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Longitudinal comparison of subjects with and without Sleep Disorders in Parkinson's Disease

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1. Introduction

Patients with Parkinson's Disease (PD) may have very different patterns of progression, corresponding to distinct disease subtypes. Here, we describe quantitatively the overall pattern of progression in subgroups of PD by using a Bayesian non-linear mixed effect model that describes the continuous progression of biomarkers at both population and individual level. This approach allows to model variability in progression patterns and disease stage between patients. We analyzed two subgroups of patients, with (RBD+) and without sleep disorders (RBD-), that are known to present different patterns of progression [1]. We compared the two groups by extracting the ordering of abnormalities that occurred over the disease course, and by studying their disease onset and speed of progression.

2. Methods

2.1 Data

We used the Idiopathic PD patients of the PPMI Dataset. We considered eight biomarkers to describe the disease progression. First four clinical scores, the MDS-UPDRS part III, MoCA, SCOPA-AUT and REM-quizz, measuring respectively motor, cognitive, autonomy and sleep dysfunctions. Second, we included four measures from DatScan imaging, the Striatal Binging Ratios (SBR) of left and right side of both Putamen and Caudate. From the 362 idiopathic PD patients of the PPMI dataset, we excluded patients that had less than two visits of the biomarkers to obtain 349 patients. Patients that reached a REM-quizz score of 6 over 9 at least once over the course of the study were labeled as REM+ (94 patients), the others as REM- (249 patients).

2.2 Modeling approach

We used a multivariate non-linear Bayesian mixed-effect model, introduced in [2] and extended in [3], to estimate the longitudinal progression of clinical and imaging scores. We estimated both population and individual parameters of patients, to obtain the average and individual trajectories, respectively. Sub-group trajectories were obtained by averaging individual parameters over the patient sub-groups. Then, to assess the robustness of our method, accounting for both sampling bias and stochastic variations in the estimation algorithm, we performed a patient-wise repeated cross validation (10x5 folds) on our dataset.
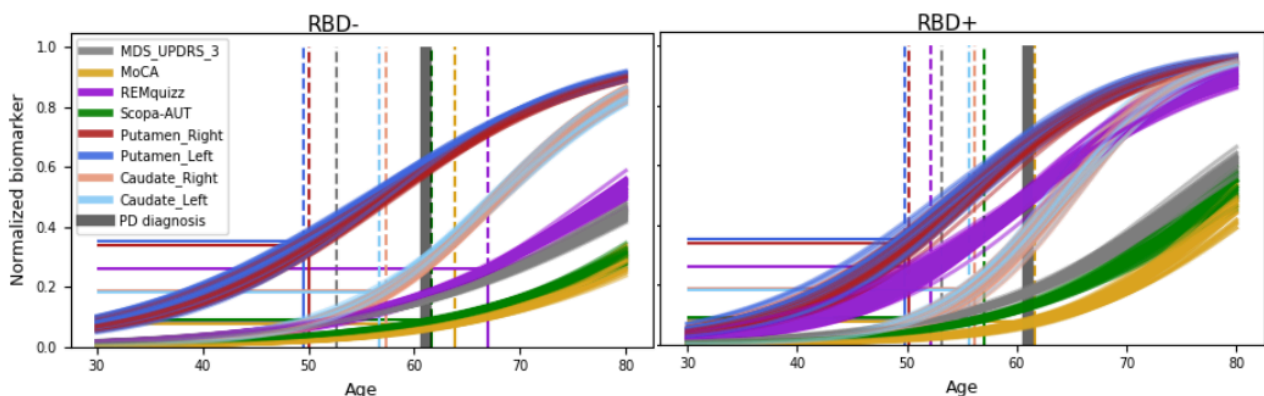

Figure 1: Cross validated (10x5) average scenario of progression for the 2 subgroups, relative to age. Abnormality thresholds (straight lines) are mapped to the corresponding age of occurrence (dotted lines). Note the major difference for the REM-quizz (chosen split criterion).

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2.3 Average progression RBD+ RBD-

With the methodology described above, we obtained 50 sub-population average trajectories for each group (RBD- and RBD+), shown in Figure 1. To build a hierarchy of arrival of abnormalities of PD biomarkers that may progress at very different speeds and occur at different ages, we introduced abnormality thresholds. For each biomarker independently, thresholds were computed from the data as the optimal cut-off for a balanced logistic regression between PD patients and controls at baseline. We then computed the times of intersection between the averaged trajectories of the sub-groups and these abnormal thresholds to assess an abnormality timing density for each modality. Densities are shown as boxplots in Figure 2.
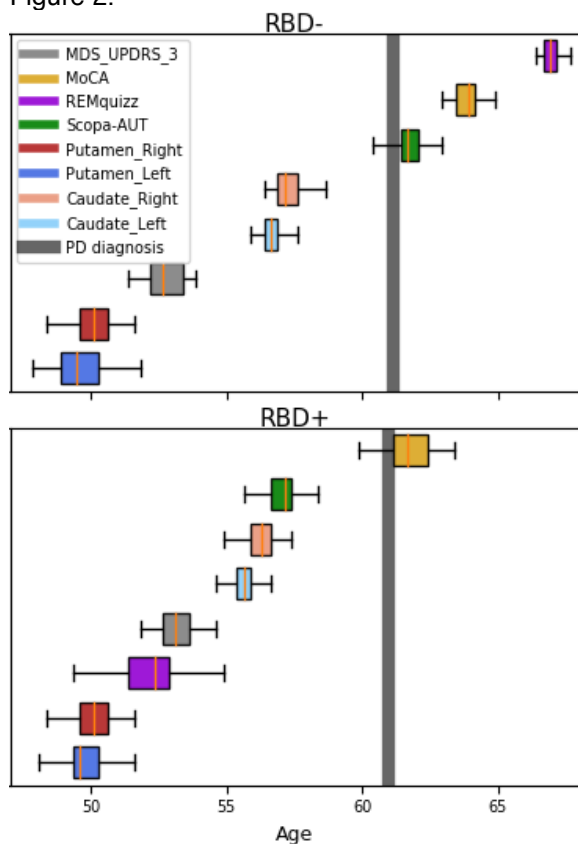

Figure 2: Boxplot of cross validated (10x5) times of intersection with threshold of abnormalities for each considered biomarker. Average age of conversion to PD is mostly the same for both groups.

3. Results and discussion

The ordering of abnormalities between modalities in the two groups was the same, at the exception of REM-quizz since it discriminated our 2 groups (Figure 2). The first abnormality was observed in the putamen, followed by MDS-UPDRS part III then, caudate,

scopa and finally MoCA. Note that MDS-UPDRS abnormality occurred early, as even few points of MDS-UPDRS label patients as PD in our logistic regression. Thus, we could also consider the age at disease onset, mainly based on motor scores, to represent a more advanced stage of motor abnormality. Noticeably, the distance to PD average age at diagnosis differed between the two subgroups. In RBD- patients, autonomic dysfunction occurred shortly after conversion to PD, whereas in RBD+, the SCOPA-AUT was already abnormal up to 4 years before conversion. To a lesser extent, MoCA abnormalities occurred earlier in RBD+ than in RBD-. Finally, considering only the individual parameters estimated by the model, we found that RBD+ were affected in average 6 years earlier than RBD-, and progressed 30% faster in average.

4. Conclusions

Using a longitudinal model, we were able to compare two sub-populations of a longitudinal cohort in several ways: progression speed, age at onset and ordering of abnormalities. RBD+ were affected 6 years earlier and progressed 30% faster. They also presented autonomic dysfunction up to 4 years before PD diagnosis whereas these symptoms occurred around PD onset in RBD- patients.

These results stand as a proof of concept for longitudinal group comparison methodology, which could be applied to other types of diseases. Furthermore, this first subgroup analysis lay the foundations of a more precise subtyping of patterns of progression in PD.

5. Acknowledgements

6. References

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