

**Apathy and cognitive dysfunctions in Multiple Sclerosis:
a 4-year follow-up study.**

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Objectives: Cognitive dysfunctions are highly prevalent in people with Multiple Sclerosis¹ (MS), and negatively impact on occupational and social functioning². Early detection and prediction of cognitive decline in people with MS remain a key challenge of the healthcare systems. In the present longitudinal study we applied recent statistical approach to model cognitive changes and to assess whether apathy could be a behavioural predictor of cognitive decline in people with in MS.

Methods: We assessed 77 individuals with MS at three-time points (baseline, T0; 2-year follow-up, T1; 4-year follow-up, T2), by means of several clinical, behavioural, and cognitive measures. We applied a multivariate general linear model and a linear regression model to explore factors associated with cognitive change over time. We used a discrepancy-based evidence for loss of thinking abilities (DELTA) approach³ to measure cognitive decline during the follow-up period.

Results: Higher level of apathy at baseline predicted the progressive cognitive decline at follow-up, in particular of executive functioning (Beta= 0.372; t= 3.236; p= 0.002; 95% CI= 0.078 – 0.327); whereas higher level of depression at baseline predicted decline in visuospatial abilities (Beta= 0.278; t= 2.471; p= 0.016; 95% CI= 0.011 – 0.107). Interestingly, higher levels of education were significantly associated with a reduced rate of cognitive decline over time (Beta= -0.249; t= -2.153; p= 0.035; 95% CI= -0.682 – -0.026), whereas age, age at onset, disease duration, and level of disability were not. Moreover, participants with persistent apathy (diagnosis of apathy at T0, T1, and T2, A+A+A+) showed poorer inhibitory control (p<0.0001) than participants who had never received diagnosis of apathy (A-A-A-), and worse global cognitive functioning (p=0.004) and visuospatial planning (p=0.001) than participants who remitted from apathy (A+A+A-). Finally, global cognitive and executive functioning worsened during the 4-year follow-up in participants with persistent apathy (A+A+A+) and in those that developed apathy (A-A-A+; p ≤ 0.038).

Conclusion: Apathy represents an early marker of cognitive decline in MS. These findings have important clinical and prognostic implications.

1. Grzegorski et al. Reviews in the Neurosciences 28, 845-860 (2017).

2. Raimo et al. Neuropsychology 31, 811-821 (2017).

3. Asken et al. Journal of the International Neuropsychological Society 26, 464-479 (2020).