**Origins of Fatigue in an Early Multiple Sclerosis Cohort**
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**Objective:** To better understand fatigue in MS and to inform treatment.

**Background:**
Fatigue is a common and early symptom in multiple sclerosis (MS). The cause of fatigue is still unclear. Neuroimaging results have been contradictory and inconclusive. Fatigue co-occurs with depression, and there is some evidence linking fatigue with circulating pro-inflammatory processes and elevated body temperature. We examined the relationship between fatigue and several variables including MRI measures, mood, systemic inflammation, and disability in one MS cohort, which has not been done before.

**Design/Methods:**
Fatigue Severity Scale (FSS) assessed fatigue in 185 early MS patients (RADIEMS cohort). T2 lesion volume and normalized volumes of cortical and subcortical gray matter were measured from 3D T1 and T2 MRIs. Mental Health Inventory (MHI) assessed mood. Body temperature was measured aurally. BMI was recorded. Erythrocyte sedimentation rate (ESR rank) assessed systemic inflammation. EDSS assessed disability. Controlling for age and sex, stepwise regression (entry p=.05) predicted FSS with all variables.

**Results:** Negative mood (MHI, p<.001) and higher ESR (p=.017) were the only independent predictors of worse fatigue. When categorized as clinically-elevated versus non-elevated fatigue (FSS ≥4.0), negative mood (p<.001) and higher inflammation (p=.012) were again the only predictors. The probability of an elevated ESR (≥15) was almost double among patients with fatigue (27.9%) than without (14.7%, p=.028).

**Conclusions:** The results suggest that fatigue in MS is related to negative mood and inflammation. Damage to white matter tracts and cerebral atrophy may help explain fatigue in patients with more advanced disease, but we did not see this in our early cohort. We suspect that there may be different phenotypes of fatigue throughout the disease process and failure to consider this may explain why we’ve had difficulty determining what causes fatigue. Identification of phenotypes may lead to more targeted and effective treatments.