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Abstract Title: Similarities in Brain Damage Across the Spectrum of Multiple Sclerosis

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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.
Objectives/Aims:
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:
Using clinical and imaging data from ~8000 patients across the spectrum of MS (RRMS n=5986; SPMS n=1445, PPMS n=625) from the Novartis-Oxford MS database (9 clinical trials), we first selected key baseline variables (among demographics, clinical and MRI measures including the T2 lesion volume) in determining the baseline normalized brain volume (NBV) using random forest variable importance in the RRMS-SPMS continuum. Secondly, we used a linear regression with the selected covariates to model baseline NBV in RRMS/SPMS patients. To compare NBV prediction accuracy for RRMS/SPMS versus PPMS, 10-fold cross-validation was used and the prediction accuracy of the model on the corresponding RRMS/SPMS hold-out data was compared to the prediction accuracy of the same model on the PPMS dataset. Accuracy for NBV was measured with mean absolute percentage error (MAPE) with a scale-invariant approach. Jacobian maps derived from MRIs of placebo-treated relapsing-onset MS vs PPMS patients over two years were qualitatively compared.
Results:
At baseline, 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 patients. Comparing PPMS patients to patients in the RRMS-SPMS continuum, PPMS patients had a notable T2 lesion volume and a NBV more comparable to SPMS rather than RRMS. From the tested variables, T2 lesion volume was the most relevant disease related predictor of the NBV (other relevant baseline predictors were age, duration of MS, EDSS and sex). Across the RRMS-SPMS continuum, NBV was predicted with a MAPE of 3.74%. Similar accuracy

(MAPE=3.63%) was obtained when the RRMS-SPMS model was used to predict PPMS patients' NBV. The averaged Jacobian maps showed that regional contraction and expansion in PPMS patients were similar to those in relapsing-onset 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.

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