-one-subject-out scheme. Accuracy, sensibility and specificity were reported to different classification analysis. CT combined to LGI limited revealed the best discrimination with accuracy of 82,98%, sensitivity of 85.71% and specificity of 80.77%. A validation process using independent and more heterogeneous data set and further longitudinal studies, are necessary to confirm our results.

Keywords: Naive-Bayes classifier, PCA, Accuracy, Parkinson's disease, MCI, Cortical Thickness, Cortical Folding, LGI, MRI, Surface-based morphometry.

1 Introduction

In Parkinson's disease (PD) exist a spectrum of cognitive dysfunction, ranging from mild cognitive impairment (MCI) to dementia (PDD). MCI is common in non-demented PD patients and predicts the development of dementia in PD patients over a long period of time [1,2]. Specific patterns of gray matter atrophy occur across all stages of PD and functional and metabolic changes also are measurable, but it is too early to determine their utility as biomarkers for cognitive impairment in PD [3,4,5]. Therefore, additional evidence is necessary and validation of biomarker candidate as an objective method of diagnosis and prognosis is an active research field nowadays.

Medical imaging is widely used for above purpose and a general approach is to detect subtle differences in the composition, morphology or other behavior in organs and relating these differences to clinical phenomena of interest[6]. In

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particular, surface-based morphometry has been used to identify pattern of atrophy associated to cognitive decline in PD patients[3]. However, only a few of then have considered PDMCI stage [7,8]. A recently research found that disease stage in PD was associated with thinning of the medial frontal region and discriminant analysis showed that mean cortical thickness and hippocampus volume have 80% accuracy in identifying PD patients with dementia [8]. However, it remains unclear how cortical changes is related to cognitive impairment and disease stage in PD, in addition, as far as we know, not any study report accuracy of cortical folding and cortical thickness for identifying PDMCI stage. In this study we used based-surface morphometry for contributing with additional evidence about associated cortical regions to cognitive dysfunction and to assess accuracy of cortical thickness combined with cortical folding for discriminating PDNC and PDMCI stages.

2 Methods

2.1 Patients and Controls

This study enrolled 64 patients with idiopathic PD and 19 healthy controls (HC). All the participants underwent an extensive neuropsychological assessment, including the Mini-Mental State Examination (MMSE) and Blessed Dementia scale for global cognitive functions. In order to evaluate motor disabilities at PD patients, the motor subset of the Unified Parkinson Disease Rating Scale (UPDRS-III) and the Hoehn and Yahr scale were applied. Significant co-morbidity at PD patients and controls were excluded by neurological and psychiatric evaluation, imaging and laboratory tests. Demographic and clinical data for the study groups are given in Table 1. PD patients were classified in three groups according to cognitive performance: cognitively normal PD patients (PDCN), PD with mild cognitive impairment (PDMCI), based on established MCI criteria[9] and PD with dementia (PDD); based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)[10]. All the participants provided informed consent for the study in accordance with Helsinki Declaration.

2.2 MRI Acquisition

MRI examinations were performed on a 1.5 T Magnetom Symphony MRI scanner (Siemens, Erlangen, Germany). All subjects were investigated with a whole brain T1-weighted coronal oriented Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (repetition time TR = 13 ms; echo time TE = 10 ms; inversion time TI= 1100 ms; flip angle =15; 1 mm isotropic resolution; slice gap = 0 mm). Head motion was minimized with restraining foam pads provided by the manufacturer.

2.3 Cortical Variables Estimation

Cortical Thickness (CT) and Local Gyrification Index (LGI) estimation was performed with Freesurfer software, which is documented and freely available for download online (`http://surfer.nmr.mgh.harvard.edu/`). The technical details of these procedures were described in prior publications. Briefly, this processing included, removal of non-brain tissue using a hybrid watershed/surface deformation procedure[11], automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures [12,13], intensity normalization [14], tessellation of the gray matter white matter boundary, automated topology correction[15,16]. This method used both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface[17]. Local Gyrification Index was measured in each vertex as the ratio between areas of pial surface and an outer smoothed surface tightly wrapping the pial surface[18] using Matlab toolbox distributed with Freesurfer.

Table 1. Demographic and clinical characteristics of the study participants

	HC	PDNC	PDMCI	PDD	Differences
No. Subjects	19	21	26	17	
Sex (M/F)		15/7	15/13		
Age	68.0/3.1	67.0/7.0	71.6/3.8	73.2/7.3	0.001a
Education	2.55/1.0	3.30/1.5	2.52/1.0	2.31/0.8	N.S
Evolution (yr)	N.A	12.4/3.6	14.5/6.1	13.9/4.7	N.S
UPDRS III	N.A	32.3/8.5	35.0/12.2	50.0/10.0	$P < 0.0$a
HY	N.A	2.54/0.6	2.89/0.7	3.78/0.7	$P < 0.001$a
MMSE	29.2/1.1	29.0/1.4	26.4/2.6	18.3/3.8	$P < 0.001$a

N.S: no significant; UPDRS : Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr stage. (a) One way analysis of variance with Fisher LSD post-hoc comparisons

2.4 Features Extraction and Classification

Using general linear model (GLM) with Age and Gender as covariate nuisance with Freesurfer module MRI_GLMFIT and MATLAB scripts was investigated the regional difference patterns of CT and LGI between the different groups in pairs-wise analysis. Changes were examined with a threshold of $p<0.001$ (uncorrected) on the vertex level and $p<0.05$ (corrected for multiple comparison using Montecarlo simulation with 10,000 iterations) on the cluster level. Each one of the identified clusters expands to several cortical regions, using t-test ($p <0.001$) we had determined cortical regions with significant difference in average value

of each variable using Destrieux Atlas (a 148 regions atlas)[19], once eliminated, age and gender, confounding. CT was smoothed using a Gaussian kernel of 15 mm FWHM.

All contrast was evaluated to select those that gave us more information to differentiate between PD and PDMCI in both directions; first, changes at topographic extension and second on the intensity of variation. Average value of CT and LGI for each significant region integrated the feature-vector. Principal Component Analysis (PCA) was used to identify a set of orthogonal modes that capture the greatest amount of variance expressed spatially by the two feature-vectors. We proceeded on selecting a number of modes that accounted to per-model variance of 80%. Lineal Discriminant Analysis (LDA) assuming a common diagonal covariance matrix (or Naive-Bayes classifier) with same prior probability to all group and cross-validation was performed, using the leave-one-subject-out scheme in all analysis. Accuracy, sensibility and specificity was reported to five different analysis: CT-only/selected-regions, LGI-only/selected-regions, CT & LGI/selected-regions and CT & LGI/all-cortical-regions and CT & LGI/selected-regions/random-assigning-group.

3 Results

3.1 Global Analysis

Whole-cortex average CT was 2.44/0.09, 2.35/0.19, 2.19/0.17, 2.0/0.22 in HC, PDNC, PDMCI and PDD group respectively. ANCOVA revealed a significant difference between all groups except PDNC vs PDMCI and correlation with Age ($p<0.05$, tukey-kramer to compensate for multiple comparisons), no difference was found in Gender. Whole-cortex average LGI was 2.81/0.11, 2.77/0.15, 2.69/0.11, 2,69/0.12 in HC, PDNC, PDMCI and PDD group respectively, significant difference between HC vs PD and HC vs PDD and significant difference between Gender was revealed (ANOVA, $p=0.05$, tukey-kramer multiple comparisons). To avoid any possible effects of Age and Sex, both variables were included as covariates in the further analysis. A significant correlation between CT and LGI was found using four groups data (Pearson r=0,33, $p=0.002$).

3.2 Regional Analysis

Table 2 shows the number of clusters and regions identified with significant difference to CT and LGI. CT revealed significant changes to every contrast. HC-relative contrasts showed a progressive thinning from PDNC to PDD con values of 8.29%, 9.11% and 11.95% respectively. Topographic extension included 4 *regions (G_pariet_inf-Supramar_left, S_postcentral_left/right and S_intrapariet_ and_P_trans_right),* 54 and 124 respectively. PDNC-relative contrast (PDNC vs PDMCI and PDNC vs PDD) revealed relative changes of 15% and 10.98%, the first one revealed significant different in *G_occipital_superior_left* and the last one a number of 30 regions. LGI showed

only significant clusters for HC-relative contrasts. The principal difference on its is reflexed by topographic extension, 2 regions in HC vs PDNC *(G_ cuneus_ left_ and S_ parieto_ occipital_ left)* compared to 14 and 7 in HC vs PDMCI and HC vs PDD respectively. In according to above results, we selected 31 regions (11 left and 20 right) provided by PDNC vs PDMCI and PDNC vs PDD contrasts to form a feature-vector to CT variable . In a similar way a feature-vector to LGI variable was compound for average value of LGI in 16 regions (11 left and 5 right) provided by HC vs PDNC and HC vs PDMCI contrasts. Figure 1 shows statistical parametric maps highlighting significant clusters that contains the selected regions (more details in supplementary material).

Table 2. Number of clusters and regions with significant difference in pairs-wise analysis for CT and LGI variables

	CT			**LGI**		
Groups	NoC	NoR	%	NoC	NoR	%
HC vs PDNC	7	4	8.29	2	2	6.72
HCvsPDMCI	18	54	9.11	10	14	6.30
HC vs PDD	6	124	11.95	6	7	6.41
PDNC vs PDMCI	3	1	15.00	0	0	
PDNCvsPDD	16	30	10.98	0	0	
PDMCI vs PDD	10	11	9.49	0	0	

NoC: Number of significant cluster (p=0.05 cluster-wise, p=0.001 to form cluster)

NoR: Number of regions in clusters (Destrieux Atlas 2009, 148 regions) with significant difference (p=0.001) according to average value.

%: Relative percent of variation between pairs of groups

3.3 Classification

The 80% of variance of feature-vector CT was explained by the first five principal components. MANOVA discriminated between groups ($p<0.05$, chisq=15.02, wilk's lamda=0.7) using this modes of variations. With feature-vector LGI was necessary the first four principal components, witch ones discriminate between groups too (MANOVA, $p<0.05$, chisq=28.87, wilk's lamda=0.5). Table 3 summarizes classification results of different analysis. Multivariate classification using combined modes of CT and LGI limited to selected regions revealed the best discriminant accuracy with 82,98% compared to remainder analysis. Using all cortical regions was obtained a accuracy of 72.34%, using CT variable only 65.96% and using LGI variable only the result was of 78.72%. Similar results showed the sensitivity (85,71%) and specificity (80.77%) values. Using 10 trials of random assigning to all subjects of the two groups accuracy result was 38.30%.

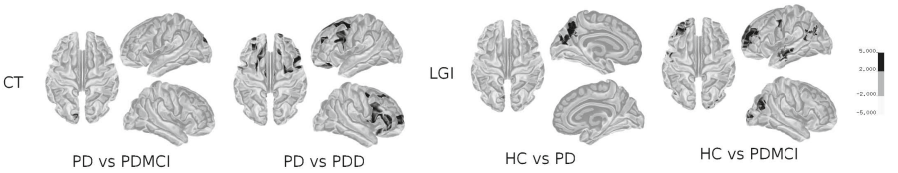

Fig. 1. Statistical parametric maps showing significant clusters on the four main contrasts selected to classification between PDNC and PDMCI *(Freesurfer MRI_ GLMFIT module and GLM, CT smoothed 15 mm FWHM, p=0.001 uncorrected and p=0.05 FWE cluster-wise*, corrected for multiple comparison using Montecarlo simulation with 10,000 iterations.

3.4 Discussion

We assessed cortical thickness combined with cortical folding accuracy for differentiate MCI in PD patients. In this first exploratory stage we have used LDA assuming diagonal covariance matrix or Naive-Bayes classifier on the basis of we have considered both CT and LGI variables normally distributed and independent each other within each group in accordance with the results of previous study[20], where no significant correlation were found between that variables in the control's group; In addition, feature-vector for classification was formed by first orthogonal modes of variation or principal components. However a comparison to a discriminative classifier, such as Logistic Regression or Support Vector Machine would be advisable to confirm the results. The used approach for discrimination not only captures univariate relationships of a single region across all subjects, but also detect multivariate relationships between different structures in each cortical variable[6]. CT showed a progressive reduction consistent with preview studies ([7,8]) and discriminate PDMCI with 65.96% of accuracy. In contrast with a recently study [8] and according to a previous one [20]LGI revealed structural changes between PDNC, PDMCI and PDD relative to control subjects. Figure 1 illustrate a extension of differences to others regions that should be associated to cognitive decline, that subtle differences between PDNC and PDMCI are no detected by univariate analysis, however, multivariate approach revealed difference between PDNC vs PDMCI of LGI with an accuracy of 78.72%. All classification results exceeded the accuracy obtained by chance (38.30%). By combining CT and LGI and using proposed regions we obtained the better accuracy (82,98%), similar to reported accuracy to differentiate dementia[8] . This results endorse the using of selected regions for classification. However, as the groups used in this study were recruited from a single clinical center, the results might be less generalizable to other clinical data and a validation process with more heterogeneous data sets is necessary, other lack is that we modeled a apparent progression of cognitive impairment using information relate to different contrasts obtained from cross-sectional design, this fact influences the results, witch ones should be confirm with longitudinal study fallowing quality criteria as were recommended recently [3,4] .

Table 3. Accuracy, sensitivity and specificity values to differentiate PDNC and PDMCI groups. Five different classification analysis are reported.

Variables/Regions	Sensitivity	Specificity	Accuracy
CT and LGI/selected-regions	85.71%	80.77%	82.98%
CT-only/selected-regions	66.67%	65.38%	65.96%
LGI-only/selected-regions	80.95%	76.92%	78.72%
CT and LGI/all-cortical regions	71.43%	73.08%	72.34%
CT and LGI/selected-regions/randomly-assigning-group*	28.57%	46.15%	38.30%

Naive-Bayes classifier with cross-validation leave-one-subject-out squeme for all analysis.

(*) Average value resultant of ten trials of random assignations.

4 Conclusions

Our study supply additional evidence about existent relations between cognitive impairment and structural changes in brain cortex and reveal the capacity of cortical thickness and cortical folding to discriminate MCI, specially, when both features are combined and we use specific cortical regions, PCA and a Naive-Bayes classifier. A validation process using independent and more heterogeneous data set and further longitudinal studies are necessary to confirm our results.

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