MRI-BASED HEALTHY BRAIN AGING MODELS REVEAL SPECIFIC ATROPHY PATTERNS DRIVEN BY MULTIPLE SCLEROSIS ACCORDING TO AGE, SEX, AND AGE AT ONSET

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INTRODUCTION and PURPOSE

Physiological aging is accompanied by various structural changes in the brain, including gray matter (GM) atrophy. These modifications are the result of complex neurobiological processes such as neuronal loss, synaptic pruning, and alterations in glial function.

Understanding the normal patterns and extent of GM atrophy during aging is essential, as it provides a baseline against which pathological changes can be compared. This distinction becomes especially important in neurological conditions like multiple sclerosis (MS), where disease-related brain abnormalities can overlap with or mimic those seen in normal aging. Gaining deeper insights into the mechanisms and manifestations of age-related brain changes will improve our ability to differentiate physiological aging from MS-related neurodegeneration, ultimately aiding in diagnosis, monitoring, and treatment strategies.

The aim of this study was to model healthy aging trajectories of whole brain and GM volumes in a multicenter dataset of healthy controls (HC) and apply these normative models to a large multicenter cohort of MS patients, to disentangle disease-specific patterns of atrophy across age, sex, and age at onset.

METHODS

Study population.

- 3D T1- and T2-weighted MRI scans from a large cohort of **995 HC** and **2016 patients with MS** were analyzed.

MRI Acquisition and Processing.

- MRI data were collected through the **Italian Neuroimaging Network Initiative (INNI)** repository (https://www.inni-ms.org/).
- Lesion-filled 3D T1-weighted images were used to quantify brain tissue volumes.
- Normalized brain volumes, including cortical and deep GM structures, were measured using FSL-SIENAx for whole brain and cortical GM, and FSL-FIRST for deep GM segmentation.

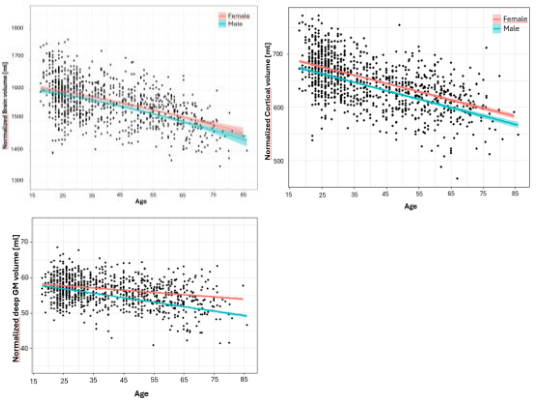
Statistical analysis.

- In the HC group, we developed **linear regression models to characterize age-related trajectories of brain volumes**. These models incorporated not only a linear age term but also an age-squared term to test for potential nonlinear patterns of atrophy during aging.
- Models were adjusted for sex and scanner differences, including their possible interactions with age.
- Using the regression models derived from the HC, we then generated **z-scores for each MS patient**, which represent the degree of deviation from expected age-related brain volume loss. This approach allowed us to isolate disease-specific atrophy by accounting for normal aging effects.
- **Analyses were stratified by sex and by age at disease onset**, distinguishing between pediatric-onset (POMS), adult-onset (AOMS), and late-onset MS (LOMS) groups, to explore potential differences in brain atrophy patterns across these clinical categories.

RESULTS

- In HC, **brain volume declined non-linearly with age**, while **cortical and deep GM volumes exhibited a linear decrease** (**Figure 1**).
- In **patients**, z-scores **showed a significant linear decline with age** ($p<0.01$), reflecting progressively more pronounced MS-driven brain, cortical, and deep GM atrophy over time.

Figure 1. Age-related trajectories of normalized brain, cortical and deep GM volumes in HC, according to sex.



- The decline associated with MS was **more pronounced in men for the cortex** ($p=0.03$), particularly after age 40, and **in women for deep GM** after age 30 ($p<0.001$).
- **POMS showed faster MS-driven atrophy with age** in the brain and cortex compared with AOMS ($p<0.001$ and $p<0.01$, respectively) and in the deep GM compared to LOMS ($p=0.01$).
- **LOMS patients exhibited accelerated MS-driven brain and cortical atrophy compared to AOMS** with age ($p=0.05$ and $p=0.01$).

CONCLUSIONS

- **MS leads to accelerated brain atrophy** that exceeds the typical volume loss observed during normal physiological aging.
- The **patterns and extent of this disease-related atrophy are influenced by** factors such as patient's **sex** and **age at onset.**
- These findings highlight the need to **carefully consider** not only the natural aging process but **also key demographic and clinical characteristics** when evaluating atrophy in MS.
- Incorporating these factors enhances the accuracy of interpreting global and regional brain volume changes, which can ultimately improve diagnosis, monitoring of disease progression, and personalization of therapeutic strategies.

DISCLOSURES

Loredana Storelli declared the receipt of grants and contracts from FISM within a fellowship program and received speakers' honoraria from Biogen.
Elisabetta Pagani and Alessandro Meani have nothing to disclose.
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