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Similarities in Brain Damage Across the Spectrum of Multiple Sclerosis

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SUMMARY

1 Across the RRMS-SPMS continuum, NBV was predicted with an error of 3.74% using the most relevant variables (i.e. T2 lesion volume, sex, age, duration since first symptom, and EDSS). Similar accuracy was obtained when the same model was used to predict PPMS patients' NBV, indicating that PPMS could be integrated in the continuum

2 Brain changes occurring over two years in RRMS, SPMS and PPMS affected similar regions, suggesting a common mechanism

INTRODUCTION

- Multiple Sclerosis (MS) clinical phenotype descriptors have been defined and revised based on consensus definition. However, relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive MS (PPMS) have no biologically distinct features

OBJECTIVE

- Our objective was to study disease related brain damage across the MS disease spectrum and to investigate whether PPMS could be integrated into the RRMS-SPMS continuum

METHODS

- Clinical and imaging data from ~8000 patients across the spectrum of MS from 9 clinical trials included in the Novartis-Oxford MS database were used for this analysis
- Key baseline variables (among demographics, clinical and MRI measures) in determining the baseline normalized brain volume (NBV) were selected via random forest variable importance using data from RRMS and SPMS patients. Linear regression models with the selected variables were then used to model baseline NBV in RRMS/SPMS patients
- To compare NBV prediction accuracy in RRMS/SPMS versus PPMS, 10-fold cross-validation was used to repeatedly split the RRMS-SPMS dataset into model training data and hold-out data. Prediction accuracy of the models on RRMS/SPMS hold-out data was compared to the prediction accuracy of the same models on the PPMS dataset. Accuracy for NBV was measured with mean absolute percentage error (MAPE) with a scale-invariant approach
- Regarding brain changes happening across the spectrum of MS, T1-weighted images acquired at Month 24 were non-linearly registered to the baseline ones after pre-processing, generating Jacobian maps of placebo RRMS, SPMS and PPMS patients that were subsequently qualitatively compared

RESULTS

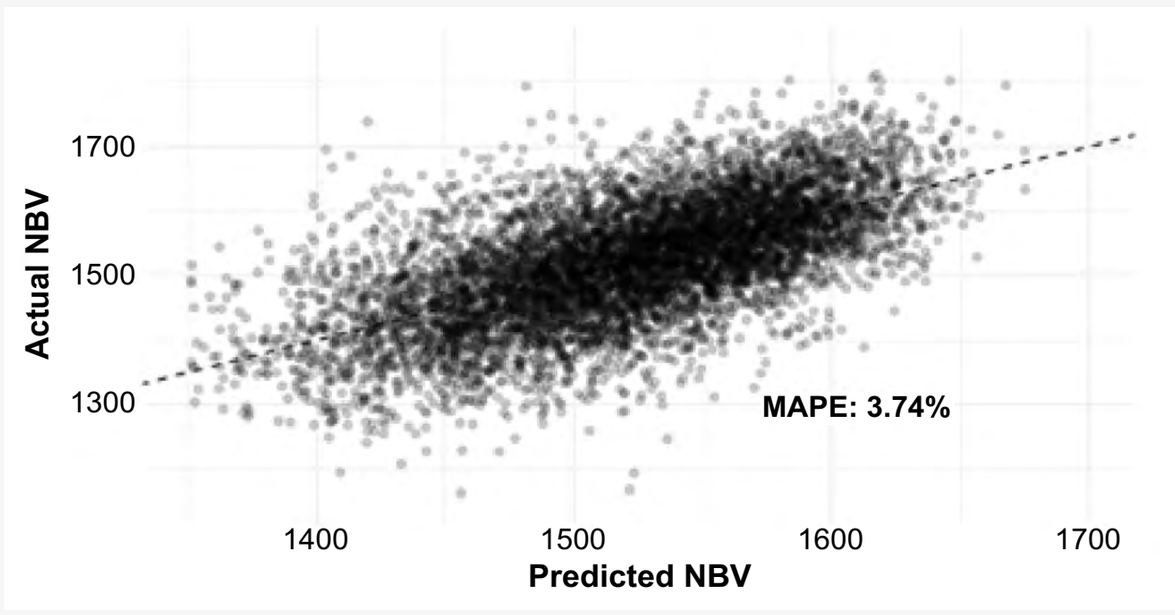
- The baseline characteristics are typical for RRMS, SPMS and PPMS patients (**Table 1**). The cumulative level of brain damage (reflected by higher T2 lesion volume and lower NBV) and disability levels were higher in SPMS patients compared to RRMS and PPMS patients
- In the baseline analysis of RRMS/SPMS data, from the tested variables, T2 lesion volume was the most relevant disease-related predictor of NBV, followed by age, duration since first symptom, EDSS and sex
- Using those covariates in the linear model, NBV was predicted with a MAPE of 3.74% across the RRMS-SPMS continuum (**Figure 1**)
- Similar accuracy (MAPE=3.63%) was obtained when the RRMS-SPMS model was used to predict PPMS patients' NBV (**Figure 2**)

Table 1. Population characteristics at baseline

Characteristic	RRMS (N=5986)	SPMS (N=1445)	PPMS (N=625)
Age, years, mean ± SD	37.4 ± 9.95	47.8 ± 7.82	48.5 ± 8.13
Sex, female, number (%)	4221 (70.5)	863 (59.7)	304 (48.6)
Duration since first symptom, years, mean ± SD	8.0 ± 7.18	16.7 ± 8.23	5.7 ± 2.4
EDSS, median [min, max]	2.0 [0, 6.5]	6.0 [1.0, 7.0]	4.5 [2.0, 6.5]
NBV, cm^3, mean ± SD	1530 ± 87.8	1460 ± 87.9	1490 ± 79.6
T2 lesion volume, cm^3, mean ± SD	7.1 ± 8.90	15.2 ± 14.70	5.1 ± 7.31
Gd-enhancing T1 lesions, number, mean ± SD	1.8 ± 4.15	0.9 ± 3.18	1.0 ± 2.18

EDSS, expanded disability status scale; Gd, gadolinium; MS, multiple sclerosis; NBV, normalized brain volume; RRMS, relapsing-remitting MS; SD, standard deviation; SPMS, secondary progressive MS; PPMS, primary progressive MS.

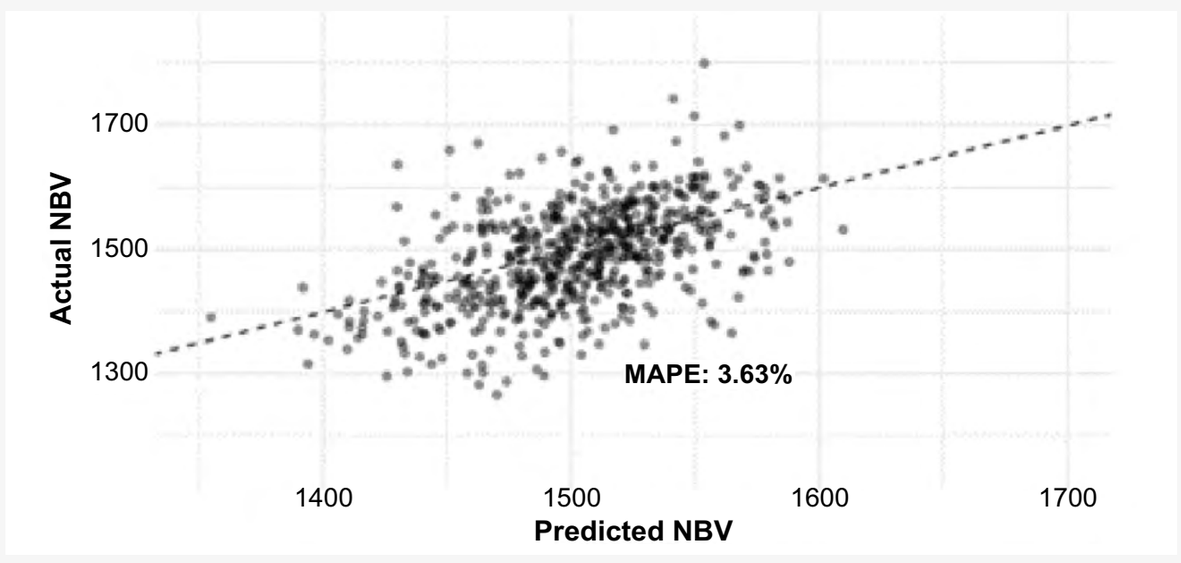
Figure 1. RRMS/SPMS: Predicted vs actual NBV (cm^3) at baseline



Predicted NBV derived from linear model adjusted for T2 lesion volume, age, sex, duration since first symptom, and EDSS. Predicted NBV values and MAPE was obtained from RRMS/SPMS hold out data.

EDSS, expanded disability status scale; NBV, normalized brain volume; MAPE, mean absolute percentage error.

Figure 2. PPMS: Predicted vs actual NBV (cm^3) at baseline

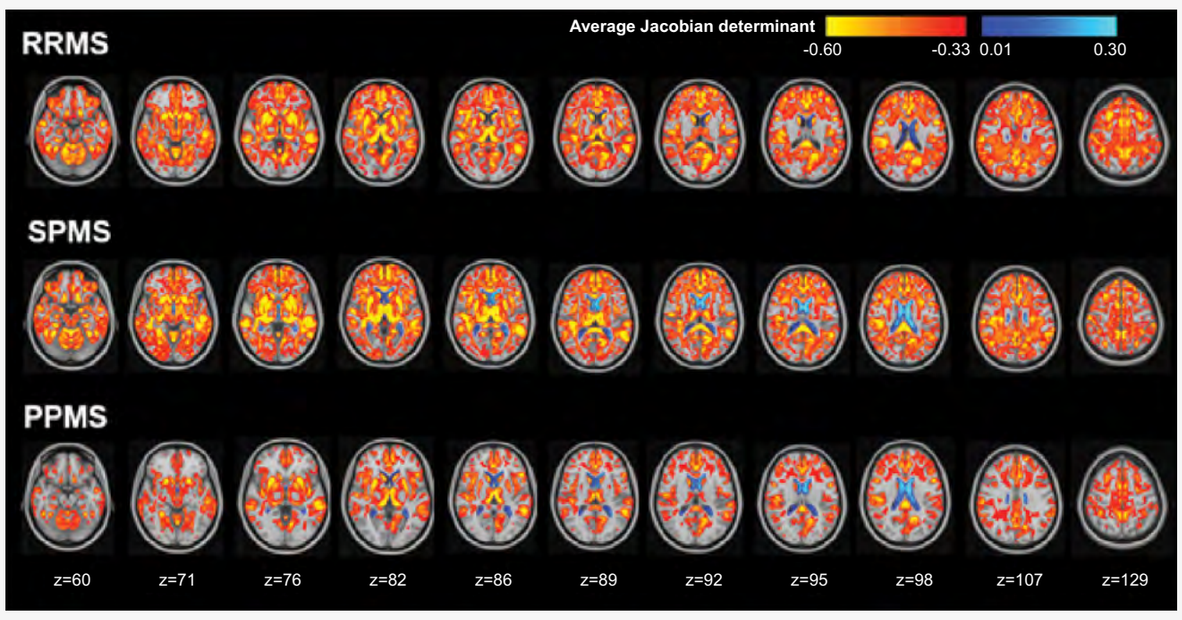


Predicted NBV derived from linear model fit on RRMS/SPMS patients adjusting for T2 lesion volume, age, sex, duration since first symptom and EDSS. Predicted NBV for each patient was obtained as the average prediction from the 10 different models trained during cross-validation.

EDSS, expanded disability status scale; NBV, normalized brain volume; MAPE, mean absolute percentage error.

- After quality controls of the non-linear registration, Jacobian maps in the MNI template space were average for each MS subtype (RRMS: n=523, SPMS: n=191, PPMS: n=271)
- Qualitatively, the averaged Jacobian maps showed more extensive changes in RRMS and SPMS. Regional contraction and expansion in PPMS patients were affecting similar regions to those in relapsing-onset MS suggesting a common mechanism (**Figure 3**)

Figure 3. Longitudinal brain changes in placebo RRMS, SPMS and PPMS patients over two years



Brain changes were expressed as average Jacobian determinant mapped to the MNI space. Corrections for age, duration since first symptom, EDSS or other baseline variables were not applied. Red/yellow color represents contraction, blu/light blue represents expansion. EDSS, expanded disability status scale; MS, multiple sclerosis; RRMS, relapsing-remitting MS; PPMS, primary progressive MS.

CONCLUSION

- Our analysis supports the view that, biologically, at the level of the brain, RRMS-SPMS can be regarded as a disease spectrum over time, and that PPMS is fundamentally part of that same spectrum

Abbreviations: EDSS, expanded disability status scale; **Gd**, gadolinium; **MS**, multiple sclerosis; **MAPE**, mean absolute percentage error; **NBV**, normalized brain volume; **RRMS**, relapsing-remitting MS; **SD**, standard deviation; **SPMS**, secondary progressive MS; **PPMS**, primary progressive MS.

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