The Role of T1-Weighted Derived Measures of Neurodegeneration for Assessing Disability Progression in Multiple Sclerosis

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Introduction: Multiple sclerosis (MS) is characterised by the accumulation of permanent neurological disability secondary to irreversible tissue loss (neurodegeneration) in the brain and spinal cord. MRI measures derived from T1-weighted image analysis (i.e., black holes and atrophy) are correlated with pathological measures of irreversible tissue loss. Quantifying the degree of neurodegeneration in vivo using MRI may offer a surrogate marker with which to predict disability progression and the effect of treatment. This review evaluates the literature examining the association between MRI measures of neurodegeneration derived from T1-weighted images and disability in MS patients.

Methods: A systematic PubMed search was conducted in January 2017 to identify MRI studies in MS patients investigating the relationship between “black holes” and/or atrophy in the brain and spinal cord, and disability. Results were limited to human studies published in English in the previous 10 years.

Results: A large number of studies have evaluated the association between the previous MRI measures and disability. These vary considerably in terms of study design, duration of follow-up, size, and phenotype of the patient population. Most, although not all, have shown that there is a significant correlation between disability and black holes in the brain, as well as atrophy of the whole brain and grey matter. The results for brain white matter atrophy are less consistently positive, whereas studies evaluating spinal cord atrophy consistently showed a significant correlation with disability. Newer ways of measuring atrophy, thanks to the development of segmentation and voxel-wise methods, have allowed us to assess the involvement of strategic regions of the CNS (e.g., thalamus) and to map the regional distribution of damage. This has resulted in better correlations between MRI measures and disability and in the identification of the critical role played by some CNS structures for MS clinical manifestations.

Conclusion: The evaluation of MRI measures of atrophy as predictive markers of disability in MS is a highly active area of research. At present, measurement of atrophy remains within the realm of clinical studies, but its utility in clinical practice has been recognized and barriers to its implementation are starting to be addressed.

Keywords: multiple sclerosis, disability, neurodegeneration, magnetic resonance imaging, atrophy, black holes
INTRODUCTION

The application of magnetic resonance imaging (MRI) techniques is integral to our understanding of the pathogenesis of multiple sclerosis (MS). Historically, MS was considered to be an autoimmune-driven inflammatory disease characterised by focal white matter (WM) demyelination (1), visualized as gadolinium-enhancing T1 and hyperintense T2 lesions on conventional MRI scans (2). However, the correlation between conventional MRI measures and the extent of clinical disability is limited, particularly when applied to individual patients—a phenomenon known as the “clinical–MRI paradox” (3).

Two major advances in our understanding of MS are helping to resolve this paradox. First, the pathological substrates of MS extend well beyond focal WM lesions. Advanced MRI techniques, as well as postmortem histopathological findings, have shown that MS is also characterised by more widespread damage to the so-called “normal-appearing” WM (NAWM), as well as focal and diffuse damage to the grey matter (GM) of the brain and spinal cord (3, 4). Second, it is also now apparent that at least some of the neurodegenerative changes in MS are independent of inflammatory demyelination (5, 6). Indeed, a number of pathogenic changes have been suggested to drive neurodegeneration, including mitochondrial damage, iron deposition, microglial activation, and altered ion channel activity (7–9).

It is well accepted that neurodegenerative changes, irrespective of their aetiology, underlie the accumulation of permanent neurological disability that characterises MS (10–13). As a consequence, a key area of research in the field of MS is the evaluation of neurodegenerative changes using MRI techniques and their association with clinical disability and cognitive dysfunction. The ultimate aim is to find predictive biomarkers for neurodegeneration and disability and to develop sensitive and specific imaging markers that can be used to monitor disease progression and evaluate the response to treatment.

The aim of this review was to discuss the literature examining the association between MRI measures of neurodegeneration derived from the analysis of T1-weighted images (black holes and atrophy) and disability in patients with MS. Black holes represent areas of focal axonal damage and irreversible tissue destruction (14), while atrophy is a more widespread axonal loss that is thought to be caused by tissue damage within lesions and Wallerian degeneration in related fibre pathways (15). At the level of the GM, neuronal loss and shrinkage also contribute to atrophy (16).

Atrophy is most commonly quantified as the loss of overall brain tissue from T1-weighted images. Some methods for atrophy quantification also work on T2 and FLAIR images. Advances in the methods of analysis have made it possible to measure atrophy of spinal cord, GM, WM, and specific regions and structures of the brain (e.g., thalamus, hippocampus, etc.). A number of techniques are used to quantify atrophy, ranging from manual bi-dimensional assessment to automated or semi-automated volumetric measurement. Methods for the quantification of atrophy are continuously evolving, improving not only image acquisition and analysis strategies but also in terms of increased understanding of the technical (e.g., sequence geometry, WM lesion influence, etc.), physiological (e.g., age, sex, hydration, etc.), lifestyle (e.g., alcohol consumption, smoking, diet), genetics (e.g., apolipoprotein E expression), and other factors (e.g., diabetes, cardiovascular risks) that may affect brain volume results. For instance, it is now established that WM lesions affect atrophy calculations, since they influence the detection of GM/WM/cerebrospinal fluid intensity differences. Different techniques, that can be applied in a wide range of atrophy tools, have been proposed to fill in the signal from these lesions and alleviate this problem. For a review of these techniques and factors, the reader is referred to review articles on this topic (17–20). With regards to the measurement of disability in patients with MS, a number of scales and tests are available. The most commonly used (at least in clinical trials) is the Expanded Disability Status Scale (EDSS), which is measured on a scale of 0 (no disability) to 10 (death due to MS) (21). Others include the timed 25-foot walk (T25FW) (22), the 9-hole peg test (9HPT) (23), and the Multiple Sclerosis Functional Composite (MSFC) (24), which is a composite of the T25FW, 9HPT, and a test of cognitive function. Although of significant interest, studies focusing on the association between atrophy and cognitive dysfunction were beyond the scope of this review and the reader is referred to a recent comprehensive review of the topic (25).

METHODS

A systematic PubMed search was conducted in January 2017 to identify studies investigating the relationship between disability and black holes and/or atrophy in the brain and spinal cord. Results were limited to human studies published in English in the previous 10 years. Studies that examined the effect of disease-modifying treatments on measures of neurodegeneration were excluded, as this was outside the scope of this review. The search terminology is summarized in the Table S1 in Supplementary Material.

Results are presented first for studies that assessed black holes/atrophy in the brain, followed by studies that assessed these measures in the spinal cord. Studies that assessed both brain and spinal cord atrophy in relation to disability are presented in a separate section.

RESULTS

Brain Black Holes and Atrophy

Overall, 59 key studies evaluating the association between MRI measures of brain neurodegeneration and disability were identified (Table 1). Of these, 38 were cross-sectional and 21 were longitudinal in design (either for clinical or MRI variables). Most were non-phenotype specific (n = 35), while 10 focused on relapsing-remitting multiple sclerosis (RRMS), four on primary progressive multiple sclerosis (PPMS), three on relapsing MS, two on clinically isolated syndrome (CIS), and one on relapsing onset (i.e., CIS, RRMS, and secondary progressive) MS. The remaining four studies compared MS subtypes. In the majority of studies, the EDSS score was used to assess disability; other disability measures included the MSFC, the Multiple Sclerosis Severity Score (MSSS),
TABLE 1 | MRI studies evaluating the relationship between brain black holes/atrophy and disability.

(a) Cross-sectional studies

| Reference | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results |
|-----------|--------------|-------------------------------------------------|----------------------|---------|
| CiS       | 73           | • GM fraction • WM fraction [3D T1w/SPM]          | EDSS                 | GM fraction, but not WM fraction, correlated with EDSS ($r = -0.48; p < 0.001$) and MSFC ($r = 0.59; p < 0.001$) |
|           |              |                                                 |                      | GM fraction explained more of the variability in clinical measures than did WM lesion load |
| Audoin et al. (27) | 62 | • Regional GM atrophy • GM atrophy of specific structures [3D T1w/VBM] | EDSS | Significant correlation between EDSS and atrophy of the right cerebellum ($r = -0.37; p = 0.0027$) |
| RRMS      |              |                                                 |                      |         |
| Prinster et al. (28) | 128 | • Global GM volume • Global WM volume • Regional GM volume [T1w and PD-T2w/VBM] | EDSS | No significant correlation between global GM loss and EDSS |
|           |              |                                                 |                      | Significant correlation between global GM loss and EDSS ($p < 0.0001$) |
|           |              |                                                 |                      | Significant linear correlation between regional bilateral GM loss and EDSS in the primary motor and somatosensory areas and the middle frontal gyr, with extension to the right middle temporal gyrus |
| Riccitelli et al. (29) | 78 | • Regional WM atrophy • Regional GM atrophy [3D T1w/VBM] | EDSS | In patients with EDSS scores ≤3.0, WM atrophy was restricted to a few WM tracts; in those with EDSS scores >3.0, several tracts of the cerebral and cerebellar hemispheres were involved. |
|           |              |                                                 |                      | In patients with EDSS scores >3.0, regions with more severe GM atrophy were the left basal ganglia and thalamus and the right precentral gyr |
| Nygaard et al. (33) | 61 | • Cortical surface area, thickness and volume [3D T1w/FreeSurfer] | EDSS | No significant correlation between EDSS and cortical surface area, thickness, or volume |
| Hasan et al. (31) | 54 | • Regional volume-to-intracranial volume % of a wide range of GM and WM structures [3D T1w/FreeSurfer] | EDSS | Significant correlations between EDSS and % volume of frontal lobe WM ($r = 0.286; p = 0.04$), CLWM ($r = 0.28; p = 0.045$), insular WM ($r = 0.301; p = 0.03$), entire corpus callosum ($r = 0.411; p = 0.002$), periventricular WM ($r = 0.279; p = 0.045$), anterior corpus callosum ($r = 0.37; p = 0.01$), middle anterior corpus callosum ($r = 0.35; p = 0.01$), truncus corpus callosum ($r = 0.32; p = 0.03$), corpus callosum isthmus ($r = 0.30; p = 0.03$), and corpus callosum splenium ($r = 0.31; p = 0.03$) |
| Duan et al. (32) | 26 | • Global GM volume [3D T1w/VBM and SPM] | EDSS | No correlation between GM loss and EDSS |
| Mesaros et al. (33) | 28 (pediatric) | • Regional GM loss [T1w conventional spin-echo/SIENAX] | EDSS | No correlation between thalamic GM loss and disability |
| Liufru et al. (34) | 21 | • Corpus callosum area (total) • Corpus callosum area (segments 1–7) • Corpus callosum volume [3D T1w/SIENAX] | EDSS | Area of segment 1 of corpus callosum correlated with EDSS ($r = -0.442; p = 0.045$) |
|           |              |                                                 |                      | No significant correlation between other corpus callosum measures and disability |

(Continued)
### Table 1 (Continued)

#### (a) Cross-sectional studies

| Reference | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results |
|-----------|--------------|-------------------------------------------------------------------|----------------------|---------|
| **RELAPSING** | | | | |
| Tao et al. (35) | 88 | • Deep GM atrophy [3D T1w/TBM] | • EDSS | • Significant correlation between EDSS and atrophy of the thalamus ($r = -0.51$), caudate nucleus ($r = -0.43$), and putamen ($r = -0.36$) ($p < 0.0001$ for all) |
| **RELAPSING ONSET** | | | | |
| D’Ambrosio et al. (36) | 95 | • Whole brain volume • GM volume • WM volume • Cerebellar volume (total, anterior, posterior) [3D T1w/SIENAX and SPM] | • EDSS • 9HPT | • Significant correlation between the EDSS and all cerebellar volumes; only anterior cerebellar volume remained significant in multivariate analysis (beta coefficient, $-0.320$; $p = 0.003$) • Significant correlation between the 9HPT and whole brain volume and all cerebellar volumes; only anterior cerebellar volume remained significant in multivariate analysis (beta coefficient, 0.264; $p = 0.02$) |
| **REMITTING** | | | | |
| Mineev et al. (37) | 65 | • Brain atrophy (cerebral parenchymal volume) [Semiautomatic computer program] | • FSS • EDSS | • Significant correlations between brain atrophy and EDSS and FSS for pelvic dysfunction ($r = -0.36$; $p < 0.05$) |
| **PPMS** | | | | |
| Bodini et al. (38) | 35 | • Regional GM volume [3D T1w/VBM] | • EDSS • MSFC subtests | • Patients with greater GM atrophy in the right sensory-motor cortex had greater upper limb disability measured using 9HPT (coefficient = 1.27; $p = 0.01$) • No correlation between GM atrophy and predefined EDSS groups (EDSS score $\leq 3.5$; 4–5.5; $\geq 6$) |
| Galego et al. (39) | 19 | Volumes of: • Neocortex • Total WM • Total subcortical GM • Putamen, caudate, globus pallidus, thalamus, hippocampus, brainstem, corpus callosum, and precentral gyrus [3D T1w/FreeSurfer] | • EDSS | • No correlation between EDSS and any of the GM or WM structures analyzed |
| **MS** | | | | |
| Roosendaal et al. (40) | 927 | • GM volume • WM volume [3D T1w/SIENAX] | • EDSS | • Significant correlation between EDSS and GM volume (OR = 0.67; $p < 0.001$), but not WM volume |
| Steenwijk et al. (41) | 208 | • Global cortical thickness [3D T1w/SIENAX] | • EDSS | • Reduced cortical thickness was one of the significant predictors of EDSS in a multivariate model (beta = $-0.227$; $p < 0.001$) |

(Continued)
### (a) Cross-sectional studies

| Reference         | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results |
|-------------------|--------------|------------------------------------------------------------------------|-----------------------|---------|
| Howard et al. (42) | 194          | - Brain volume<br>- Global WM volume<br>- Global GM volume [3D T1w/SIENAX] | - Need for ambulatory assistance | Significant difference in brain volume ($p = 0.001$), GM volume ($p = 0.0008$), and WM volume ($p = 0.02$) in those requiring ambulatory assistance vs those who did not |
| Tauhid et al. (43) | 175          | - Brain atrophy [T2w dual echo/BPF]                                   | - EDSS                | Data were analyzed according to four phenotypes: Type 1, low T2LV/mild atrophy; Type 2, high T2LV/mild atrophy; Type 3, low T2LV/high atrophy; Type 4, high T2LV/high atrophy<br>- Significant correlation between BPF and EDSS for overall population ($r = -0.57; p < 0.0001$) and Type 4 patients ($r = -0.46; p < 0.0001$) |
| Preziosa et al. (44) | 172          | - Cerebellar WM and GM volumes [3D T1w/SPM and SIENAX]                | - EDSS scores $<$ 4.0 or $\geq$ 4.0<br>- Cerebellar FSS $= 0$ or $\geq$ 1<br>- Brainstem FSS $= 0$ or $\geq$ 1 | Significantly lower cerebellar GM volume in patients with disability according to EDSS ($p = 0.01$) and cerebellar FSS ($p = 0.006$)<br>Significantly lower cerebellar WM volume in patients with disability according to EDSS ($p = 0.03$) and brainstem FSS ($p = 0.004$) |
| Yaldizli et al. (45) | 146          | - Olfactory bulb volume [3D T1w/AMIRA]                                | - EDSS                | No correlation between olfactory bulb volume and EDSS |
| Calabrese et al. (46) | 115          | - Global and regional cortical thickness [3D T1w/BPF and Freesurfer]    | - EDSS<br>- FSS       | No correlation between mean cortical thinning and EDSS in patients with possible or definite MS<br>Significant correlation between motor FSS and precentral gyrus thinning in both groups ($r = -0.487, p = 0.006$ for possible MS; $r = -0.626, p < 0.001$ for definite MS)<br>Significant correlation between visual FSS and primary visual cortex thinning in both groups ($r = -0.489, p = 0.006$; $r = -0.389, p = 0.02$, respectively) |
| Caramanos et al. (47) | 110 (untreated) | - Black hole lesion load (cube-rooted) in brain [3D T1w/Bayesian tissue classification] | - EDSS                | Significant correlation between cube root of black hole lesion load and EDSS ($r = 0.619; p < 0.001$) |
| Ramasamy et al. (48) | 88           | - Regional subcortical tissue volume<br>- Cortical thickness [3D T1w/FreeSurfer] | - EDSS                | Significant correlation between EDSS and third ventricle volume ($r = 0.415$), right caudate volume ($r = -0.371$), right accumbens volume ($r = -0.411$), right parahippocampal thickness ($r = -0.409$), left lateral occipital thickness ($r = -0.360$), and left postcentral thickness ($r = -0.421$) (all $p \leq 0.01$) |
| Van de Pavert et al. (49) | 80           | - GM atrophy in the cerebellum, medial temporal lobe, postcentral gyrus, precenral gyrus, insula, prefrontal cortex and thalamus [3D T1w/SPM] | - EDSS<br>- T25FW<br>- 9HPT | Voxel-wise models:<br>- No correlation with volume loss and any clinical metric<br>Region of interest analyses:<br>- EDSS: correlated with GM volume in cerebellum (adjusted $r^2 = 0.203$; $p = 0.018$) and postcentral gyrus (adjusted $r^2 = 0.242$; $p = 0.002$)<br>- T25FW: correlated with GM volume in cerebellum (adjusted $r^2 = 0.156$; $p = 0.02$) and postcentral gyrus (adjusted $r^2 = 0.164$; $p = 0.014$)<br>- 9HPT: correlated with GM volume in cerebellum (adjusted $r^2 = 0.100$; $p = 0.018$) |
### TABLE 1 | Continued

| Reference                  | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results                                                                                                                                                                                                 |
|----------------------------|--------------|-----------------------------------------------------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Motl et al. (50)           | 79           | • Volumes of subcortical GM structures (thalamus, caudate, putamen, and pallidum) [3D T1w/SIENAX] | • T25FW              | Thalamus volume partially accounted for compromised ambulation in MS patients compared with controls                                                                                                      |
| Anderson et al. (51)       | 73           | • Cerebellar GM volume                                               | Cerebellar FSS 9HPT T25FW | Cerebellar GM volume significantly lower in those with cerebellar dysfunction vs those without \( (p = 0.001) \); borderline significance for cerebellar WM volume \( (p = 0.059) \); Significant association between 9HPT and cerebellar GM volume (but not cerebellar WM volume) in multiple regression model \( (p = 0.001) \); No significant association between cerebellar GM or WM volume and T25FW |
| Motl et al. (52)           | 61           | • Volume of subcortical GM structures (thalamus, caudate, putamen and pallidum) Global WM volume Global GM volume [3D T1w/SIENAX] | • 6 MW T25FW          | Significant correlation between global WM volume and 6 MW and T25FW \( (p < 0.01 \text{ for both}) \); Significant correlation between global GM volume and 6 MW \( (p < 0.05) \); Significant correlation between 6 MW and T25FW and volumes of the thalamus, caudate, pallidum and putamen \( (p < 0.05 \text{ for putamen}; p < 0.01 \text{ for others}) \); Results for caudate and pallidum remained significant after controlling for age, MS clinical course, and whole brain GM and WM volumes \( (p < 0.05) \); Linear regression: pallidum volume was the only significant correlate of 6 MW and T25FW performance \( (p < 0.01) \) |
| Shiee et al. (53)          | 60           | • Cortical GM volume                                               | EDSS MSFC MSSS        | EDSS \( r = -0.40; (p = 0.001) \), MSFC \( r = 0.35; (p = 0.005) \), and 9HPT \( r = -0.45; (p < 0.01) \) correlated with WM volume \( 9HPT \text{ and MSFC correlated with cerebral volume fraction } \ | (Continued)
### TABLE 1 | Continued

#### (a) Cross-sectional studies

| Reference                  | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results                                                                 |
|----------------------------|--------------|------------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------------|
| Granberg et al. (56)       | 37           | • Corpus callosum area                                                   | EDSS                  | Significant correlations between EDSS and:                             |
|                            |              | • Corpus callosum index (CCI)                                            |                       | • Corpus callosum area ($r = -0.56; p < 0.001$)                        |
|                            |              | • Corpus callosum volume                                                 |                       | • CCI ($r = -0.45; p = 0.001$)                                         |
|                            |              | • Brain volume                                                           |                       | • Corpus callosum volume ($r = -0.55; p < 0.001$)                      |
|                            |              | • GM volume                                                              |                       | • Brain volume ($r = -0.45; p = 0.001$)                                 |
|                            |              | • WM volume                                                              |                       | • GM volume ($r = -0.50; p < 0.001$)                                   |
|                            |              | [3D T1w/Freesurfer and Lesion Segmentation Toolbox]                      |                       |                                                                         |
| Sbardella et al. (57)      | 36           | • Regional GM volume                                                    | EDSS                  | Significant correlation between cerebellar volume and 9HPT ($p < 0.05$) |
|                            |              | • WM volume                                                              |                       |                                                                         |
|                            |              | [3D T1w/VBM]                                                            |                       |                                                                         |
| Chu et al. (58)            | 26           | • BPV                                                                   | EDSS                  | 1.5 T MRI: BPV correlated with EDSS ($r = -0.43; p = 0.027$) and         |
|                            |              | [3D T1w/STIENAX]                                                        |                       | T25FW ($r = -0.48; p = 0.018$)                                         |
|                            |              |                                                                       |                       | 3 T MRI: BPV correlated with EDSS ($r = -0.49; p = 0.011$) and           |
|                            |              |                                                                       |                       | T25FW ($r = -0.56; p = 0.003$)                                         |
| Tam et al. (59)            | 24           | • Black hole volumes                                                    | EDSS                  | Significant correlation between black hole volume and EDSS             |
|                            |              | [T1w/Semi-automated method]                                              |                       |                                                                         |
| Zimmermann et al. (60)     | 19 (with predominantly spinal cord lesions)                             | • Putamen fraction                                                    | EDSS                  | Significant correlation between putamen fraction and MSSS ($r = -0.521; p = 0.027$) |
|                            |              | • Putamen volume/BPF                                                    | MSSSS                 |                                                                         |
|                            |              | [3D T1w/VBM and ROI-based analyses]                                     |                       |                                                                         |
| Gorgoraptis et al. (61)    | 11 patients with history of hemiparesis due to corticospinal tract lesion | • Volume, thickness, surface area and curvature of precentral and paracentral cortices | EDSS                  | Significant correlation between:                                        |
|                            |              | [3D T1w/FreeSurfer]                                                     |                       | • Paracentral cortex volume and T25FW ($r = -0.71; p = 0.022$)         |
|                            |              |                                                                       |                       | • Paracentral cortex surface area ($r = -0.65; p = 0.030$) and          |
|                            |              |                                                                       |                       | • pyramidal FSS ($r = -0.63; p = 0.037$)                               |
|                            |              |                                                                       |                       | No correlation between cortical thickness and disability               |

#### COMPARiSON Of SUBTyPeS

| Reference                  | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results                                                                 |
|----------------------------|--------------|------------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------------|
| Varoglu et al. (62)        | RRMS (n = 14) and SPMS (n = 13) | • Cerebellar volume                                                   | EDSS                  | Cerebellar volume was negatively correlated with EDSS in both groups of patients ($r = 0.896$ for RRMS, $r = -0.854$ for SPMS; $p < 0.01$ for both) |
|                            |              | [T2w FLAIR/Cavalieri method]                                            |                       |                                                                         |
| Anderson et al. (63)       | RRMS (n = 14) and PPMS (n = 12) | • Cerebellar GM atrophy                                               | EDSS                  | Cerebellar WM volume was associated with 9HPT in patients with         |
|                            |              | • Cerebellar WM atrophy                                                |                       | PPMS, independently of cerebellar GM volume                           |
|                            |              | [3D T1w/SPM]                                                           |                       |                                                                         |
|                            |              | • EDSS                                                                 |                       | No association between cerebellar GM volume and any of the             |
|                            |              | • Cerebellar FSS                                                       |                       | disability measurements                                               |
|                            |              | • 9HPT                                                                |                       |                                                                         |
|                            |              | • T25FW                                                               |                       |                                                                         |

(Continued)
### TABLE 1 | Continued

| (b) Longitudinal studies |   |   | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results |
|--------------------------|---|---|-------------------------------------------------------------------|----------------------|---------|
| Reference                 | Follow-up period (years) | Patients (n) |                                                                 |                      |         |
| **RRMS**                 |   |   |                                                                 |                      |         |
| Hofstetter et al. (64)    | 1 | 239 | • Regional GM volume [3D T1w/VBM]                               | • EDSS               | • Significant difference in volume of right precuneus ($p < 0.001$) and postcentral gyrus ($p < 0.001$) between patients with stable and progressive disability measured using EDSS |
| Vaneckova et al. (65)     | ≤5| 181 | • Brain volume (BPF) [3D T1w/In-house software]                  | • EDSS               | • Patients with low baseline lesion load: significant correlation between increased brain atrophy in first 2 years and increase in EDSS at years 4 and 5 ($r ≤ −0.71; p < 0.01$) • Patients with high baseline lesion load: no correlation between early brain atrophy and later change in EDSS |
| Giorgio et al. (66)       | 10 (±0.5) | 58 | • Black holes [T1w/Jim software]                                | • EDSS               | • Higher EDSS at 10 years correlated with greater baseline black hole number ($r = 0.53; p < 0.001$) and volume ($r = 0.42; p < 0.001$) • Moderate correlation between increase in EDSS and increasing black hole volume over 10 years ($r = 0.47; p < 0.001$) • In stepwise multiple regression analysis, increase in EDSS over 10 years was best correlated with the combination of baseline black hole number and increasing black hole volume ($r = 0.61; p < 0.001$) |
| **RELAPSING ONSET**       |   |   |                                                                 |                      |         |
| Rocca et al. (67)         | 8 | 73  | • Thalamic fraction [PD-weighted images/Manual segmentation]    | • EDSS               | • Baseline thalamic fraction was an independent predictor of worsening disability at 8 years (OR = 0.62; $p = 0.01$) |
| **PPMS**                 |   |   |                                                                 |                      |         |
| Mesarcos et al. (68)      | 1.25 (mean) | 54 | • Thalamic volume [PD-weighted images/SPM]                     | • EDSS               | • Neither baseline thalamic volume nor the average change in thalamic volume were predictive of increase in EDSS in univariate analysis |

(Continued)
### Table 1: Longitudinal studies

| Reference                  | Follow-up period (years) | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results                                                                                                                                 |
|----------------------------|--------------------------|--------------|-----------------------------------------------------------------------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Eshaghi et al. (69)        | 5                        | 36           | • Volume of GM structures [3D T1wR/VBM]                              | • EDSS                | • Higher rate of volume loss in the bilateral cingulate cortex associated with greater clinical disability (MSFC) measured at 5 years ($r = 0.49; p = 0.003$) |
| Tedeschi et al. (70)       | 2                        | 267          | • Abnormal WM fraction • NAWM fraction • Global WM fraction • GM fraction • Whole brain fraction [T1w and dual echo/multispectral, fully automated method] | • EDSS                | • Significant correlation between all MRI parameters and EDSS at end of follow-up ($p < 0.0001$); $r = -0.423$ for GM fraction, $r = -0.431$ for whole brain fraction, $r = -0.256$ for global WM fraction, $r = -0.220$ for NAWM fraction and $r = 0.267$ for abnormal WM fraction • Baseline GM fraction and whole brain fraction significantly lower in patients with progression of disability vs those with stable or improved disability ($p < 0.05$) • Baseline MRI measures not related to EDSS change during follow-up |
| Gauthier et al. (71)       | ≤5                       | 218          | • Brain volume (BPF) [Dual echo PD and T2w/template-driven segmentation] | • EDSS                | • Univariate analysis: lowest baseline BPF quartile was associated with EDSS progression (OR = 1.99; $p = 0.02$) • Covariate specific disability curves: in patients with 6-month EDSS of 2, probability of progression to EDSS of 3 within 3 years was 0.277 for a patient with low BPF and a high T2 lesion volume vs 0.055 for a patient with high BPF and a low T2 lesion volume |
| Yaldizli et al. (72)       | 7.1 (mean)               | 169          | • CCI a [T1w/picture archiving and communication system] | • EDSS                | • CCI at diagnosis significantly correlated with EDSS at diagnosis ($r = -0.428; p < 0.001$) • Associated with disability progression, but was not an independent predictor of long-term disability |
| Figueira et al. (73)       | 5                        | 128          | • CCI b [T1w/semi-automated system]                                | • EDSS                | • No correlation between reduction in CCI and change in EDSS |
| Neema et al. (74)          | 4                        | 97           | • Brain atrophy (BPF) [T2w dual echo/automated template-driven segmentation] | • EDSS                | • No association between baseline BPF or % change in BPF and change in disability (stable vs progressive) |

(Continued)
| Reference          | Follow-up period (years) | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results                                                                 |
|--------------------|--------------------------|--------------|-----------------------------------------------------------------------|-----------------------|------------------------------------------------------------------------|
| Moodie et al. (76) | 3.2 ± 0.3 (mean ± SD)    | 84           | • Brain volume (BPF)\[^{c}\] [Dual echo/automated template-driven segmentation] | • EDSS                | - No significant association between baseline BPF and EDSS-defined clinical progression                           |
| Jacobsen et al. (77) | 5 and 10                 | 81           | • Brain volume • WM volume • Regional GM volume • Volume of subcortical deep GM structures [3D T1w/SIENAX and SIENA] | • EDSS                | - 5 years: significantly higher brain (p < 0.001), cortical (p = 0.009), and putamen volume changes (p = 0.003) in patients with disability progression vs those without progression; no significant difference in WM volume between groups  
- 10 years: trend for greater decrease in whole brain volume (p = 0.015) in patients with disability progression [Level for statistical significance set at p < 0.01] |
| Filippi et al. (78) | 13                       | 73           | • Black holes • GM fraction • WM fraction • Thalamic fraction [Black holes: T1w/semi-automated local thresholding technique] [GM/WM fraction: T1w/SPM] [Thalamic: PD-weighted images/Manual segmentation] | • EDSS • MSSS         | - Baseline GM fraction was the only significant predictor of worsening EDSS in multivariate model (OR = 0.79; p = 0.01) 
- Baseline GM fraction also predicted MSSS at follow-up (p = 0.0009) |
| Fisher et al. (79) | 4                        | 70           | • Brain atrophy (BPF) • GM fraction • WM fraction [BPF: T2w FLAIR/3D segmentation algorithm] [GM fraction: T1w/intensity-based and regional probability maps] [WM fraction = BPF—GM fraction] | • EDSS • MSFC • T25FW • 9HPT | - GM atrophy at last visit correlated with disability; correlations were greatest with the MSFC (r = 0.52) |

Table 1 (Continued)
(b) Longitudinal studies

| Reference                          | Follow-up period (years) | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results                                                                 |
|------------------------------------|--------------------------|--------------|-----------------------------------------------------------------------|------------------------|-------------------------------------------------------------------------|
| Minneboo et al. (81)               | 12.2 (mean)              | 46           | • Black hole lesion load  
  • BPF  
  • Ventricular fraction  
  [Black holes: semi-automated thresholding technique]  
  [BPF and ventricular fraction: T1w spin-echo] | • MSSS                  | • Univariate analyses:  
  Black hole lesion load (baseline and change/year) and ventricular fraction (cross-sectional and change/year) were associated with MSSS (adjusted \( r^2 = 0.07 \) to 0.18; \( p = 0.063 \) to 0.003)  
  • Multiple regression model:  
  Final model included change in black hole lesion load only (% of explained variance in MSSS was 28–34%) |
| Martola et al. (82)                | 9 (mean)                 | 37           | • Corpus callosum area  
  [T2w/picture archiving and communication system] | • EDSS  
  • MSSS                  | • Persisting association between corpus callosum area with disability status at baseline and end of study (\( p < 0.05 \)) |
| Martola et al. (83)                | 9.25 (mean) 7.3–10 (range) | 37           | • Supratentorial ventricular volume  
  [T1w/picture archiving and communication system] | • EDSS  
  • MSSS                  | Low to moderate association between supratentorial ventricular enlargement and disability status at baseline and end of follow-up |
| Martola et al. (84)                | 9.25 (mean) 7.3–10 (range) | 37           | • Brain volume (BPV)  
  • Supratentorial ventricular volume  
  [T1w/semiautomatic tool] | • EDSS  
  • MSSS                  | Supratentorial ventricular volumes were associated with disability and this association persisted during the follow-up  
  Annual rate of volume change in third ventricle: \( p = 0.053 \) for EDSS (OR = 1.36) and \( p = 0.044 \) for MSSS (OR = 1.52)  
  Annual rate of volume change in lateral ventricle: \( p = 0.037 \) (OR = 1.24) and \( p = 0.006 \) (OR = 1.46), respectively |

COMPARISON OF DIFFERENT SUBTYPES

| Pichler et al. (85)               | 3.6 (mean)               | CIS (n = 63) vs definite MS (n = 57) | • Brain volume  
  • Cortical GM volume  
  • WM volume  
  • Thalamic and basal ganglia volume  
  [3D T1w/SIENA and SIENAX] | • EDSS                  | No association between decline in global, compartmental or regional brain volume parameters and disability  
  Quartiles of percentage change in brain volume were associated with disability (\( p = 0.01 \)) |

(Continued)
the 9HPT, and the T25FW. Most of the studies evaluated whole brain atrophy as a measure of neurodegeneration; other measures included black holes and atrophy of the global GM, global WM, regional GM, and/or GM of specific structures.

Black Holes

Historically, black holes were introduced as the first MRI measure of neurodegeneration and prevention of the evolution of newly formed lesions into persistent black holes is currently being evaluated as a possible measure of neuroprotection in several treatment trials in patients with MS.

The relationship between black holes and disability was assessed in seven studies (three cross-sectional and four longitudinal) (47, 55, 59, 66, 81, 86, 87). Giorgio et al. evaluated the association between black holes and EDSS scores in patients with RRMS who were followed up for 10 years (66). Higher EDSS scores at the end of the study were significantly correlated with higher numbers and volumes of black holes at baseline ($p < 0.001$ for both). Over the 10-year follow-up, there was a modest correlation between the increase in EDSS score and black hole volume ($p < 0.001$). In a stepwise multiple regression analysis, EDSS score worsening over 10 years was best associated with the combination of baseline black hole numbers and increasing black hole volume ($p < 0.001$) (Figure 1). In another study with a follow-up duration of approximately 12 years, the change in black hole lesion load was the only parameter remaining in the multiple regression model as a predictor of MSSS (81). In contrast, in the 13-year study conducted by Filippi et al., baseline black hole volume did not predict worsening disability assessed using the MSSS or EDSS (78). In a cross-sectional study of patients with untreated MS, the cube root (used to eliminate skew) of the black hole lesion load significantly correlated with the EDSS score ($p < 0.01$) (47).

Several strategies have been proposed to increase black hole detection and improve the correlation with disability, including

![FIGURE 1](https://www.frontiersin.org)
the restriction of black hole measurements according to their intensity (59) or relaxation time thresholds (55).

Whole Brain Atrophy

Twenty studies (7 cross-sectional and 13 longitudinal) evaluated the association between whole brain atrophy and disability; most included patients with mixed disease phenotype. Five of the cross-sectional studies reported a significant correlation between whole brain atrophy and EDSS ($p < 0.05$ for all; see Table 1 for individual $p$-values) (37, 43, 54, 56, 58). In the sixth cross-sectional study, the level of brain atrophy was significantly greater in patients requiring ambulatory assistance compared with those not requiring assistance ($p = 0.001$) (42).

Of the 13 longitudinal studies, 5 demonstrated a correlation between brain atrophy and disability (75, 77, 80, 81, 86), while 4 indicated that there was no correlation (74, 76, 79, 84). Among these, the study by Jacobsen et al. had the longest follow-up period (5 and 10 years) (77). At 5 years, patients with disability progression had significantly greater whole brain volume loss than those with no progression ($p < 0.001$), while at 10 years, there was a trend for greater decrease in whole brain volume in patients with disability progression ($p = 0.015$; statistical significance set at $p < 0.01$) (77).

Results were mixed in two of the other longitudinal studies. In the study by Tedeschi et al., which included 267 patients with MS, there was a significant correlation between baseline brain volume and the EDSS score at follow-up (2 years) ($p < 0.0001$). In addition, brain volume was significantly lower in patients with progression vs those with stable or improved disability ($p < 0.05$). However, baseline brain volume was not related to the change in EDSS score during the follow-up period (70). Pichler et al. found that although there was no association between the decline in whole brain volume and disability, quartiles of percentage change in brain volume were associated with the degree of disability ($p = 0.01$) (85).

The two remaining longitudinal studies evaluated the predictive value of baseline brain volume and T2 lesion load for subsequent disability. In a 5-year study in patients with RRMS, Vanecakova et al. demonstrated a significant correlation between increased brain atrophy in the first 2 years and EDSS score increase at years 4 and 5 in patients with a low lesion load at baseline ($p < 0.01$); this correlation was not observed for those with a high baseline lesion burden (65). In another study, the probability of sustained disability progression (an EDSS score ≥3 within 3 years) was almost five times higher in patients with a low brain volume and a high T2 lesion volume compared with patients with a high brain volume and low T2 lesion volume (71).

GM Atrophy

Global

Twelve studies (eight cross-sectional and four longitudinal) evaluated the correlation between global GM loss and disability. Of the six cross-sectional studies that assessed disability using the EDSS, three studies [including one with a large patient population ($n = 927$)] demonstrated a significant correlation with EDSS score (26, 40, 56), while three showed no significant correlation (28, 32). In the cross-sectional study by Motl et al., GM volume significantly correlated with results of the 6-minute walk (6 MW; $p < 0.05$), but not the T25FW (52). In the remaining cross-sectional study, in patients with MS, there was a significant difference in GM atrophy in those requiring ambulatory assistance vs those who did not ($p = 0.0008$) (42).

In the 13-year longitudinal study of patients with MS conducted by Filippi et al., a lower baseline GM fraction predicted worsening disability at final follow-up, as assessed using EDSS ($p = 0.01$) and MSSS ($p = 0.0005$) (78). A correlation between GM atrophy and disability (the MSFC score in particular) was also noted in a longitudinal study in an MS population that included patients with CIS, RRMS, and secondary progressive multiple sclerosis (SPMS) (Figure 2) (79). In the large 2-year longitudinal study of patients with MS (78% of whom had RRMS) conducted by Tedeschi et al., there was a significant correlation between GM volume and EDSS score at the end of the follow-up period ($p < 0.0001$), and baseline GM volume was significantly lower in patients with disability progression compared with those who did not progress ($p < 0.05$) (70). However, baseline GM atrophy was not related to EDSS change during the 2-year follow-up period. Finally, in the study by Rudick et al., a low baseline GM fraction correlated with an EDSS score ≥6 at final follow-up (mean, 6.6 years), and patients with disability progression (measured using the MSFC, but not the EDSS) had significantly higher GM atrophy rates compared with those who did not progress ($p = 0.03$) (80).

Regional GM, Including Specific GM Structures

Several studies have applied different methods of analysis to assess the role of atrophy of specific GM structures (cortex, deep GM structures, etc.) in disability. Many of these studies (mostly cross-sectional) have evaluated the association between cortical GM loss and disability, but with mixed results (see Table 1). The largest of the cross-sectional studies included 208 patients with RRMS, PPMS, or SPMS (41), 128 patients with RRMS (28), and 115 patients with CIS, possible MS, RRMS, or SPMS (46). In the study by Steenwijk et al., reduced cortical thickness was one of the significant predictors of EDSS in a multivariate model ($p < 0.05$) (41). In the study by Prinster et al., there was a correlation between EDSS score and GM loss in the bilateral primary motor and somatosensory areas and middle frontal gyri (28). Calabrese et al. were unable to demonstrate a correlation between diffuse cortical thinning and EDSS score; however, significant correlations were observed between some of the functional system scores and atrophy of the corresponding cortical areas, e.g., the visual functional system score and atrophy of the visual cortex (46).

Three of the four longitudinal studies demonstrated an association between disability and atrophy of the cortex ($p = 0.009$) (77), the bilateral cingulate cortex ($p = 0.003$) (69), and the right precuneus and postcentral gyrus ($p < 0.001$ for both) (64). In the fourth longitudinal study, conducted in patients with CIS or definite MS, there was no association between the decline in cortical GM volume and progression of disability (85).

A number of studies have shown that there is an association between disability and GM atrophy in the thalamus and basal ganglia (29, 35, 48, 50, 52, 53, 60, 67, 77). For example, Tao et al. demonstrated a significant correlation between atrophy of the thalamus, caudate nucleus, and putamen and EDSS score in a
cross-sectional study in patients with relapsing MS (all \( p < 0.0001 \)) (35). In another cross-sectional study in patients with RRMS, those with EDSS scores \( > 3.0 \) had more severe GM atrophy in the left basal ganglia and thalamus compared with those with scores \( \leq 3.0 \) (29). In the longitudinal study conducted by Jacobsen et al., atrophy of the putamen was implicated in disability progression at 5 years (77), and early thalamic atrophy was an independent predictor of disability at 8 years in the study by Rocca et al. (67). However, other studies have not shown a correlation between disability and GM loss in the thalamus and/or basal ganglia (31, 68, 78). This includes the 13-year longitudinal study by Filippi et al., in which baseline thalamic fraction was not an independent predictor of change in EDSS score or MSSS at the final follow-up (78). Also, in the study by Mesaros et al., neither baseline nor mean change in thalamic volume significantly correlated with change in EDSS score over 5 years (68).

Another structure that has been evaluated in a number of studies is the cerebellum. These studies have shown a significant correlation between GM atrophy of the cerebellum and EDSS score (27, 49) and 9HPT (49, 51, 57); the correlation with T25FW was statistically significant in one study (49), but not another (51). In the small study by Anderson et al., however, there was no significant correlation between cerebellar GM volume and a number of disability measures, including EDSS and 9HPT (63). D’Ambrosio et al. evaluated the correlation between the EDSS/9HPT and whole and sub-regional cerebellar volumes; in a multivariate analysis, only the anterior cerebellar volume remained significant (\( p = 0.003 \) for the EDSS and \( p = 0.02 \) for the 9HPT) (36).

**WM Atrophy**

Thirteen studies (seven cross-sectional and six longitudinal) assessed the association between global WM atrophy and disability (39, 40, 42, 52, 56, 57, 70, 77–80, 85). In the cross-sectional study by Prinster et al., WM loss correlated with EDSS score (\( p < 0.0001 \)) (28), while Howard et al. demonstrated a significant difference in WM atrophy in patients requiring ambulatory assistance vs those who did not (\( p = 0.02 \)) (42). Although Motl et al. showed that there was a significant correlation between global WM atrophy and results of the 6 MW and T25FW tests (\( p < 0.01 \) for both), these did not survive in linear regression analysis (52). Three cross-sectional studies—including the large study (\( n = 927 \)) conducted by Roosendaal et al.—did not show a correlation between WM atrophy and EDSS score (40, 56).

In five of the longitudinal studies, there was no association between global WM atrophy and disability (26, 77–79, 85). In the longitudinal study by Tedeschi et al., there was a significant correlation between WM atrophy and EDSS score at the end of the follow-up period (2 years) (\( p < 0.0001 \)), but not with the change in the EDSS score during follow-up (70). Finally, in the study by

![Correlation between GMF and various clinical measures of disability. Republished with permission of John Wiley and Sons Inc, from (79).](image-url)
## TABLE 2 | MRI studies evaluating the relationship between spinal cord atrophy and disability.

| Reference                  | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results |
|----------------------------|--------------|-----------------------------------------------------------------------|-----------------------|---------|
| **CROSS-SECTIONAL STUDIES**|              |                                                                       |                       |         |
| Rocca et al. (95)          | 335 with MS  | • Cervical cord CSA (C2 to C5) [3D T1w/active surface method]         | • EDSS                |         |
|                            |              |                                                                       |                       | Cord CSA correlated with EDSS in patients with RRMS ($r = -0.30; p = 0.001$), SPMS ($r = -0.34; p = 0.001$), and PPMS ($r = -0.27; p = 0.01$), but not in patients with CIS or benign MS |
| Biberacher et al. (91)     | 267 with CIS or RRMS | • Upper cervical cord CSA at C2/C3 [3D T1w/FSL software] | • EDSS                | Cord CSA correlated with EDSS ($r = -0.131; p = 0.044$) |
| Weier et al. (102)         | 202 with MS  | • Whole spinal cord atrophy [T2w/visual assessment]                    | • EDSS                | Weak correlation between cord atrophy and EDSS scores ($r = 0.30$) |
| Daams et al. (92)          | 196 with MS  | • Upper cervical cord CSA [3D T1w/semi-automated method]               | • EDSS                | Cord area was independently associated with EDSS ($r = -0.296; p < 0.001$), T25FW ($r = 0.240; p = 0.001$), and 9HPT ($r = -0.206; p = 0.005$) |
| Bernitsas et al. (90)      | 150 with MS  | • Cervical cord CSA (C2) [3D T1w/Losseff semi-automated method (104)] | • EDSS                | Significant correlation between CSA-C2 and EDSS ($r = -0.75; p < 0.0001$) | Multivariable regression showed that CSA-C2 was a significant predictor of disability independent of disease duration and phenotype ($p < 0.0001$) |
| Oh et al. (94)             | 133 with MS  | • C3–C4 cord volume [3D T1w/fully automated segmentation protocol (105)] | • EDSS                | Correlations between clinical measures (EDSS: $r = -0.20$, $p = 0.02$; MSFC: $r = 0.16$, $p = 0.06$; hip flexion strength: $r = 0.35$, $p = 0.0001$; vibration threshold: $r = -0.19$, $p = 0.03$) and cord volume |
| Yiannakas et al. (99)      | 120 with MS  ([in longitudinal subgroup; 1-year follow-up])          | • Cervical cord CSA (two segments: C2/C3 and C2/C5) [3D T1w/Propseg vs semi-automated active surface method] | • EDSS                | Baseline CSA was significantly associated with baseline clinical variables (both segments) ($p < 0.001$ for all) |
|                            |              |                                                                       |                       | CSA measures at 1 year were significantly associated with ASIA motor and sensory scores only ($p = 0.048$ to $p = 0.001$) |
|                            |              |                                                                       |                       | Baseline CSA for both segments predicted ASIA motor scores at 1 year ($p < 0.003$) |
| Schlaeger et al. (98)      | 113 with MS  | • Spinal cord WM area (C2/C3) and C2/C5 [2D PSiR/Active surface method] | • EDSS                | GM, WM, and cord CSA significantly correlated with EDSS ($r = -0.60, -0.32, and -0.42$, respectively; all $p < 0.001$) and T25FW ($r = -0.50, -0.28, and -0.36$, respectively; $p < 0.001$, $p = 0.004$ and $p < 0.001$, respectively) |
|                            |              |                                                                       |                       | GM area ($r = -0.37$) and cord CSA ($r = -0.22$) significantly correlated with 9HPT ($p < 0.001$ and $p = 0.024$, respectively) |
|                            |              |                                                                       |                       | GM area was the strongest correlate of disability in multivariate models |
| Rocca et al. (106)         | 77 with MS   | • Regional cervical cord atrophy (voxel-based) [3D T1w/voxel-based analysis, active surface method] | • EDSS                | SPMS: cord atrophy at C1/C2 correlated with pyramidal FSS ($r = -0.91; p < 0.001$) |
|                            |              |                                                                       |                       | PPMS: cord atrophy at C1/C2 correlated with EDSS ($r = -0.68$) and pyramidal FSS ($r = -0.89$) ($p < 0.001$) |
|                            |              |                                                                       |                       | No correlation between regional cord atrophy and clinical variables for other MS phenotypes |
| Valsasina et al. (98)      | 71 with RRMS or SPMS | • Regional cervical cord atrophy [3D T1w/voxel-based analysis, active surface method] | • EDSS                | Regional cervical cord atrophy was correlated with clinical disability ($r = -0.46$ to $-0.57; p < 0.001$) |
| Benedetti et al. (100)     | 68 with benign MS or SPMS | • Cervical cord CSA [3D T1w/semi-automated method of Losseff (104)] | • EDSS                | Cord CSA was an independent predictor of EDSS ($p = 0.001$) |
| Horsfield et al. (93)      | 40 with RRMS or SPMS | • Cervical cord CSA (C2 and C2–C5) [3D T1w/semi-automated active surface vs Losseff method (104)] | • EDSS                | Strong correlations between the EDSS (C2: $r = -0.51$; C2–C5: $r = -0.59$) and ambulation index (C2: $r = -0.58$; C2–C5: $r = -0.648$) and CSA ($p < 0.001$) | (Continued)
Studies within each subsection are ordered according to size of patient population. 9HPT, 9-hole peg test; AS, active surface; ASIA, American Spinal Injury Association; CIS, clinically isolated syndrome; CSA, cross-sectional area; EDSS, Expanded Disability Status Scale; FSS, Functional Scale Score; GM, grey matter; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; T1w, T1-weighted; T2w, T2-weighted; T25FW, timed 25-foot walk; WM, white matter.

**Spinal Cord Atrophy**

Spinal cord abnormalities at the onset of MS have important prognostic implications and extensive spinal cord pathology is common as the disease progresses (88). Sixteen studies were identified evaluating the relationship between spinal cord atrophy and disability (Table 2); all but one (89) were cross-sectional, although the study by Yiannakas et al. included a longitudinal subgroup. These studies consistently demonstrated a significant correlation between clinical disability and cerebral cord cross-sectional area (CSA) at various cord levels (89–100) as well as regional (C2/C3) and overall volume of the cerebral cord (101). Exceptions were the studies by Weier et al. in 202 patients with MS, which found a weak correlation between signs of spinal cord atrophy and EDSS scores (102), and the study by Blamire et al. (n = 11), which found no correlation between spinal cord atrophy and various measures of disability (103). The largest study, which included 335 patients with MS, demonstrated that although cord CSA correlated with EDSS in the overall population (p < 0.0001), there were different effects according to MS clinical phenotype. The association was significant for RRMS (p = 0.001), SPMS (p = 0.001), and PPMS (p = 0.01), but not for CIS or benign MS (95).

In the longitudinal study of 35 patients with MS conducted by Valsasina et al., there were significant associations between cord CSA and EDSS, both at baseline and follow-up (89). In the subgroup analysis of 40 patients from the study conducted by Yiannakas et al. who were followed up for 1 year, cervical spinal cord CSA at the end of follow-up was significantly associated with American Spinal Injury Association (ASIA) motor and sensory scores (p = 0.048 to p = 0.001), but not with EDSS, MSFC, T25FW, or 9HPT (99). Cord CSA predicted ASIA motor scores at 1 year (p ≤ 0.001) (99).

The association between regional cervical cord involvement and disability has also been explored. In the voxel-based study by Valsasina et al., regional cord atrophy was more widespread in patients with SPMS than in those with RRMS. In the overall population, cervical cord atrophy correlated with clinical disability (p < 0.001) (98). In the study by Rocca et al., the regional distribution of cord atrophy differed significantly among the main
### TABLE 3 | MRI studies evaluating the relationship between brain and spinal cord black holes/atrophy and disability.

#### (a) Cross-sectional studies

| Reference | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results |
|-----------|--------------|------------------------------------------------------------------------|-----------------------|---------|
| **CIS**   |              |                                                                        |                       |         |
| Bonati et al. (111) | 70 (patients were assessed 20 years after presentation with CIS) | - Upper cervical cord CSA  
[Cord CSA: 3D T1w/semi-automated method of Losseff et al (104)]  
[GM fraction: 3D T1w/SPM] | - EDSS  
- MSFC  
- 9HPT  
- T25FW | Cord CSA  
- Significant correlation with EDSS ($r = -0.42; p < 0.001$), MSFC ($r = 0.42; p < 0.001$), 9HPT ($r = 0.39; p = 0.001$), T25FW ($r = -0.34; p = 0.004$)  
GM fraction  
- Significant correlation with EDSS ($r = -0.47; p < 0.001$), MSFC ($r = 0.56; p < 0.001$), 9HPT ($r = 0.60; p < 0.001$), T25FW ($r = -0.42; p = 0.001$)  
Cord CSA and GM fraction were independently associated with EDSS and MSFC |
| **PPMS**  |              |                                                                        |                       |         |
| Ruggieri et al. (112) | 26 | - Brain volume  
- Deep GM volume  
- Cervical cord CSA  
- Cervical cord volume  
[3D T1w/SIENAX (brain volume) and active surface method (spinal cord)] | - EDSS  
- T25FW  
- 9HPT  
- T25FW | Significant correlation between 9HPT results (non-dominant hand) and thalamic volume ($r = -0.48; p = 0.02$) and spinal cord volume ($r = -0.44; p = 0.03$)  
No association between brain and WM volumes and 9HPT for non-dominant hand |
| Kolind et al. (113) | 15 (PPMS) | - Brain volume (ventricular cerebrospinal fluid)  
- Cervical cord volume  
[3D T1w/SIENAX (brain volume) and semiautomatic method (114) (cord volume)] | - EDSS  
- MSFC  
- 9HPT  
- T25FW | Brain volume correlated with MSFC ($r = -0.73; p = 0.002$), 9HPT ($r = -0.67; p = 0.007$), but not MSFC or T25FW  
Cervical cord volume correlated with T25FW only ($r = -0.54; p = 0.04$) |
| **SPMS**  |              |                                                                        |                       |         |
| Furby et al. (115) | 117 | - Brain volume  
- GM volume  
- WM volume  
- Central cerebral volume  
- Cervical cord CSA (C2/C3)  
[Brain/GM/WM volume: 3D T1w/SIENAX]  
[Central cerebral volume: 2D T1w/Losseff et al. (113)]  
[Cord CSA: 3D T1w/Losseff et al. (104)] | - EDSS  
- MSFC  
- 9HPT  
- T25FW | All MRI measures correlated significantly with MSFC, strongest correlation with brain volume ($r = 0.47; p < 0.001$)  
Stepwise regression model:  
- Only brain volume ($p = 0.001$) and cervical cord CSA ($p = 0.008$) were significant independent predictors of MSFC  
- Cervical cord CSA was the only measure with significant association with EDSS score ($r = -0.22; p = 0.02$) |
| **MS**    |              |                                                                        |                       |         |
| Lukas et al. (110) | 440 | - Upper cervical cord CSA  
- Brain black holes  
- Brain volume  
- GM volume  
- WM volume  
[Brain/GM/WM volume: 3D T1w/SEINAX]  
[Black holes: 3D T1w/AMIRA semiautomatic software]  
[Cord CSA: 3D T1w/semi-automated segmentation method] | - EDSS  
- T25FW  
- 9HPT | Cord CSA correlated with EDSS score ($r = -0.39$) and T25FW and 9HPT ($r = -0.27; p < 0.001$ for all comparisons)  
Cord CSA and number of brain black holes were the strongest explanatory factors for EDSS score  
Cord CSA and GM volume were the strongest explanatory factors for T25FW |

(Continued)
### TABLE 3 | Continued

| Reference | Patients | MRI measure of neurodegeneration | Measure of disability | Results |
|-----------|----------|----------------------------------|-----------------------|---------|
| Kearney et al. (117) | 159 | - Brain GM fraction  
- Brain WM fraction  
- Upper cervical spinal cord CSA  
[3D T1w/SPM (GM and WM fraction) and active surface method (cord CSAs)] | - EDSS |  
- Significant correlation between EDSS and WM fraction ($r = -0.32$; $p < 0.01$) and cord CSA ($r = -0.31$; $p < 0.01$)  
- Binary model: cord CSA associated with requirement for walking aid (EDSS score ≥ 6) ($p < 0.01$)  
- 4-category EDSS model: cord CSA ($p < 0.01$) and GM fraction ($p = 0.04$) associated with disability |
| Schlaeger et al. (108) | 142 | - Total cord CSA  
- GM and WM area at disc levels, C2/C3, C3/C4, T8/9 and T9/10  
- Brain GM volume  
[Cord: 2D PSIR/Active surface method]  
[Brain: MP-RAGE/FreeSurfer] | - EDSS  
- T25FW  
- 9HPT  
- Hip flexion strength  
- All spinal cord measurements (GM, WM and total cord areas) correlated with EDSS score (all $p < 0.001$) and T25FW (all $p < 0.001$)  
- Thoracic cord GM areas correlated with lower limb function  
- Multivariable model: cervical cord GM areas had strongest correlation with EDSS followed by thoracic cord GM area and brain GM volume |
| Oh et al. (118) | 102 | - Cervical spinal cord CSA  
- BPF  
[Cord: gradient-echo images/Automated method]  
[Brain: diffusion tensor images/BPF] | - EDSS  
- MSFC  
- Hip flexion strength  
- Vibration sensation threshold  
- Cord CSA was an independent predictor of EDSS (beta coefficient, $-0.075$; $p < 0.01$), MSFC (beta coefficient, 0.013; $p < 0.01$), hip flexion strength (beta coefficient, 0.67; $p < 0.01$) and vibration threshold (beta coefficient, $-0.65$; $p = 0.01$)  
- BPF was an independent predictor of MSFC (beta coefficient, 4.97; $p < 0.01$) |
| Kearney et al. (119) | 92 | - Upper cervical cord area  
- BPV  
[Cord: 3D-PSIR/active surface method]  
[Brain: 3D T1w/SPM] | - EDSS  
- MSFC |  
- Multiple regression model:  
- Cord area was independently associated with EDSS ($p = 0.003$)  
- BPV independently associated with 9HPT ($p = 0.007$) |
| Zivadinov et al. (120) | 66 | - Cervical cord absolute volume  
- Cervical cord fraction  
- Cervical cord to intracranial volume fraction  
- Brain volume (BPV)  
[Cord: 3D T1w/three different methods]  
[Brain: 3D T1w/SIENAX] | - EDSS |  
- Cervical cord absolute volume ($r = -0.51$; $p < 0.0001$) and BPV ($r = -0.43$; $p = 0.001$) showed robust correlation with disability; cervical cord fraction showed modest correlation ($r = -0.31$; $p = 0.018$)  
- Only 8% of the variance in disability was explained by brain MRI measures when co-adjusted for the amount of cervical cord atrophy |
| Liptak et al. (121) | 45 | - Medulla oblongata volume  
- Upper cervical cord volume  
- Brain volume (BPV)  
[Medulla and cord: T2w/manual segmentation]  
[Brain: dual echo spin-echo/template-driven segmentation] | - EDSS  
- Ambulation index |  
- A model including both medulla oblongata volume and BPV better predicted ambulatory index than BPV alone ($p = 0.04$) |
| Liu et al. (122) | 35 | - Upper cervical cord CSA  
- Brain volume (BPV)  
- GM fraction  
- WM fraction  
[Cord: T2w and 3D T1w/NeuroQLab]  
[Brain: 3D T1w/SPM] | - EDSS |  
- Cord CSA was the only independent predictor of EDSS ($r^2 = 0.17$; $p = 0.013$) |
### TABLE 3 | Continued

#### (a) Cross-sectional studies

| Reference         | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results |
|-------------------|--------------|-----------------------------------------------------------------------|-----------------------|---------|
| Cohen et al. (123)| 21           | Brain GM volume                                                      | EDSS                  | Only upper cervical cord volume significantly correlated with EDSS ($r = -0.515; p = 0.020$); this was largely driven by the results from patients with SPMS |
|                   |              | Brain WM volume                                                      | T25FW                | None of the MRI variables significantly correlated with T25FW |
|                   |              | Cervical cord volume                                                |                       |         |
|                   |              | [Brain: 3D sequence/Jim software]                                   |                       |         |
|                   |              | [Cord: T2w sequence/Jim software]                                    |                       |         |

#### (b) Longitudinal

| Reference         | Follow-up period (years) | Patients (n) | MRI measure of neurodegeneration [acquisition/quantification methods] | Measure of disability | Results |
|-------------------|--------------------------|--------------|-----------------------------------------------------------------------|-----------------------|---------|
| Lukas et al. (109)| 1 and 2                  | 352 with MS  | Brain volume                                                          | EDSS                  | Multivariate analysis: atrophy parameters that correlated with EDSS at Year 2 were GM volume (beta coefficient, $-0.003; p = 0.002$), baseline cord CSA (beta coefficient, $-0.01; p = 0.047$) and cord atrophy rate (beta coefficient, $-0.08; p = 0.02$) over 2 years |
|                   |                          |              | GM volume                                                             |                       | Rate of cord atrophy but not brain atrophy was significantly higher in patients with disability progression vs those with no progression ($p = 0.003$) |
|                   |                          |              | WM volume                                                             |                       | Multivariate binary regression: significant associations between disability progression over 2 years and baseline cord CSA ($p = 0.03$) and annualized change in brain volume ($p = 0.07$) over 2 years |
|                   |                          |              | Percentage brain volume change                                        |                       |         |
|                   |                          |              | Upper cervical cord CSA                                              |                       |         |
|                   |                          |              | Percentage change in cervical cord CSA                               |                       |         |
|                   |                          |              | [Brain: 3D T1w/SIENA and SIENAX]                                     |                       |         |
|                   |                          |              | [Cord: PD and T2w/semi-automated volumetry method (110)]             |                       |         |
| Furby et al. (124)| 2                       | 56 with SPMS  | Whole brain volume                                                   | EDSS                  | Rates of whole brain ($r = 0.35; p = 0.009$), GM ($r = 0.42; p = 0.002$) and spinal cord atrophy ($r = 0.34; p = 0.01$) all correlated with change in MSFC |
|                   |                          |              | GM volume                                                             | MSFC                  | Rate of GM atrophy was the only correlate of change in MSFC |
|                   |                          |              | WM volume                                                             | GHPT                  | Rate of whole brain was the only correlate of change in T25FW ($r = 0.39; p = 0.003$) |
|                   |                          |              | Central brain volume                                                 | T25FW                |         |
|                   |                          |              | Upper cervical cord CSA                                              |                       |         |
|                   |                          |              | [3D T1w/whole brain: SIENA]                                          |                       |         |
|                   |                          |              | [GM and WM volume: 3D T1w/SPM]                                        |                       |         |
|                   |                          |              | [Central brain volume: 3D T1w/MIDAS]                                  |                       |         |
|                   |                          |              | [Cord CSA: 3D T1w/in-house software]                                  |                       |         |
| Agosta et al. (125)| 2.4 (mean)              | 42           | Cervical cord CSA                                                     | EDSS                  | Significant correlation between baseline EDSS and cervical cord CSA ($r = -0.39; p = 0.01$) |
|                   |                          |              | Percentage change in brain volume                                     |                       | Baseline cord CSA correlated with increase in disability at follow-up ($r = -0.40; p = 0.01$) |

*Studies in each section are according to size of patient population. 9HPT, 9-hole peg test; BPF, brain parenchymal fraction; BPI, brain parenchymal volume; CIS, clinically isolated syndrome; CSA, cross-sectional area; EDSS, Expanded Disability Status Scale; GM, grey matter; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSFC, Multiple Sclerosis Functional Composite; PPMS, primary progressive multiple sclerosis; PSIR, phase-sensitive inversion recovery; SPM, statistical parametric mapping; SPMS, secondary progressive multiple sclerosis; T1w, T1-weighted; T2w, T2-weighted; T25FW, timed 25-foot walk; WM, white matter.*
MS clinical phenotypes. Regional cord atrophy was correlated with clinical disability and impairment in the pyramidal system for progressive MS \( (p < 0.001) \), but there was no correlation between atrophy and disability for the other MS phenotypes (CIS, RRMS, and benign MS) \( (106) \).

Schlaeger et al. evaluated the association between spinal cord WM and GM area and various measures of disability \( (96) \). They demonstrated that GM and WM area (as well as CSA) correlated significantly with EDSS score \( (p \leq 0.001 \) for both) and T25FW results \( (p < 0.001 \) and \( p = 0.004 \), respectively), whereas only the GM area correlated significantly with the 9HPT results \( (p = 0.024) \). In a multivariate model, spinal cord GM area was the strongest correlate of the EDSS score \( (96) \). In another study by the same group, which evaluated both brain and spinal cord atrophy (see next section), there was a significant correlation between thoracic cord GM area and lower limb function \( (108) \).

**Brain and Spinal Cord Atrophy**

Fifteen studies (mainly cross-sectional) have evaluated both brain and spinal atrophy correlation with disability \( (Table 3) \). Two of the largest studies, one cross-sectional and one longitudinal, were conducted by Lukas et al. \( (109,110) \). In the cross-sectional study, which included 440 patients with MS, spinal cord (but not brain) atrophy and brain black hole volume were independent explanatory factors for the EDSS score, while spinal cord and GM brain atrophy were the strongest explanatory factors for physical disability measured using the T25FW \( (110) \). In the longitudinal study, in which 352 patients with MS were followed up for 2 years, baseline cord CSA \( (p = 0.03) \) and the annualized percentage change in brain volume \( (p = 0.07) \) were significant predictors of disability progression (EDSS score change) at year 2 \( (109) \).

In three other studies (all cross-sectional), which used multivariate regression to analyse the data, cervical cord CSA was an independent predictor of disability \( (118,119,122) \). In their cross-sectional study of 142 patients with MS, Schlaeger et al. used multivariate analysis to evaluate the impact on disability of various brain and spinal cord measures of atrophy \( (108) \). They found that cervical cord GM area had strongest correlation with the EDSS score, followed by thoracic cord GM area and brain GM volume.

**DISCUSSION**

This review summarizes the results of studies that have assessed the association between MRI measures of CNS neurodegeneration derived from the assessment of T1-weighted images (mostly atrophy) and disability progression in MS. Relevant studies were identified via a systematic evaluation of the published literature using PubMed, and it is acknowledged that some relevant studies may not have been identified if terms for atrophy and disability were not included in the publication abstract (e.g., studies that evaluated cognition as the primary endpoint). Nevertheless, over 90 studies were identified. Most, though not all, of the studies identified have shown a significant correlation between atrophy and disability. Of the various measures used to assess neurodegeneration, the most consistent results were obtained with GM and spinal cord atrophy. The results for global WM atrophy in the brain were least consistent. Overall, 18 studies assessed both global GM and global WM atrophy; in eight of these, GM but not WM atrophy was shown to correlate with disability \( (26,40,56,78,79,109,111,124) \), compared with only one study showing the opposite \( (28) \). In the large study by Tedeschi et al., the EDSS at the end of the 2-year follow-up was significantly correlated with both global GM and global WM atrophy, but the correlation was stronger for the GM \( (r = −0.423 \text{ vs } −0.256 \text{ for WM}) \) \( (70) \). It is possible that degeneration of specific WM tracts contributes to disability and that a global measurement is not sensitive enough to detect this. It should also be borne in mind that conventional MRI techniques are not able to characterise and quantify all of the heterogeneous features of MS pathology \( (126) \). Several advanced MRI techniques specific to different aspects of MS pathology have been developed to evaluate the extent and distribution of microstructural tissue abnormalities in MS. Their application is contributing to improvements in the understanding of the mechanisms responsible for the presence and worsening of clinical disability. These include magnetization transfer MRI \( (127) \), which measures microstructural tissue abnormalities, and diffusion tensor imaging \( (128) \), which allows axonal and myelin injury to be quantified. In addition, the combination of postmortem MRI and histopathological evaluation is providing important insights into the abnormalities observed on MRI, enabling translation of basic pathology to the clinical setting and validation of new MRI techniques \( (4) \).

It has been suggested that combining MRI markers may increase sensitivity to disability changes. One composite that combines three MRI measures of MS severity is the Magnetic Resonance Disease Severity Scale (MRDSS), which generates a score between 0 and 10 based on T2 lesion volume, brain volume (brain parenchymal fraction (BPF)) and the ratio of the T1:T2 lesion volume \( (129) \). Although the MRDSS showed a larger effect size than any of the individual components in distinguishing patients with RRMS from those with SPMS, the correlation with the EDSS score was similar to that observed with BPF \( (129) \). In a subsequent longitudinal study, prediction of disability (EDSS score) progression was significant for T2 lesion volume only \( (76) \). More recently, the MRDSS (MRDSS2) has been revised, replacing BPF with GM fraction and adding upper spinal cord CSA \( (130) \). The correlation between MRDSS2 and EDSS score was shown to be significant in 55 patients with MS \( (130) \). Pardini et al. have proposed a composite MRI-based measure that assesses motor network integrity \( (131) \). It is based on fractional anisotropy, magnetization transfer ratio, and normalized tract volume of motor network connections. The ability of this composite measure to predict disability was substantially greater than conventional non-network-based MRI measures \( (131) \). Another approach to improving visualization of MS-induced neurodegeneration is the use of multimodal MRI acquisition \( (132) \). A correlation with disability was observed when this method was applied to cortical GM and corpus callosum WM in patients with RRMS \( (132) \).

In most of the studies in which it was evaluated, there was a correlation between black holes and disability outcome measures.
This supports the concept that focal, irreversible tissue loss, as well as more diffuse loss of tissue, has an impact on disability in MS. A number of the studies assessing black holes also evaluated T2 lesion load, which represents focal WM lesions. In the largest of these studies (110), conducted in 440 patients, there was a significant correlation between T2 lesion load and EDSS in the univariate, but not the multivariate analysis, while black hole lesion load was significant in both analyses. Notably, neither parameter was significant in the multivariate analysis of the association with T25FW results (110). In the study by Caramanos et al., the correlation with EDSS was greater for black holes than T2 lesions (47), and in the study by Giorgio et al., EDSS worsening over 10 years was best correlated with the combination of baseline black hole lesion count and increasing black hole lesion volume (66).

When considering the results of the studies included in this review, it should be borne in mind that correlation does not prove causality, and multivariate analysis, to control for confounding variables, was not applied in all studies. It is also clear from the information presented (Tables 1–3) that studies evaluating atrophy and disability are relatively heterogeneous in terms of sample size and follow-up duration, and even within studies, patient populations are heterogeneous, including a range of MS phenotypes. Heterogeneity of patient populations may be of considerable significance as the study conducted by Lukas et al., which was large enough to allow comparisons between MS subtypes, demonstrated differences in spinal cord atrophy between the progressive and relapsing forms, and showed that brain GM atrophy also differed between subtypes (109). Furthermore, in the study by Rocca et al., the correlation between spinal cord atrophy and disability was significant in some MS phenotypes, but not others (95). These differences warrant further research. Another potential confounding factor is possible variations in patient practice. The next 10 years promises to be equally fruitful; as MRI techniques evolve, so the pathological substrates of disability will become more clearly delineated. As we work toward this goal, we should not lose sight of the challenges, both technological and financial, of introducing these techniques into everyday clinical practice.

CONCLUDING REMARKS

The evaluation of MRI measures of neurodegeneration as predictive markers of disability in MS is a highly active area of research. Over the last 10 years, a large number of MRI studies have added to the existing literature on this subject, confirming that in general, MRI measures of atrophy correlate with disability. These efforts have culminated in the use of brain atrophy measurements to assess the effects of disease-modifying therapies. Although currently limited to clinical trials, discussions are beginning on how brain atrophy measurement can be applied in clinical practice. The next 10 years promises to be equally fruitful; as MRI techniques evolve, so the pathological substrates of disability will become more clearly delineated. As we work toward this goal, we should not lose sight of the challenges, both technological and financial, of introducing these techniques into everyday clinical practice.

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