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Progression of regional grey matter atrophy in multiple sclerosis

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*Appendix 1.

See Stankoff and Louapre (doi:10.1093/brain/awy114) for a scientific commentary on this article.

Grey matter atrophy is present from the earliest stages of multiple sclerosis, but its temporal ordering is poorly understood. We aimed to determine the sequence in which grey matter regions become atrophic in multiple sclerosis and its association with disability accumulation. In this longitudinal study, we included 1417 subjects: 253 with clinically isolated syndrome, 708 with relapsing-remitting multiple sclerosis, 128 with secondary-progressive multiple sclerosis, 125 with primary-progressive multiple sclerosis, and 203 healthy control subjects from seven European centres. Subjects underwent repeated MRI (total number of scans 3604); the mean follow-up for patients was 2.41 years (standard deviation = 1.97). Disability was scored using the Expanded Disability Status Scale. We calculated the volume of brain grey matter regions and brainstem using an unbiased within-subject template and used an established data-driven event-based model to determine the sequence of occurrence of atrophy and its uncertainty. We assigned each subject to a specific event-based model stage, based on the number of their atrophic regions. Linear mixed-effects models were used to explore associations between the rate of increase in event-based model stages, and T_2 lesion load, disease-modifying treatments, comorbidity, disease duration and disability accumulation. The first regions to become atrophic in patients with clinically isolated syndrome and relapse-onset multiple sclerosis were the posterior cingulate cortex and precuneus, followed by the middle cingulate cortex, brainstem and thalamus. A similar sequence of atrophy was detected in primary-progressive multiple sclerosis with the involvement of the thalamus, cuneus, precuneus, and pallidum, followed by the brainstem and posterior cingulate cortex. The cerebellum, caudate and putamen showed early atrophy in relapse-onset multiple sclerosis and late atrophy in primary-progressive multiple sclerosis. Patients with secondary-progressive multiple sclerosis showed the highest event-based model stage (the highest number of atrophic regions, $P < 0.001$) at the study entry. All multiple sclerosis phenotypes, but clinically isolated syndrome, showed a faster rate of increase in the event-based model stage than healthy controls. T_2 lesion load and disease duration in all patients were associated with increased event-based model stage, but no effects of disease-modifying treatments and comorbidity on event-based model stage were observed. The annualized rate of event-based model stage was associated with the disability accumulation in relapsing-remitting multiple sclerosis, independent of disease duration ($P < 0.0001$). The data-driven staging of atrophy progression in a large multiple sclerosis sample demonstrates that grey matter atrophy spreads to involve more regions over time. The sequence in which regions become atrophic is reasonably consistent across multiple sclerosis phenotypes. The spread of atrophy was associated with disease duration and with disability accumulation over time in relapsing-remitting multiple sclerosis.

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