SUPPLEMENTARY STATISTICAL METHODS:

Rates of brain substructure volume fraction change were compared between DMT groups with mixed-effects linear regression models with random intercepts and random slopes in time, as shown below:

$$V_{ijk} = (\beta_0 + b_{i0} + b_{ij0}) + (\beta_1 + b_{ij1}) * Time_{ijk} + \beta_2 * DMT_{ij} * Time_{ikj} + \beta_3 * DMT_{ij} + e_{ijk}$$

The dependent variable V_{ijk} represents the volume fraction of interest for subject *i*, during DMT epoch *j*, at visit *k* and is modeled as a function of "fixed-effects" ($\beta_0 \ldots \beta_3$) and subject- and DMT epoch-specific "random-effects" b_{i0} and b_{ij0} (random intercepts at the subject and DMT epoch levels respectively) and b_{ij1} (random slope at the DMT epoch level). Random slope in time at the subject level was not included as this did not provide an improved fit in our models as assessed by comparing models utilizing likelihood ratio tests. $Time_{ijk}$ is follow-up time as a continuous variable (in years) starting at the time of the baseline MRI of a given DMT epoch and e_{ijk} is the error term. DMT_{ij} designates the DMT category for each subject at a given DMT epoch (DMT-L: 0; DMT-H: 1). Consequently β_1 represents the annualized rate of change during the DMT-L epochs and β_2 corresponds to the difference in the annualized rate of change between the DMT-L and DMT-H epochs.

Mean annualized percent change and 95% confidence intervals by DMT epochs were calculated for each volume fraction by use of a log-linear model, which involves logarithmically transforming the dependent variable of interest and then analyzing utilizing the mixed-effects models presented above. Utilizing this model, the calculated beta coefficients and their respective 95% confidence intervals (CI) correspond approximately to annualized percent change of the dependent variable of interest.

In addition to the unadjusted model shown above, analyses were performed with inclusion of covariates including baseline age (centered at 40 years), race (African-American or non African-American), sex, disease duration (centered at 8 years), EDSS (centered at 2.5), and their respective interactions with follow-up time. Furthermore, in order to investigate the contribution of inflammatory disease activity to the differences observed in the total subcortical GM, thalamic and putaminal atrophy rates between the DMT groups, these analyses were also adjusted for baseline logarithmically transformed T2 lesion volume fractions (inflammatory disease activity prior to study period), DMT epoch-specific rates of T2 lesion volume fraction change during the study (inflammatory disease activity during follow-up), and their respective interactions with follow-up time. DMT epoch-specific rates of T2 lesion volume fraction change during the study were calculated from the unadjusted mixed-effects linear regression models using empirical best linear unbiased predictors (BLUPs) to assign values to the treatment interval-specific slopes. In order to ease interpretation of the beta coefficients, the baseline T2 lesion volume fractions and treatment interval-specific rates of T2 lesion volume change were transformed to Z-scores for this analysis. The full results from these multivariate analyses are presented in the Supplementary Results.

Residuals from the fitted models were visually examined and did not show any significant deviations from normality or homoscedasticity.