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**Proceedings Paper:**

Stabile, M.R., Manca, R., Bevilacqua, F. et al. (1 more author) (2016) White matter integrity and processing speed function in secondary progressive multiple sclerosis. In: Multiple Sclerosis Journal. ECTRIMS 2016, 14/09/2016 - 17/09/2016, London. SAGE Publications , p. 876.

<https://doi.org/10.1177/1352458516664293>

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## **White matter integrity and processing speed function in secondary progressive multiple sclerosis.**

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**Objective:** This study aimed at investigating the influence of white matter (WM) degeneration on speeded cognition in secondary progressive multiple sclerosis (SPMS).

**Background:** Cognitive deficits, especially in processing speed (PS), and fatigue are consistently reported as more severe in SPMS compared to the other MS phenotypes. Furthermore white matter (WM) neurodegeneration rather than demyelination is thought to drive the steady functional decline in SPMS. However, the relationship between WM integrity and PS has not been clarified yet.

**Methods:** Thirty one patients with SPMS (mean age, 52.5 years; mean disease duration, 15.5 years; mean EDSS, 6.4) had detailed neuropsychological assessment. An index of complex cognitive PS was computed by combining TMT-A, Stroop speed, and Digit Cancellation. T1-weighted and diffusion weighted MR images were acquired. Voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS) techniques were used to investigate: the correlations between cognitive performance and both volumetric and microstructural measures; and the differences in brain measures between high (HP) and low speed performers (LP).

**Results:** Patients with more preserved PS function showed lower level of self-reported fatigue. Moreover both VBM and TBSS analysis showed that only the PS index and PS-dependent tasks correlated with volume and fractional anisotropy (FA) of left-lateralised WM tracts, namely the left superior longitudinal fasciculus and left inferior fronto-occipital fasciculus. Correlations did not survive after controlling for PS performance. Consistently the HP subgroup had more WM and higher FA than LP in the same WM tracts.

**Conclusions:** Complex cognitive PS seems to be associated to fatigue experienced by patients with SPMS. Moreover it relies on fronto-parietal WM associative tracts supporting attention and fast integration of information across the brain. Degeneration in these tracts may crucially affect performance in tasks requiring effective management of time and, in turn, timed everyday life activities.