

Discriminant BOLD Activation Patterns during Mental Imagery in Parkinson’s Disease

Jessica Schrouff^{1,2}, Julien Cremers^{1,3}, Kevin D’Ostilio¹, Valérie Delvaux³,
Gaëtan Garraux^{1,3}, and Christophe Phillips^{1,2}

¹ Cyclotron Research Centre, University of Liège, Belgium

² Department of Electrical Engineering and Computer Science, University of Liège,
Belgium

³ Department of Neurology, Liège University Hospital, Belgium

Abstract. Using machine learning based models in clinical applications has become current practice and can prove useful to provide information at the subject’s level, such as predicting an (early) diagnosis or monitoring the evolution of a disease. However, the performance of these models depends on the choice of a biomarker to detect the presence or absence of a disease. Choosing a biomarker is not straightforward, especially in the case of Parkinson’s disease when compared to healthy subjects. In the present work, we investigated the mental imagery of gait as a biomarker of Parkinson’s disease and showed that the signal in the mesencephalic locomotor region during the mental imagery of gait at a comfortable pace can discriminate significantly between idiopathic Parkinson’s disease patients and healthy subjects. Although there is room for improvement, the results of this preliminary study are promising.

1 Introduction

During the past decades, advances in neuroimaging techniques allowed investigating the brain structure and functioning in both health and disease. More particularly, Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) enabled the identification of biomarkers in dementias, such as Alzheimer’s disease [1] or in different states of consciousness [2]. They also allowed the characterisation of more complex paradigms such as the mental imagery of gait in both healthy [3] and Parkinson’s diseased subjects [4].

Up to now, the methods used to analyse such data focused on characterizing the individual relationship between a cognitive or perceptual state and each voxel, i.e. following a univariate approach. For functional images, a well-known univariate technique is Statistical Parametric Mapping [5], detecting which voxels show a statistically significant response to the experimental conditions at the individual subject level but also within and between groups of subjects. For structural images, a common approach is Voxel-Based Morphometry, (VBM, [6]), which investigates focal differences in grey matter density between groups of subjects. However, these studies typically infer group differences while conclusions

at the subject’s level would be desirable for diagnosis, prognosis, treatment planning or the monitoring of disease progression [7].

Recently, univariate analyses have been complemented by the use of machine learning based models [8]. These methods aim at predicting a variable of interest (e.g. mental state 1 vs. mental state 2, or patients vs. controls) from the pattern of brain activation/anatomy over a set of voxels. They have been particularly useful in clinical applications [7], e.g. to distinguish between healthy subjects and Alzheimer’s disease patients [9,10] or to assess the level of consciousness of vegetative states patients [11]. Machine learning based models have also been applied to Parkinson’s Disease (PD) when discriminating Idiopathic Parkinson’s Disease (IPD) from Parkinson Plus Syndromes (PPS) [12]. However, it seems that finding a biomarker distinguishing IPD from healthy controls remains an open issue [7,12].

In the present work, we investigated whether the mental imagery of both comfortable and brisk walking could predict the presence or absence of IPD, based on previous works [3,4].

2 Material and Methods

The material considered in this work is the same as in [4]. Therefore, only a brief description of the population and experimental design will be provided.

2.1 Population

In total, 29 subjects participated in the study: 14 patients (7 males; mean age: 65.1 ± 9.5 years) diagnosed with IPD with different degrees of severity of gait disturbances and 15 controls matched for age (63.86 ± 8.1 years) and gender (7 males). Written informed consents for this research protocol approved by the local ethics committee were obtained from all participants.

2.2 Design

Before fMRI, the subjects were asked to walk comfortably and then briskly on a 25m path. After gait evaluation, they were trained to mentally rehearse themselves walking on the path.

All subjects then underwent an fMRI session comprising three tasks: mental imagery of standing on the path (STAND), walking at a comfortable pace along the path (COMF) and walking briskly along the path (BRISK). The COMF and BRISK conditions were self-paced, subjects indicating when they had completed each trial by a key press, while each trial of the STAND condition was constrained by the duration of the previous COMF trial. Eight trials of each condition (12 for BRISK to account for a shorter duration of the trials) were randomly presented to each subject.

In addition to BOLD fMRI, all participants underwent a high-resolution volumetric anatomical MRI of the brain.

2.3 Preprocessing

fMRI data preprocessing and univariate analysis were performed using SPM8¹. Functional images were realigned and co-registered to the structural image before normalisation using DARTEL [13]. Finally, smoothing was applied using a 8mm FWHM Gaussian kernel.

A General Linear Model then summarized the time series from each subject by modelling each condition by a boxcar function convoluted with a canonical haemodynamic response function. In the end, three images per subject were considered for further analysis: the parametric maps of STAND, COMF and BRISK representing the BOLD signal activity associated with each condition.

2.4 Multivariate Modelling

The multivariate analysis was performed using PRoNTo². This Matlab based software (MathWorks, Natick, MA) provides a framework to perform pattern recognition based on machine learning models.

In its current version, PRoNTo does not provide wrapper or embedded feature selection. Three masks were therefore used as filters before building the linear kernel, based on [4]:

- A “whole brain” mask, selecting all voxels within the brain.
- A “motor mask”, built on the WFU-PickAtlas [14] and comprising the areas involved in gait (both in healthy subjects and patients), as described in Table 1 of [15].
- A mask comprising the Mesencephalic Locomotor Region (MLR) and pedunculopontine nucleus, further referred to as “MLR mask”.

Classification was performed using binary SVM [16], as in [12] and [7]. For the between groups classification, the three tasks will be combined in every possible way (e.g. BRISK, BRISK+COMF, ...) and tested for each mask, leading to 7 combinations times 3 masks, equals 21 models. In addition to the IPD vs. CTRL comparison, the discrimination between the three tasks was also assessed by pooling together the data of both groups. This multiclass classification required the use of multiclass Gaussian Processes [17]³. For both classification problems, leave-one-subject-out cross-validation was performed to compute the balanced and class accuracies, as well as Positive Predictive Values (PPV). The significance of accuracy measures was assessed by non-parametric testing using 1000 random permutations of the training labels.

¹www.fil.ion.ucl.ac.uk/spm

²Application for a demonstration of PRoNTo at NIPS has been submitted, www.mlnl.cs.ucl.ac.uk/pronto

³Binary Gaussian Processes could also have been used on the between groups comparison but [18] has shown that SVM and GP had similar performances on balanced datasets with reduced computational expenses for SVM.

3 Results

3.1 Between groups comparison

Results are presented for each (combination of) condition(s) in Table 1 in terms of balanced accuracy while weights of the COMF model are represented in Fig.1 for each mask.

Table 1. Balanced accuracy (in %) for the IPD vs. CTRL classification for each combination of the three tasks (rows) and for each mask (columns). “**All**” represents the combination of the three tasks. Significant results are displayed in bold.

Conditions used	Masks used		
Condition	Whole brain	Motor	MLR
STAND	14.3	34.5	72.6
COMF	58.3	62.1	76.0
BRISK	59.0	66.2	62.1
STAND+COMF	36.3	36.2	72.4
STAND+BRISK	36.7	39.7	65.4
COMF+BRISK	62.3	65.8	62.1
All	42.9	48.3	56.4

Overall, the whole brain mask led to a poor discrimination of IPD vs. CTRL, with the accuracy reaching 62.3% when considering both the COMF and BRISK conditions together (only significant result). Slightly better results were obtained from the features in the motor mask, as shown by a higher balanced accuracy for the BRISK-COMF combination, as well as for the BRISK condition (both significant at $p < 0.05$). The signal comprised in the MLR mask led to the best results, the highest performance being reached when considering the COMF condition. For this model, the balanced accuracy had a value of 76% ($p=0.01$), with the class accuracies reaching 78.6% for IPD and 73.3% for CTRL (both significant at $p < 0.05$). PPV are in the same range, with a PPV of 78.6% for CTRL and 73.3% for IPD.

3.2 Between tasks comparison

In terms of balanced accuracy, significant results could be obtained from the discrimination between the three tasks across the two groups of subjects when considering the whole brain and motor masks (Table 3.2). This result is confirmed by the PPV for each class, which are quite high. However, the signal in the MLR doesn't lead to a significant classification of the three tasks, which is further confirmed by the PPV (almost all samples are classified as STAND).

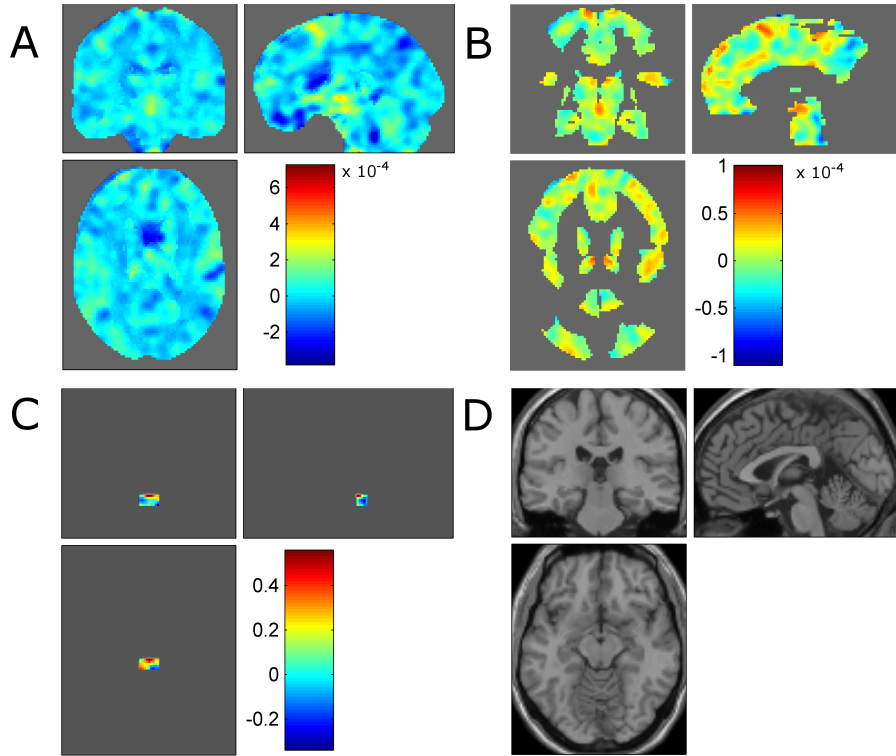


Fig. 1. Weights of the SVM model discriminating between CTRL (label +1) and IPD (label -1) based on the combination of the BRISK and COMF conditions, for **A** the whole brain, **B**, motor and **C** MLR masks (Note that the cross-hair position has been centred on the MLR for this panel). **D** displays the SPM single subject canonical structural image for better representation.

Table 2. Balanced acc_b and class accuracies (in %, PPV in brackets) of the multiclass GP model discriminating between the three tasks (STAND, COMF and BRISK) when considering both groups jointly. Significant results are displayed in bold.

Mask	acc_b	STAND	COMF	BRISK
Whole brain	65.5	58.6 (65.4)	41.4 (75.0)	96.6 (62.2)
Motor areas	66.7	62.1 (64.3)	41.4 (70.6)	96.6 (66.7)
MLR area	32.2	89.7 (32.1)	0.0 (0.0)	6.9 (33.3)

4 Discussion

In the present work, we classified the parametric maps of three tasks (STAND, COMF and BRISK) to identify idiopathic Parkinson’s disease patients from healthy controls. The best model discriminated significantly between IPD and

controls with a balanced accuracy of 76%, when using the signal comprised in the mesencephalic locomotor region. Furthermore, combining the mental imagery of gait at comfortable and brisk paces led to consistent and significant results across feature sets.

Although these results are not overwhelming, it is (to the best of our knowledge) one of the first significant classification between IPD and controls [7,12]. In view of the simplicity of the model (SVM with a filter feature selection), this result is promising and suggests that mental imagery of gait could be a biomarker of Parkinson’s disease although improvements need to be performed before being able to deal with more complex issues, such as diagnosing Parkinson’s disease in its early stage, or distinguishing between IPD and Parkinson Plus Syndroms.

However, distinguishing between the three tasks using both groups led to significant results when considering the whole brain and motor masks, suggesting that the between-subject variability within one group is large compared to the between-groups variability for those features. This result highlights the importance of feature selection in the present case and favours the use of wrapper or embedded feature selection techniques to increase the performance of the machine learning based models. Regarding the Parkinsonian group, the between-subjects variability might further be explained by the heterogeneity of the gait disorders in patients. Distinguishing between patients with light or severe gait disorders, for example by considering the Freezing of Gait (FoG, [19]), might increase the ratio of between versus within group variability and thereby improve the classification.

Finally, although a large overlap has been observed between mental imagery of gait and actual gait in healthy subjects [20], our results question the overlap between mental imagery of disturbed gait and actual disturbed gait, especially in the STAND and BRISK conditions. Solving this issue is not straightforward but developments in ambulatory Electro-EncephaloGraphy (EEG) acquisition systems and in the decoding of this type of signal might bring a solution by directly acquiring the brain activity under actual gait.

5 Conclusion

Finding a biomarker of Parkinson’s Disease allowing for the detection of IPD remains an open issue, but we have shown here that BOLD signal recorded during controlled mental imagery is a good candidate. Indeed the activity in the mesencephalic locomotor region induced by mental imagery of gait at a comfortable pace leads to promising results.

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