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# Non-parametric modeling for dopaminergic treatment effect in Parkinson's disease

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## ➤ Introduction

Disease progression models have been shown to successfully recover the natural history of the disease at a population level and also at an individual level, thus providing reliable predictions for the future disease progression. However these models usually do not account for the effect of a treatment. We propose a method to combine a disease progression model with a non-parametric conditional average treatment effect (CATE) model. We apply it to dopaminergic treatment in Parkinson's disease (PD). Our treatment model also allows for the analysis of the influence of covariates over treatment efficiency.

## ➤ Method

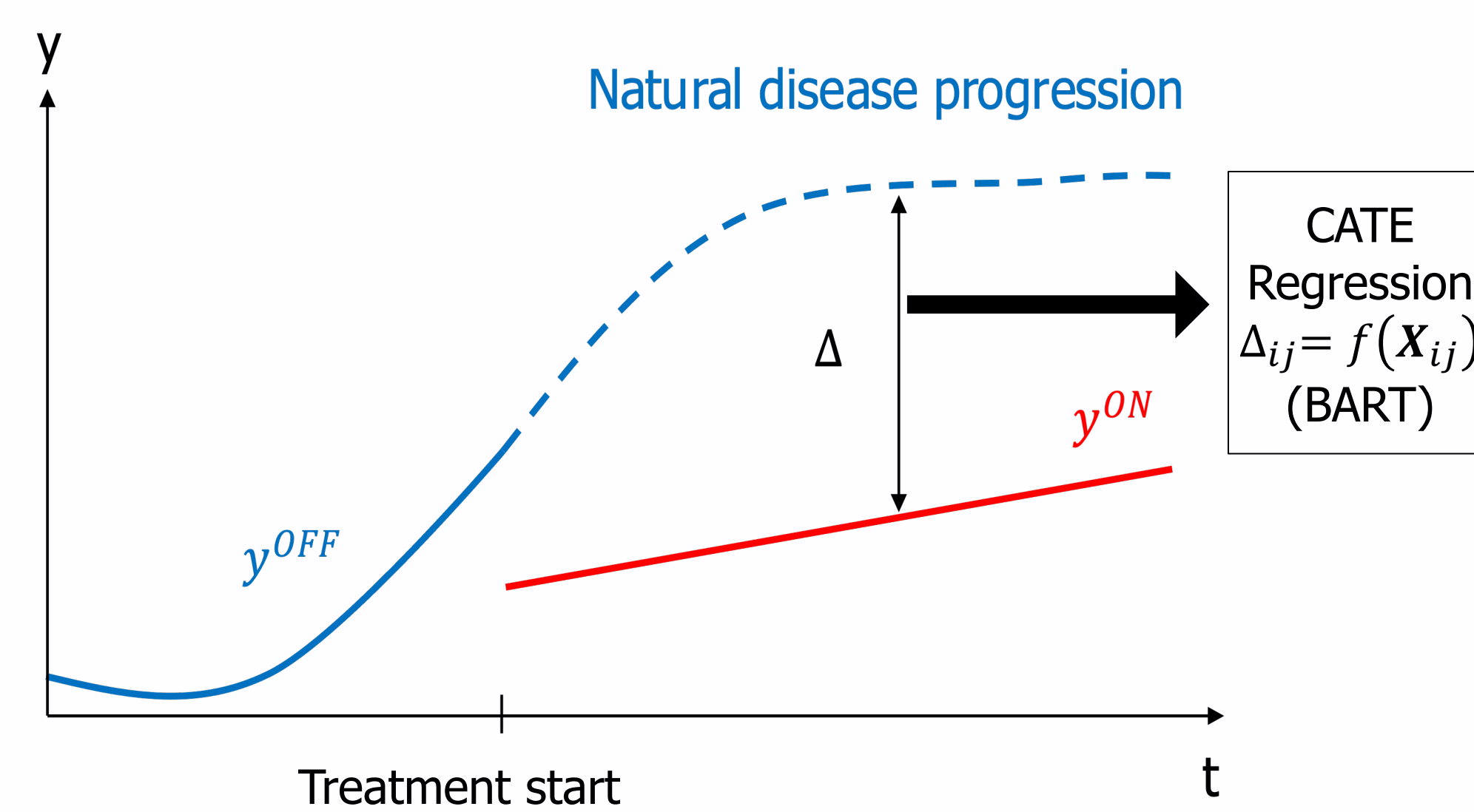
- Observations:  $y_{ij}^{ON}$  of patient  $i$  at age  $t_{ij}$  after taking drug (ON state),  $y_{ij}^{OFF}$  when treatment effect wears off (OFF state)
- Disease course mapping (DCM) model: a Bayesian mixed-effect model predicts natural progression of the disease
- Treatment effect: difference between OFF and ON states
 
$$y_{ij}^{OFF} - y_{ij}^{ON} = \Delta_{ij}$$
- In the absence of observed  $y_{ij}^{OFF}$  we use DCM predictions :
 
$$\Delta_{ij} \approx DCM(t_{ij}; z_i) - y_{ij}^{ON}$$
- CATE model:  $\Delta_{ij} = f(X_{ij})$  with time-dependent variables  $X_{ij}$
- Covariate importance  $X_{ij}$  is computed as percentage of total variance explained

## ➤ Data (from PPMI\*)

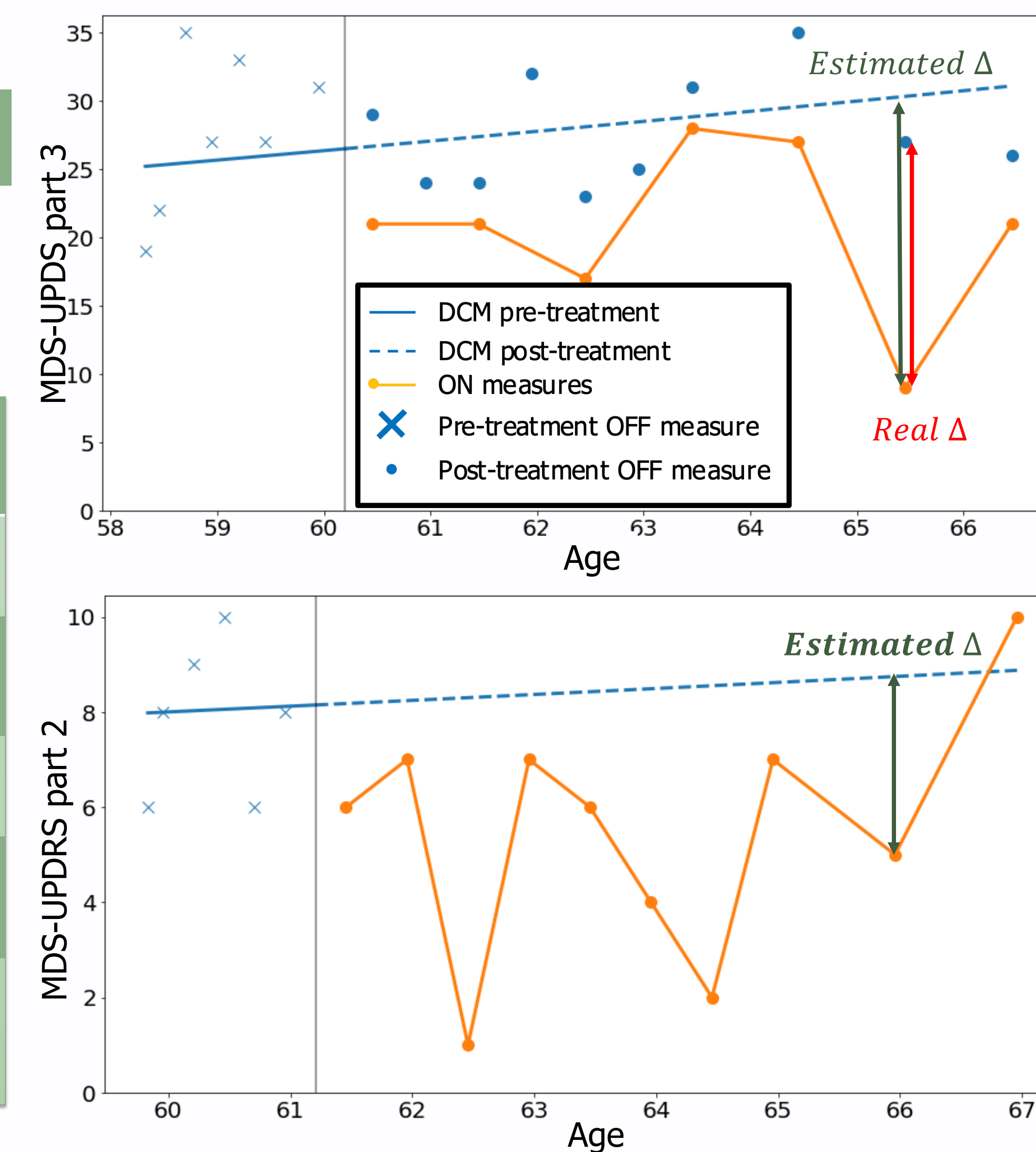
Outcome: MDS-UPDRS parts 2 and 3 (OFF only available for part 3).  
Treatment variables: Levodopa equivalent daily dose (LEDD) and category (Levodopa, dopamin agonist...)

# Patients	# Visits/patient	Mean age	Follow-up (years)	Sex
900	8.8±5.6	64.6±10.0	4.0±2.8	W:36%,M:64%
MDS-UPDRS 1	MDS-UPDRS 2	MDS-UPDRS 4	Dose (LEDD mg)	Weight
8.0±5.6	8.7±6.4	1.2±2.5	565±904	78.5±16.8
State	# observations	MDS-UPDRS 3	Time since dose (h)	PIGD score TD score
ON	2285	21.3±12.0	2.1±1.3	2.1±2.2
OFF	7519	25.5±12.4	14.9±9.3	5.4±4.5

Model scheme for one patient



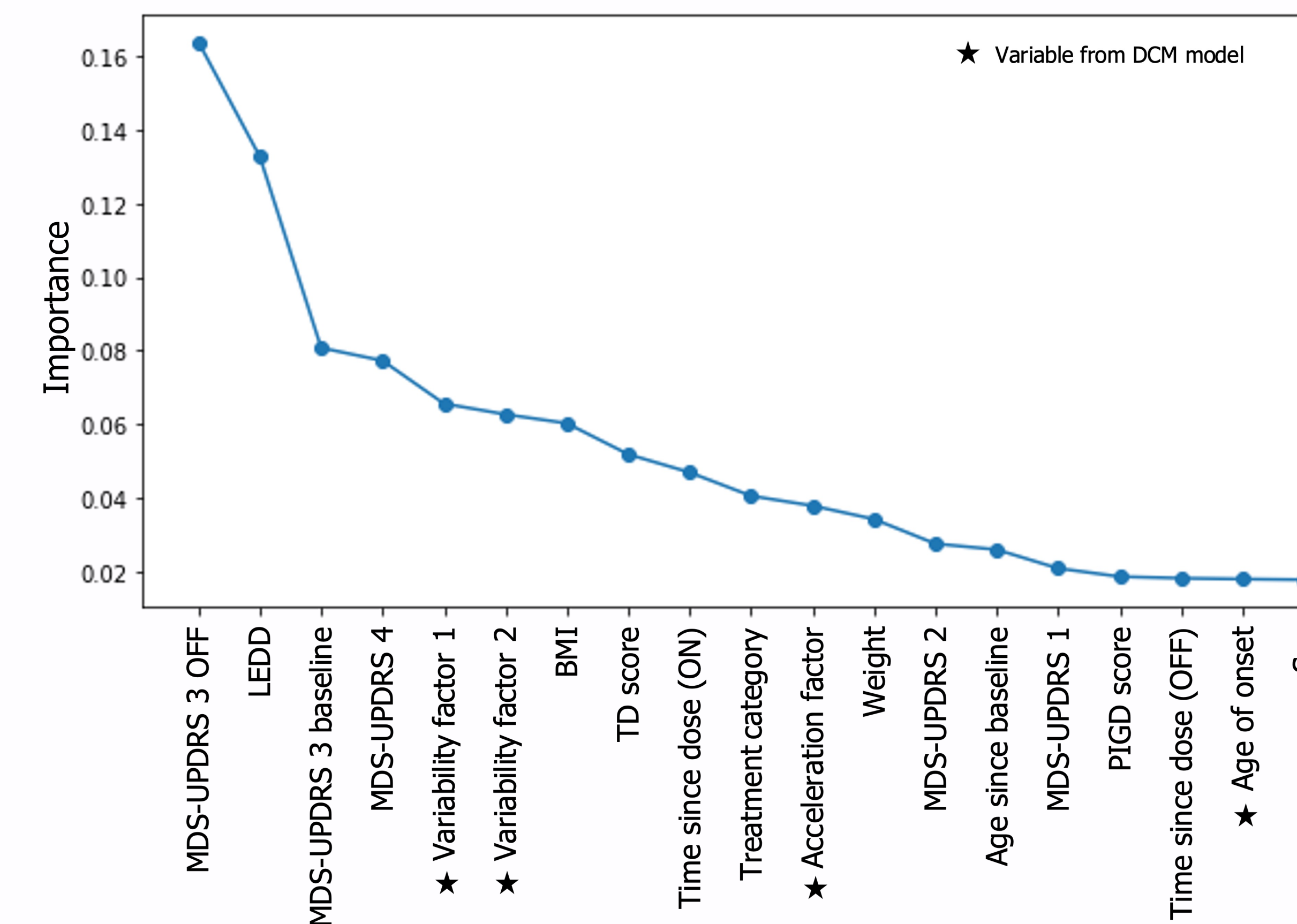
Patient samples



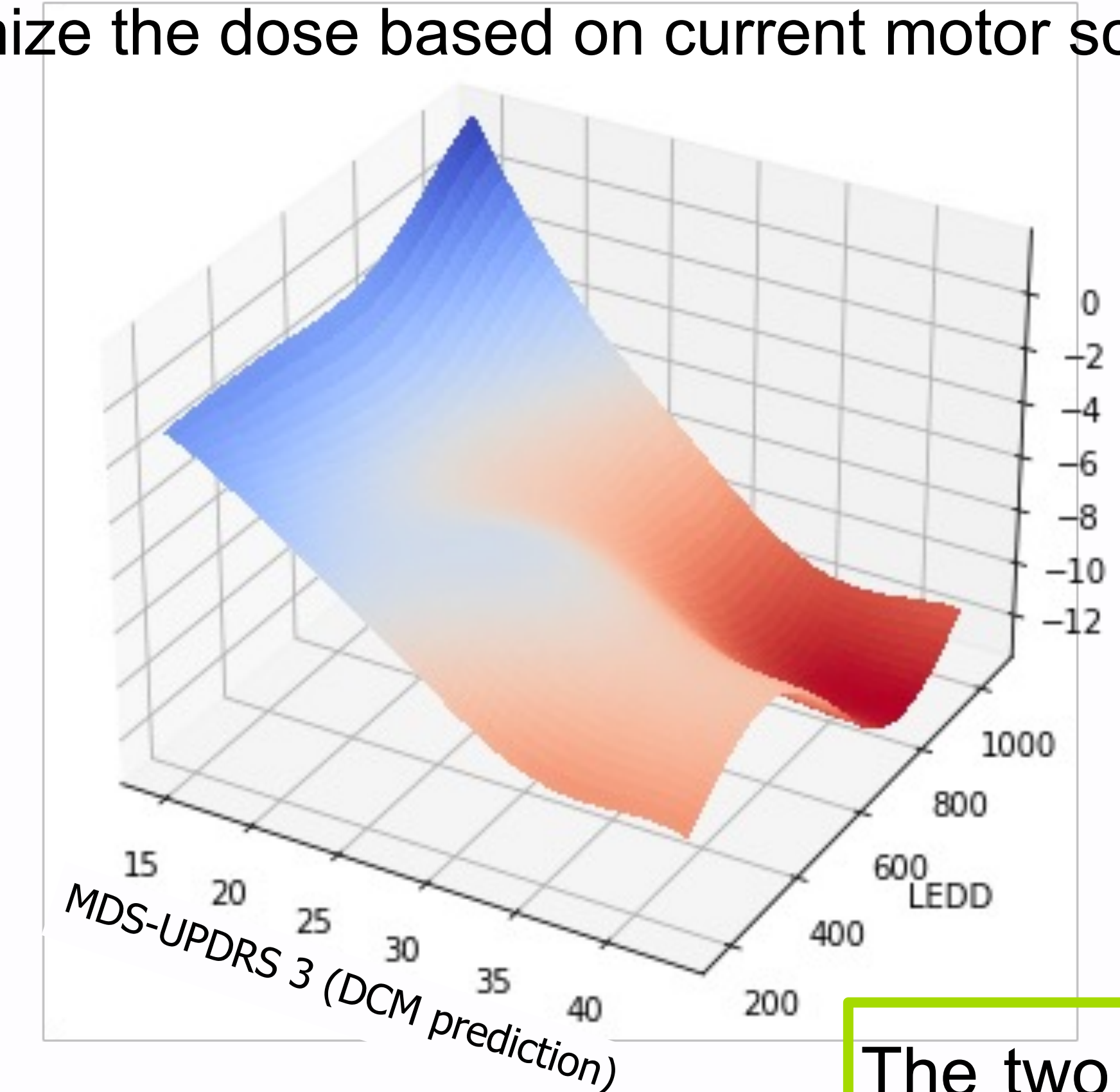
## ➤ Results

### Treatment effect on part 3 (motor)

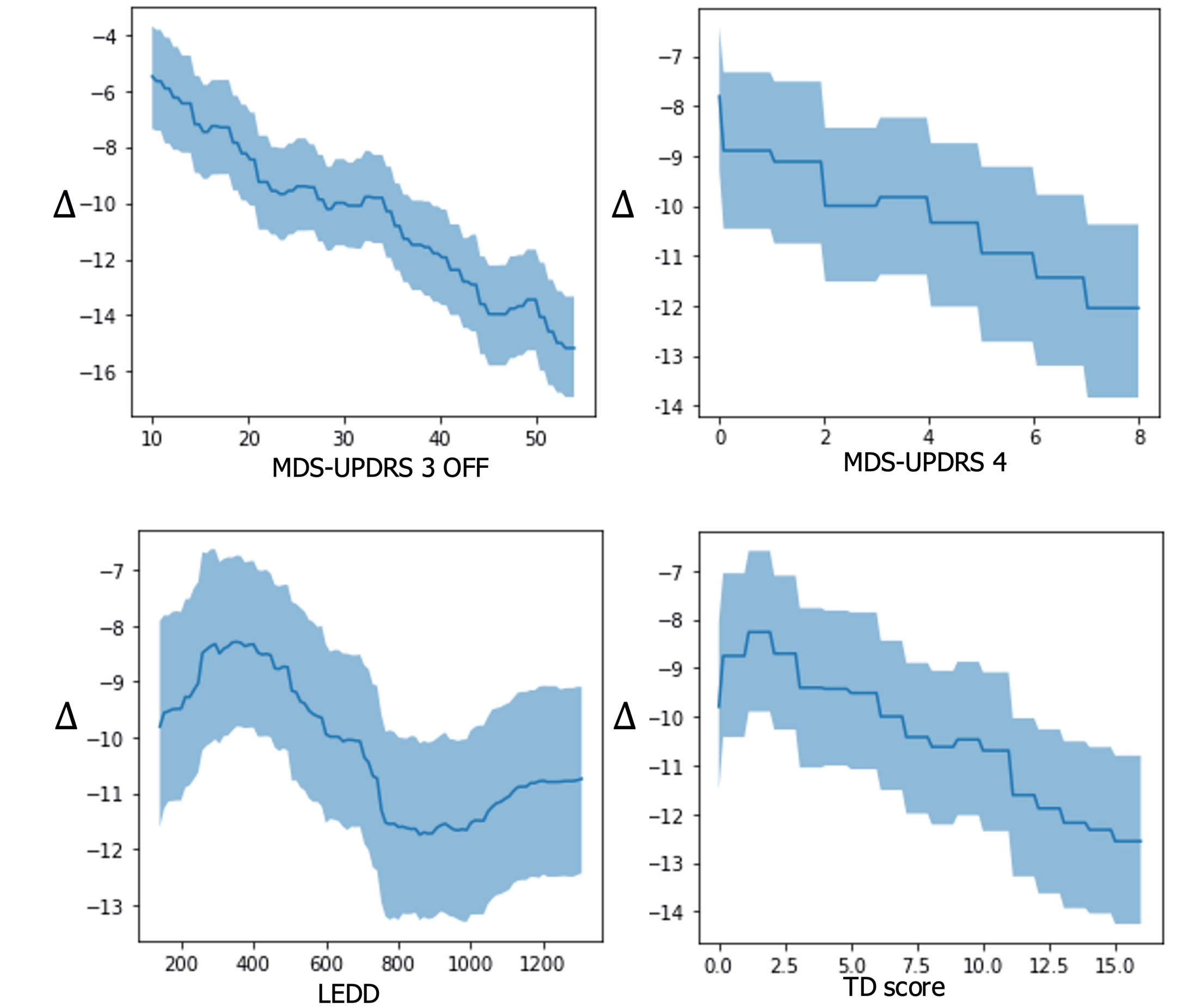
- $R^2$ : 0.82
- Variable importance: Current motor state (MDS-UPDRS 3 OFF) explains most of the variance because it is proportional to treatment effect. Dopaminergic treatment improves this score by 35% approximately. Otherwise treatment dose is most impactful .



- Covariates interaction on treatment effect: Our model allows to understand how several covariates interact. The next figure shows how we can optimize the dose based on current motor score.

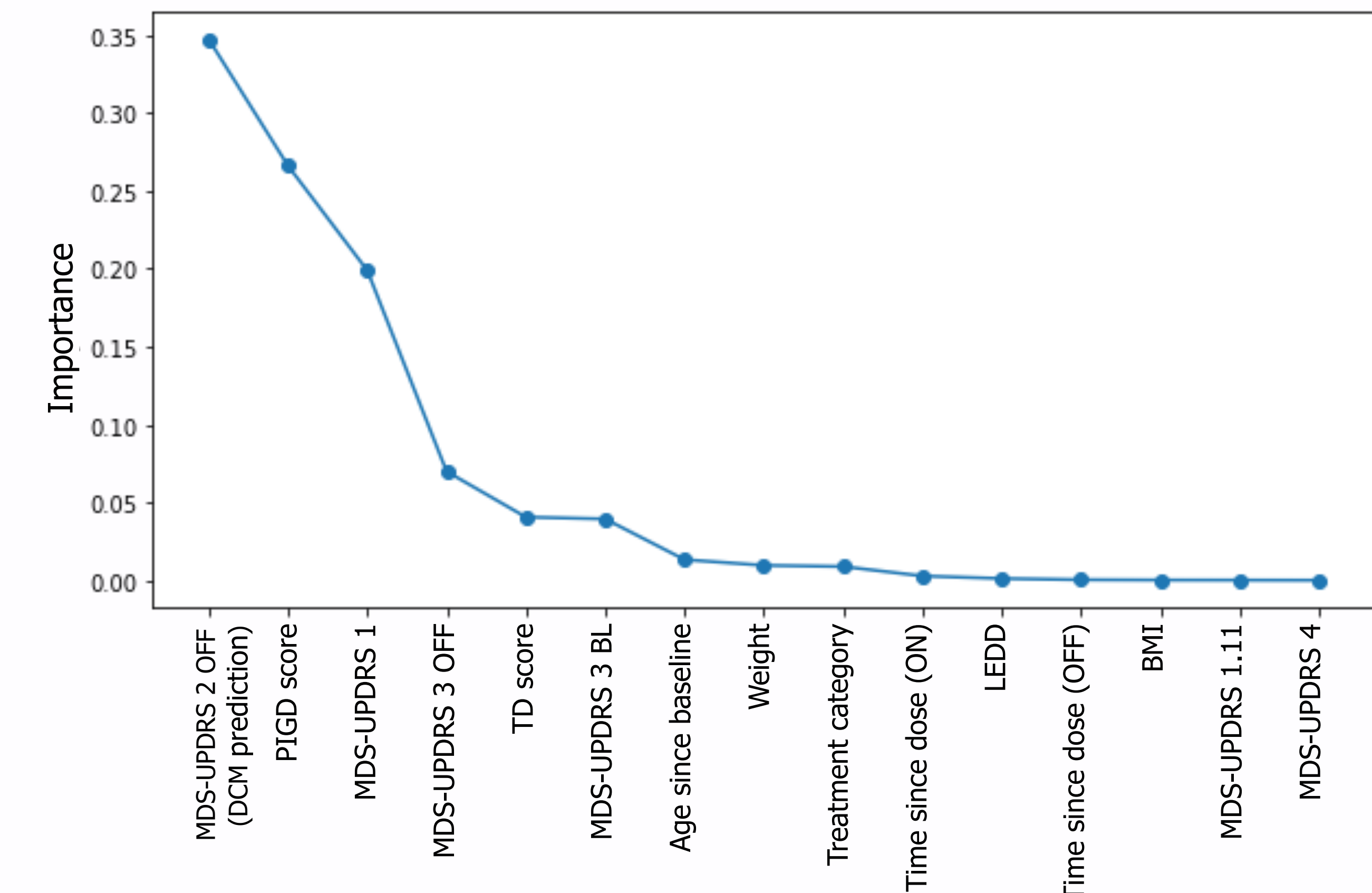


- Covariates impact on mean treatment effect: Secondary effects (MDS-UPDRS 4) are correlated to better motor outcome. Treatment effect increases with dose but plateaus at high LEDD. Patients with higher tremor (TD score) are more treatment responsive.



### Treatment effect on part 2 (Quality of life)

- $R^2$ : 0.83
- Variable importance: most notable is PIGD score, high PIGD patients experience less treatment effect.



The two variables which influence the most the treatment effect on motor outcome are the dose and the current disease state. Our model is able to learn treatment effect even in the absence of placebo or control arm.

## ➤ Conclusion