Classification of symptom-side predominance in idiopathic Parkinson's disease

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Abstract:

Asymmetry of symptom onset in Parkinson's disease (PD) is strongly linked to differential diagnosis, progression of disease and clinical manifestation suggesting its importance in terms of specifying a therapeutic strategy for each individual patient. To scrutinize the predictive value of this consequential clinical phenomenon as a neuromarker supporting a personalized therapeutic approach, we modeled symptom-side pre-dominance at disease onset based on brain morphology assessed with magnetic resonance (MR) images by utilizing machine learning classification.

The integration of multi-modal MR imaging data into a multivariate statistical model led to predict left- and right-sided symptom onset with an above-chance accuracy of 96%. By absolute numbers, all but one patient were correctly classified. Interestingly, mainly hippocampal morphology supports this prediction. Considering a different disease formation of this single outlier and the strikingly high classification, this approach proves a reliable predictive model for symptom-side diagnostics in PD. In brief, this work hints towards individualized disease-modifying therapies rather than symptom-alleviating treatments.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases resulting in motor as well as in non-motor dysfunctions. Despite its heterogeneous clinical manifestation and course, the asymmetry of motor symptoms at the time of diagnosis is a pathological hallmark indicating Parkinson's disease (i.e., idiopathic Parkinsonian Syndrome) that clinically helps to differentiate from atypical forms of PS[1]. Besides this important role in the definition of PD, side of disease onset and progression of motor impairment were reported to be strongly linked[1]: While a right-sided symptom-onset is associated with a more favorable outcome in terms of cognitive impairment, a left-sided symptom-onset appears to be associated with a better outcome regarding motor progression[1-3]. Both clinical pathways certainly imply considerable difference not only in forecasting potential progression, but also the individual therapeutic approach. Although the origin of a unilateral symptom prevalence still remains enigmatic, this has sparked much interest in studying symptom-side predominance[2]. Whilst the clinical definition of a side predominance is not trivial with respect to the individual course of disease, the determination at disease onset seems consistent[2,3].

To date, numerous studies have employed multivariate decoding methods such as support vector machines to classify disease entities; rather infrequently these methods were applied to predict a treatment outcome or prognose disease progression at an individual subject level. With respect to PD, decoding methods have been used to delineate, e.g., essential tremor with rest tremor from tremor-dominant PD patients[4]. Support vector classification involving data from quantitative MRI approaches, such as diffusion tensor imaging (DTI), has been recently applied to distinguish between PD patients and a group of patients with PD-mimicking conditions[5]. Various white matter microstructural changes associated with PD[6] thus reveal a significant hint at DTI as valuable tool when investigating this pathology. In fact, decoding methods on morphological markers from various MRI methods have changed the culture of clinical cohort analysis to the extent that they putatively reveal underlying neurobiological mechanisms, hence supporting to move beyond descriptive phenomenological categorization[7].

Following this rationale, one might argue that despite the lateralization of dopaminergic deficit, wide-spread structural differences reflecting the asymmetry of PD can be systematically found. Therefore, we introduced a multimodal approach to model symptom-side at disease onset in brain morphology based only on different aspects of diffusion MR parameters and multi-kernel support vector classification[8]. Using this approach, we deemed to identify specific morphological markers between disease forms unraveling the enigma of variety in clinical pattern of disease.

Methods

Methods and any associated references are available in the supplementary information of this paper.

Results

We used segregated brain gray (cortical aspect) and white (microarchitectural aspect) matter images of 24 male idiopathic PD patients to predict left- and right-sided symptom onset of motor signs. Remarkably, this framework yielded an above-chance accuracy of 96%. Classification performance is demonstrated by means of the receiver operating characteristics (ROC) curve with an area under the ROC curve of 0.9 (Figure 1A). The decision values that were provided by the classifier highlight the considerable separability of both groups (Figure 1B). In absolute terms, our classifier was able to correctly assign the symptom-side predominance in all but one individual (sensitivity of 100% and specificity of 92%). Post-hoc inspection of the medical records of this one misclassified patient (red circle) revealed a suicide attempt with a carbon monoxide poisoning which differentiates him from all other patients.

When mapping the MRI relevant voxel that drive prediction results onto the neuroanatomical space (cf. Figure 1C), the largest discriminative cluster identified is the posterior head of the right hippocampus (putatively CA4[9]). Since predominantly the pattern for explaining right-sided symptom onset (negative weight vector/blue color scale) occurred in this region, this finding might indicate relatively higher mean diffusivity in the right-sided symptom onset group as compared to the left-sided group.

Discussion

We demonstrate a strikingly high prediction of symptom-side predominance in iPD patients that especially benefits from a novel multimodal whole-brain approach (due to the combination of white and gray matter segregations of different images). Our multi-kernel decoding algorithm discriminates body-side asymmetry with an accuracy of 96%, indicating excellent statistical performance. Apart from one outlier, this predictive model yields a remarkable precision of 100%. The exact determination of symptom-side prevalence at disease onset is of major interest since it has recently been linked to disease progression[1]. Notably, post-hoc mapping of most relevant regions revealed an aspect of the posterior head of the right hippocampus[9]. One might speculate, that right-sided onset patients exhibit relatively more microstructural alterations in this area as compared to left-sided onset patients. This discriminative region is especially intriguing given the hippocampal role in spatio-temporal orientation and mnestic function[9]. This also resonates with previous findings, where patients with a right-sided symptom-onset were

associated with a more favorable outcome regarding cognitive impairment, and a left-sided symptom-onset appeared to be associated with a more favorable outcome in terms of motor progression[1-3]. Here, our sole outlier attempted suicide by carbon monoxide poisoning three years prior to our study. As hippocampal damage is one of the typical pathological features of carbon monoxide poisoning[10], we argue that this is a reasonable explanation for his misclassification.

We explicitly chose the utility of diffusion-weighted brain imaging data here since these data are susceptible for the neurodegenerative aspects of PD. In particular, we used a combination of fractional anisotropy (segregated white matter) as well as mean diffusivity (segregated gray matter) images to investigate both the integrity of the fiber architecture and cortical differences at the same time (multimodal aspect). Especially the use of diffusion-weighted images enables the detection of subtle anomalies as well as restricted diffusion in white and gray matter in patients suffering from carbon monoxide poisoning[10]. Given that (i) our framework is based on segments of diffusion tensor images and (ii) our major classification pattern was identified in the hippocampus, even subtle changes in this one patients' hippocampus could have misled the model to predict the wrong body-side.

In conclusion, because of the excellent performance and group separability, we are convinced this proves a reliable predictive model for symptom-side diagnostics in iPD patients based solely on parameters from diffusion tensor images. We consider these results a major step in further predictive clinical models of Parkinson's disease incorporating the many clinical aspects that determine individual prediction of progression as well as of a personalized sustainable therapeutic approach. We propose that the described asymmetry parameter should be incorporated as a covariate when striving for a comprehensive and particularly generalizable future model of this disease.

Author contributions:

MT and LT designed the research, EAP and DLF acquired data, DLF contributed analytic tools and analyzed the data, DLF wrote the first draft while MT and LT reviewed the manuscript.

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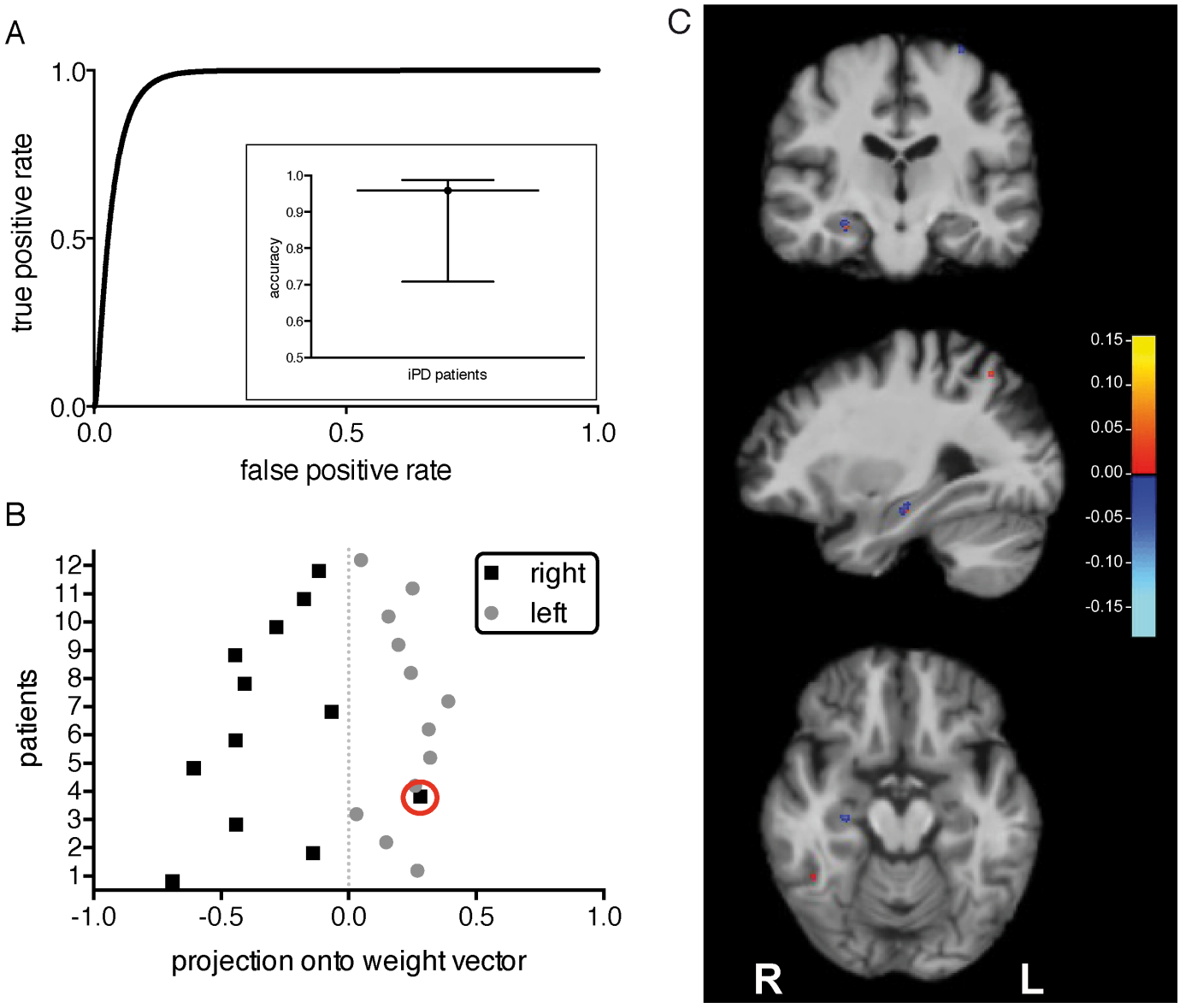
Figure legend

Figure 1: Classification performance with results mapped onto brain anatomy. (A) Receiver operating characteristic curve of the symptom-side predominance classification with an area under curve of 0.9. The inset shows the classification accuracy with its credible interval ranging from 71% to 99%. (B) Best classification accuracy (96%) provided utilizing segregated brain gray and white matter segments. (C) Neuroanatomical findings of symptom-side predominance are superimposed onto a T_1-weighted image of an individual study brain. The spatially contiguous patterns of discrimination reveal relatively higher cortical diffusivity (positive pattern vector; red color scale) or relatively lower cortical diffusivity (negative pattern vector; blue color scale) in left-sided patients. The largest predictive cluster is the posterior head of the right hippocampus (putatively CA4), which is illustrated in a coronal (first row), a sagittal (second row) and a horizontal slice (last row). The scale represents an arbitrary unit; L and R indicate the left and right hemispheres, respectively.

Feis et al. Figure 1



SUPPLEMENTARY INFORMATION

Patients and methods

Patients. Given morphological gender differences in healthy subject [1,2] as well as in PD patients and the fact that men have a higher disease prevalence[3] we exclusively studied 24 right-handed male patients with idiopathic PD (iPD). The symptom-side assignment of left and right body-side was done according to Tomer et al.[4] by a neurologist with expertise in PD (E.A.P.). Our sample constituted of 12 left-sided and 12 right-sided symptom-onset patients, who did not differ in age, disease duration, their Levodopa equivalent daily dose or the degree of motor impairment off medication as measured by the unified Parkinson's disease rating scale-III (UPDRS III). For more information see Supplementary Table S1.

MRI acquisition parameters. Anatomical high-resolution T_1-weighted image were acquired using a 12-channel array head coil with a full-brain field of view (MDEFT3D: TR= 1930 ms, TI= 650ms, TE= 5.8 ms, 128 sagittal slices, resolution = 1x1x1.25mm^3, flip angle = 18°). The VBM8 toolbox was used to preprocess these images as described in Feis et al. [5]. Additionally, diffusion-weighted magnetic resonance (MR) imaging data were collected separately with a 32-channel array head coil from our sample using spin-echo echo-planar imaging (spin-echo-EPI: TR = 11200 ms, TE = 87 ms, 90 axial slices, resolution = 1.7 × 1.7 × 1.7 mm^3). Diffusion weighting was isotropically distributed along 60 directions (b-value 1000 s/mm^2). Seven images without diffusion weighting were acquired at the beginning and after each block of ten diffusion-weighted images, providing an anatomical reference for motion correction. The arithmetic mean across three consecutive scanning sessions was computed in order to increase the signal-to-noise ratio of the diffusion-weighted images. Mean diffusivity (MD) and fractional anisotropy (FA) images were estimated by fitting a diffusion tensor to the data within each voxel. Resulting images were co-registered to T_1-weighted images and nonlinearly normalized to an MNI template before being segmented into gray and white matter segments. To exploit information jointly encoded by different diffusion parameters and to ensure a whole-brain analysis, gray matter segments of the MD images and white matter segments of the FA images were submitted to the classifier.

Prediction. To avoid statistics on a group level basis but rather classify individual patients, a multivariate machine learning technique called support vector machine (SVM, as implemented by Chang and Li [6]) with a linear kernel was employed. The procedure used here to predict the symptom-side predominance of male PD patients at disease onset was previously described in [1,5]. In order to benefit from distinct parameter-specific physical apertures to the different tissue properties, we slightly modified our algorithm by employing a multi-kernel approach with an

equal weighting of the two diffusion images [7]. Generally, an SVM learns from labeled example training data to differentiate given groups. The major aim is to create a multimodal model based on MD (gray matter) and FA (white matter) imaging data that can accurately predict previously unseen patients having either left- or right-sided symptom onset (testing step; the data was not provided in the training phase). To this end, a decision function is learnt that discriminates the given training data to one of the two group labels. In this study, left-sided patients form the positive class; right-sided form the negative class.

Since both the MD and FA images consist of more voxels than iPD patients in our study, we preselected the most important voxels via feature selection method to ensure accurate prediction accuracy. In accordance to previous articles [1,5], a method called Fisher's criterion was applied to find the top 100 most relevant features [8]. Using a (nested) leave-one-patient-out cross-validation procedure on the training set, we automatically optimized the SVM regularization parameter [9]. Subsequently, we applied the optimal model to an independent set of test patients. Statistics such as sensitivity, specificity, F-measure, classification accuracy with its 95% credible interval and the area under the receiver operating characteristics (ROC) curve were calculated [5,10] to assess the performance of our multimodal classifier.

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Table S1 Patient demographics.

	Symptom-side predominance [mean ± SD]		p-values of the Mann-Whitney U Test
	left	right	
age	61 ± 10	64 ± 10	0.45
disease duration	8 ± 5	7 ± 4	0.97
handedness	89 ± 15	78 ± 27	0.42
UPDRS III OFF medication	30 ± 8	27 ± 13	0.30
UPDRS III ON medication	16 ± 3	13 ± 7	0.14
Levadopa equivalent daily dose	768 ± 404	533 ± 260	0.21

Age and disease duration are given in years. The amount of Levadopa equivalent daily dose is indicated in milligram.