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Brain MRI atrophy quantification in MS

From methods to clinical application

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ABSTRACT

Patients with the main clinical phenotypes of multiple sclerosis (MS) manifest varying degrees of brain atrophy beyond that of normal aging. Assessment of atrophy helps to distinguish clinically and cognitively deteriorating patients and predicts those who will have a less-favorable clinical outcome over the long term. Atrophy can be measured from brain MRI scans, and many technological improvements have been made over the last few years. Several software tools, with differing requirements on technical ability and levels of operator intervention, are currently available and have already been applied in research or clinical trial settings. Despite this, the measurement of atrophy in routine clinical practice remains an unmet need. After a short summary of the pathologic substrates of brain atrophy in MS, this review attempts to guide the clinician towards a better understanding of the methods currently used for quantifying brain atrophy in this condition. Important physiologic factors that affect brain volume measures are also considered. Finally, the most recent research on brain atrophy in MS is summarized, including whole brain and various compartments thereof (i.e., white matter, gray matter, selected CNS structures). Current methods provide sufficient precision for cohort studies, but are not adequate for confidently assessing changes in individual patients over the scale of months or a few years. **Neurology® 2017;88:403-413**

GLOSSARY

BPF = brain parenchymal fraction; **CIS** = clinically isolated syndrome; **DGM** = deep gray matter; **GM** = gray matter; **ICV** = intracranial volume; **MS** = multiple sclerosis; **NAWM** = normal-appearing white matter; **PP** = primary progressive; **RF** = radiofrequency; **RR** = relapsing-remitting; **SP** = secondary progressive; **TVW** = 3rd ventricle width; **WM** = white matter.

Clinically relevant irreversible brain tissue loss (i.e., atrophy) occurs in patients with multiple sclerosis (MS) from the early stages of the disease and is useful in differentiating clinical phenotypes and explaining physical disability and cognitive impairment.¹⁻⁶ Neurodegeneration is among the pathologic hallmarks of MS and halting neurodegeneration and promoting neuroprotection are among the target outcomes of current therapeutic strategies.

Over the last 2 decades, considerable effort has been devoted to elucidating the clinical relevance of brain atrophy in MS, and developing methods for its reliable estimation. Several comprehensive review articles have already been published on this topic.^{7,8} Since their publication, important technical improvements have been made and several software tools, with differing requirements on technical ability and levels of operator intervention, have been developed. However, brain atrophy quantification is still far from a reliable application in clinical practice. This is in part due to the lack of comparative studies, so that choosing between methods is difficult; the uncertainty in the results when applied to single patient; the difficulty of developing completely automatic methods; of standardizing acquisition; of creating robust postprocessing procedures; and of fitting the lengthy acquisition and analysis procedures into the

Supplemental data at Neurology.org

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clinical routine. The absence of a normative database, combined with high intersubject brain volume variability, is another critical issue.

This review provides an update on current understanding of brain atrophy in MS. After a brief summary of the pathologic substrates, we discuss methodologic aspects of quantification, including imaging protocols and clinical applications in cross-sectional and longitudinal settings. Important physiologic factors affecting brain atrophy estimation, which should be controlled for, are also considered. All of this has a profound influence on the feasibility of measuring atrophy in clinical practice. To emphasize the importance of bringing such an assessment closer to clinical use, we then summarize the most recent research into MS brain atrophy (multiple compartments and structures). The effects of currently available disease-modifying treatments on atrophy are not discussed, since they have been the topic of recent reviews.^{8,9}

PATHOLOGIC BASIS Within white matter (WM) lesions, there is loss of myelin, oligodendrocytes, and axons. Atrophy of nonlesional or normal-appearing WM (NAWM) is likely secondary to myelin loss and axonal damage and loss, the latter partially caused by Wallerian degeneration. Gray matter (GM) pathology is also frequent and widespread. GM demyelination is common in neocortical areas, but is also found in other GM areas, such as the thalamus, hippocampus, and cerebellum. A study relating GM atrophy patterns measured using postmortem MRI to histopathology showed that atrophy is explained predominantly by (neuro)axonal loss and neuronal shrinkage, and is largely independent of demyelination.¹⁰ This finding was later confirmed by relating GM lesions and normal-appearing GM more directly (figure 1).¹¹

Postmortem work compared the results from different GM atrophy MRI analysis tools to cortical thickness measured histopathologically, and showed that there are substantial differences in accuracy between them,¹² indicating that future research should focus on improving and validating these different analysis techniques.

METHODOLOGIC ISSUES Atrophy measures rely on the precise quantification of the volume, or change in volume, of relevant structures. With MRI, the volume of any structure that can be seen with good contrast (that is, a difference in brightness between tissues that exceeds the level of noise) can be quantified.

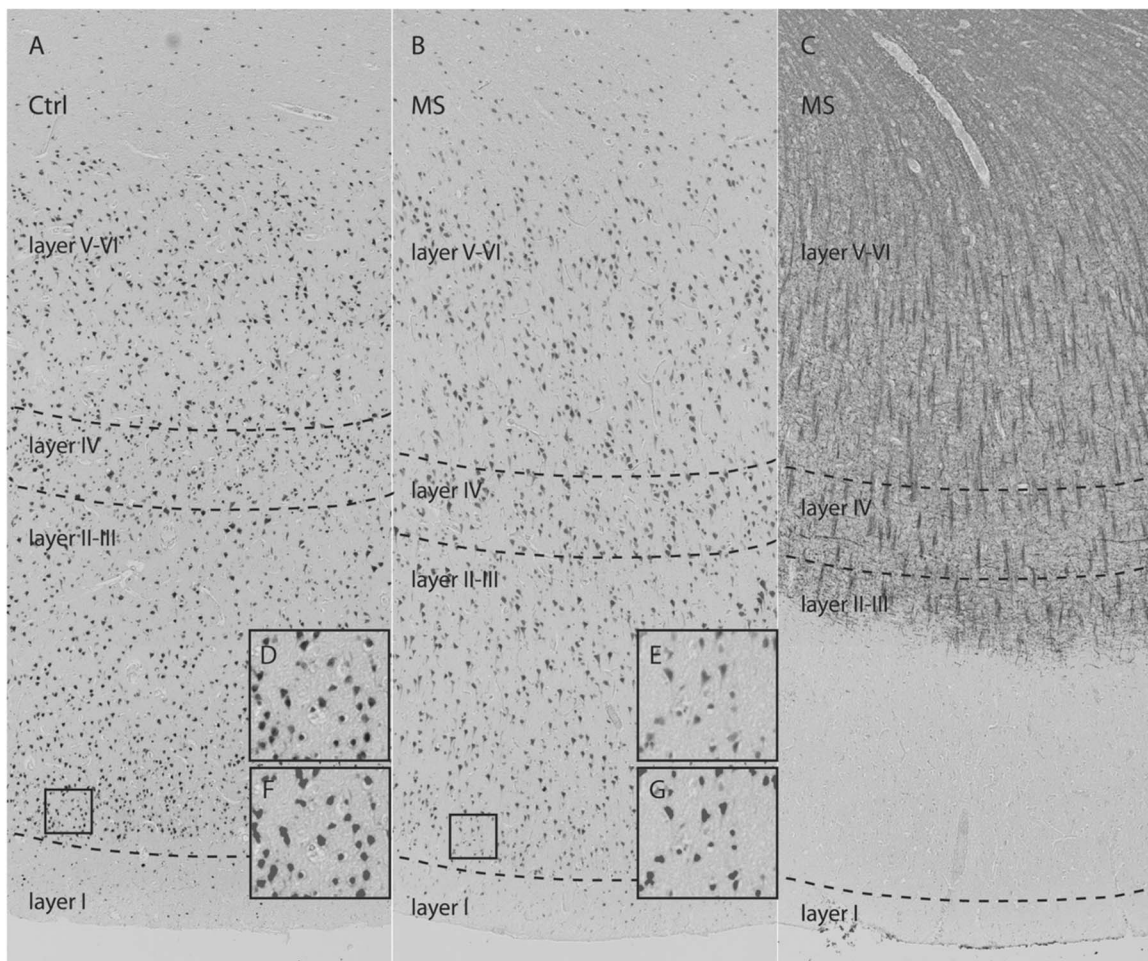
However, raw volumes usually need to be scaled to remove confounding factors that affect volume, giving an index of atrophy that can be compared to normative data. One example is the so-called brain parenchymal fraction (BPF), which is the ratio of the brain volume to the intracranial volume. When follow-up scans of the same patient are acquired, volume changes can be quantified, and indices of change can be made with respect to a baseline scan.

MRI data acquisition. With careful setup and quality control, an MRI scanner is capable of making precise volume measurements that are not achievable by other means. MRI uses no ionizing radiation and there is no known risk from the low-level heating of the body that occurs during a scan. As a consequence, it can safely be used in serial follow-up studies.

In scientific terminology, accuracy refers to the degree of bias in any measurement, while precision reflects the reproducibility of measurements. The assessment of accuracy and precision is an essential part of the validation process when introducing a new measurement method.¹³ In the context of MRI assessment of atrophy, precision can be assessed by repeated MRI measurements over a short enough period of time where little real change in volume can have occurred. Accuracy is more difficult to evaluate, unless simulated data or test objects are used, consisting of different structures with known dimensions. Validation should involve measurements made under conditions of different signal-to-noise ratio, contrast, and image geometry, to optimize acquisition and processing parameters, to test method robustness, and to characterize the measurement error. It will only be possible to determine the context in which a method may be applied after rigorous validation involving both healthy controls and patients, studied both cross-sectionally and longitudinally.

The size at which scanned objects appear in MRI is governed by the accurate calibration of the magnetic field gradients used to encode spatial information. The contrast in the images is affected by the radiofrequency (RF) pulse flip angles used to create the signal; this indirectly affects atrophy measures since tissue compartments (CSF, GM, WM) are assigned based on their relative brightness in the image. Thus, stability of the gradient and RF systems are important factors. For longitudinal studies, it is imperative to image any given study participant using the same scanner without upgrades, especially in hardware. This is difficult in clinical practice; however, patients with MS are often referred to the same neurologic center during the course of the disease, and it is likely that they will undergo MRI in the same radiology department. In cases where more than one scanner is available, and it is difficult to guarantee the

Figure 1 Neuronal loss in type III cerebral cortical lesions in multiple sclerosis (MS)



Control (Ctrl) (A) and MS (B) sections immunostained for NeuN demonstrate overall neuronal loss in MS cortex. (C) Antimyelin PLP-immunostained section from a patient with MS (B) shows subpial demyelination. High-magnification images from cortical layer II (D, E) with matching pictures (F, G) demonstrate the quality of segmentation scripts. The frontal cortex was selected to investigate possible differences in neuron density and axon density between MS (normal-appearing gray matter and type III lesions) and control cortex. Neuron density (-25.4% ; $p = 0.001$) and axon density (-31.4% ; $p = 0.001$) were significantly reduced in type III lesions compared with control cortex. There was no significant difference in neuron sizes between type III lesions and matched sclerotic control cortex. From Klaver R, Popescu V, Voorn P, et al. Neuronal and axonal loss in normal-appearing gray matter and subpial lesions in multiple sclerosis. *J Neuropathol Exp Neurol* 2015;74:453-458,¹¹ by permission of the American Association of Neuropathologists, Inc., Copyright © 2015.

study of a patient always using the same scanner, the use of quantitative measures may still be possible.¹⁴ Attention should also be paid to correction of the effects of gradient distortion.

Brain atrophy is mostly measured from T1-weighted images, where there is good contrast between a bright parenchyma against a dark CSF background and good GM/WM contrast. T2/fluid-attenuated inversion recovery contrast can be utilized for BPF. Most recent studies of atrophy have used high-resolution 3D acquisition, with near-isotropic voxel sizes of around 1 mm^3 . The high resolution allows the assessment of smaller, thinner structures such as the cortical ribbon, while 3D acquisition and isotropic voxel sizes can minimize the reduction in quality when coregistering serial scans.

Current methods provide sufficient precision for cohort studies, since errors and confounding effects

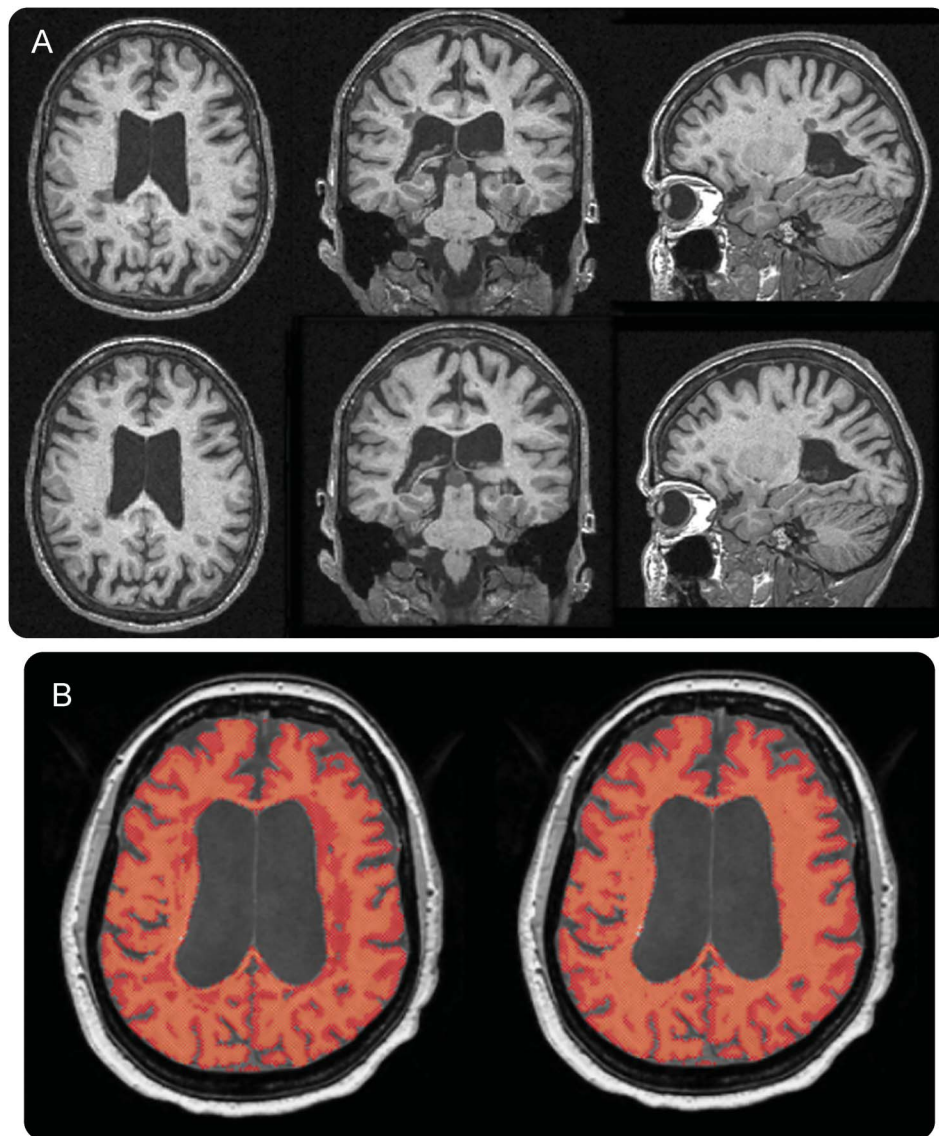
are averaged out, but do not always give enough confidence in the assessment of changes in individual patients with MS. The ability to measure change in a single patient reliably in a particular region depends on the precision of the method used relative to the true change in atrophy over the follow-up, and confounding effects, such as hydration.¹⁵ Natural history studies have shown brain atrophy rates in patients with MS in the range 0.7%–1% per year,⁷ while validation studies report, for example, a median absolute error of 0.15% for longitudinal changes in brain atrophy.¹⁶ Thus, it should be possible to measure brain atrophy reliably in a single patient with, say, annual follow-up, although we need to take confounding effects, clinical events, and treatment into account. Regional measures will have poorer precision; for example, cortical thickness has an average variability of around 2.5%–3%.¹⁷ The ability to use

Table 1 Comparison of various widely used, freely available software tools for cross-sectional and longitudinal atrophy measurement

Software library	Tool	Images	Target anatomy	Measure	Segmentation	Registration	Normalization	Validation
ANTs	Atropos ^{a1} [F]	T1 or other modalities	GM, WM, CSF	Volume	Uses a priori information or K-means or Otsu initialization			Healthy controls; manual segmentation; simulated data
	Registration-based cortical thickness ^{17,e2} [L F]	T1 or other high-resolution modalities	GM cortex	Cortical thickness	Uses a priori information	Continuous one-to-one mapping between GM-WM interface and GM-CSF interface	Intracranial volume	Healthy controls; scan-rescan; others' methods
	Atropos + antsMalLabeling.sh ^{e3,e4} [F]	Multimodality	Deep GM structures, GM cortex	Volume	Multi-atlas labeling + uses a priori information + needs training dataset	A priori information deformed using symmetric normalization algorithm		Healthy controls; manual segmentation; others' methods
FreeSurfer	FreeSurfer ^{e5} [L S F]	T1	Deep GM structures	Volume of structure	Uses training dataset; model-based; uses a priori information	Nonlinear alignment to the Talairach atlas	Scale factor derived from a skull-based transformation to a reference atlas	Scan-rescan; patients with AD and controls; reproducibility across scanners, field strengths; manual segmentation
	FreeSurfer ^{e5} [L S F]	T1	GM cortex	Cortical thickness	Uses training dataset; model-based; uses a priori information	Nonlinear registration algorithm of inflated surfaces to align cortical folding to the spherical atlas		Scan-rescan; patients with AD and controls; reproducibility across scanners, field strengths; manual segmentation
FSL	SIENA ¹⁶ [L F]	T1	Global GM, WM	Global volume change	Uses edge information initialized (but not constrained) by tissue segmentation	Halfway-space rigid transformation	Scale factor derived from a skull-based transformation of the longitudinal image pair	Scan-rescan; patients with MS and controls; others' methods
	SIENAX ^{e6} [F]	T1	Global GM, WM	Global volume	Uses a mixture model to segmentation tissues, without using priors, but with some registration-based cleanup of brain mask	Affine transformation to atlas	Scale factor derived from a skull-based transformation to a reference atlas	Scan-rescan; patients with MS and controls; others' methods
	FIRST ^{e7} [F]	T1	Deep GM structures	Local shape or volume of structure	Bayesian appearance model, including intensity and shape information derived from a (prepackaged) training set	2-Stage linear registration (second stage subcortical only)	Intracranial volume	Manual segmentation; patients with MS and controls; others' methods
MINC	CIVET ^{e8,e9} [S]	T1 + dual echo	GM, WM, CSF; GM cortex; deep GM structures	Volume, area, length	Single- or multispectral classification, partial volume estimation; uses a priori information; needs training dataset (for lesion identification only); surface extraction	Linear + nonlinear spatial normalization to a population template		Manual segmentation; simulated data; others' methods
SPM	VBM ^{e10,e11} [F]	T1	GM	Local GM volume	Tissue probability priors + unified registration/segmentation	Diffeomorphic registration (DARTEL)	Registration to a study-specific template	Patients with MS and controls; others' methods
	Longitudinal toolbox ^{e12} [L]	T1	GM, WM	Local volumes (via Jacobians)	Segmentation optional	DARTEL can be used for intersubject registration	Registration to a study-specific template	Preliminary so far ^{e13}

Abbreviations: AD = Alzheimer disease; ANT = advanced normalization tool; DARTEL = diffeomorphic anatomical registration using exponentiated lie algebra method; F = lesion refilling applicable; FIRST = FMRIB's Integrated Registration and Segmentation Tool; GM = gray matter; L = longitudinal method; MS = multiple sclerosis; S = automatic lesion segmentation available; SIENA = structural image evaluation, using normalization, of atrophy; VBM = voxel-based morphometry; WM = white matter.

Explanation of what each column indicates can be found in the main text, and further details of the workings of the tools can be found in the indicated online references (see supplemental data at Neurology.org).



(A) Three orthogonal views (axial, coronal, and sagittal) of the same patient with multiple sclerosis are shown before (top row) and after (bottom row) T1-hypointense lesion refilling. (B) Results of segmentation without (left) and with (right) T1-hypointense lesion refilling. The gray and white matter tissue classes are shown in 2 different shades of red. Without lesion refilling, the misclassification of lesions as gray matter is evident.

shorter follow-up periods or to assess substructures must be evaluated case by case.

Methods: Cross-sectional and longitudinal applications.

In radiologic practice, simple linear measures, such as ventricular enlargement, were reproducible at the cost of long training and time spent in manual analysis. Automatic methods now exist that usually involve complex pipelines, combining lesion segmentation, registrations, and tissue/structure segmentation. Table 1 shows a comparison of the current most widely used, freely available software.

In table 1, the target anatomy of each tool indicates which parts of the brain it examines (e.g., cortex or deep GM), and the measure indicates which aspect

of the target anatomy is quantified (e.g., volume or thickness) and whether it is done locally or as a global summary across the brain or structure. Global measures often benefit from averaging over a larger volume and can have greater precision and statistical power. Local measurements more richly describe the anatomical changes and are not diluted by areas where there is little or no change. Prior information is often required when performing segmentation and is usually provided via registration to an atlas. Segmentation of deep GM structures also requires, together with registration, prior anatomical knowledge, though the measures it provides are often more sophisticated (e.g., shape variation or intensity distributions). The set of images used to generate the

prior information needs to be appropriate to the studied participants: for example, healthy control priors can cause biases when used with patient images. Some methods (e.g., advanced normalization tools, statistical parametric mapping) mainly use registration to measure local shape differences, having a standard anatomy or the longitudinal acquisition of the same subject as a reference.

WM lesions affect atrophy calculations, since they influence the detection of GM/WM/CSF intensity differences. Lesion filling techniques (table 1) are often employed to alleviate this. This approach is suitable for use with a wide range of atrophy tools (table 1) and is recommended for increased accuracy (figure 2).

Volumes and thicknesses of brain tissue structures correlate with head size, so it is common practice to produce normalized values. The normalization factors (table 1) are often based on automated measurements of intracranial volume (ICV) or on scaling factors from skull-based or whole-head-based registration to a standard template.

Tools for longitudinal assessment of atrophy are normally designed and optimized to work specifically with pairs of images from each participant. Due to drift in scanner calibration, corrections based on the skull volume (or ICV) are commonly used to isolate true biological changes. Registration of scans of the same subject achieves greater precision than registration to an atlas, because the brain has the same cortical folding pattern.

Pitfalls and limitations. Various sources of error related to image acquisition and processing and variability due to pathophysiologic changes can affect MRI atrophy quantification.^{8,18} Table 2 lists the main errors due to image acquisition and processing. High-quality and consistent acquisition protocols, together with clear procedures for repositioning, are mandatory for assessing brain atrophy.

The interpretation of apparent brain volume loss needs caution, since numerous factors can have a confounding effect, causing overestimation or underestimation.^{7–9,18} Factors such as lifestyle (e.g., alcohol, smoking, diet, and dehydration),¹⁵ genetics,¹⁸ and others (e.g., diabetes, cardiovascular risks) may affect brain volumes. For example, fast (1.5 L in 90 minutes) rehydration after dehydration resulted in a 0.36% increase of brain volume.¹⁵ A J-formed association was found between the extent of alcohol ingestion and brain atrophy progression, with heavier drinkers having the highest annual brain atrophy rate ($-0.54 \pm 0.26\%$).¹⁸ Brain atrophy progresses with age and may be more pronounced when aging is complicated by other risk factors.¹⁸ Moreover, brain volumes seem to fluctuate throughout the day, decreasing from morning to evening.¹⁹

Because of these difficulties, individualized longitudinal brain volume assessment may not be ready for widespread clinical use. Further studies are needed to establish normative values for brain volume changes (both for healthy individuals and patients with MS).

CLINICAL APPLICATIONS Global measurements.

Brain atrophy, ventricular system enlargement, and widening of cortical sulci and gyri is evident on visual inspection in the large majority of MS scans. Brain atrophy occurs through all stages of the disease, from clinically isolated syndromes (CIS) to secondary progressive (SP) and primary progressive (PP) disease, being more pronounced in the latter groups.⁷

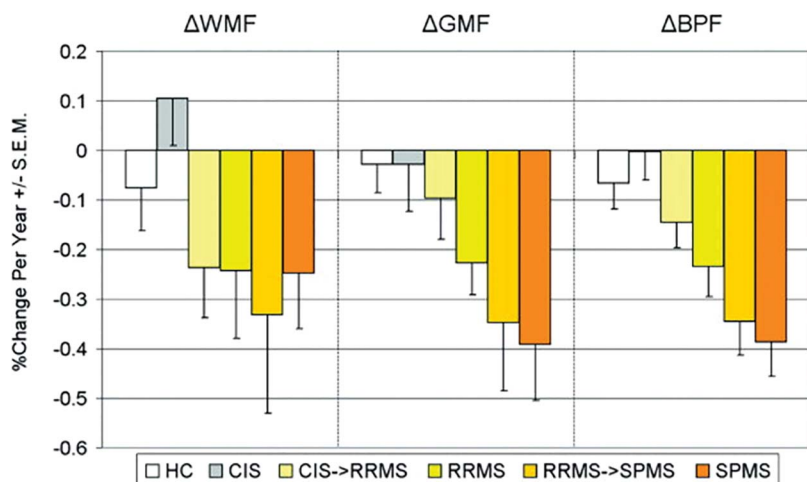
In clinically stable and untreated patients, brain volume loss occurs at a rate of about 0.5%–1% per year⁷ compared to 0.1%–0.3% for healthy controls. Longitudinal studies of different cohorts of patients (including a large group of untreated patients with MS)²⁰ have suggested that the annual rate of brain atrophy loss is not influenced by clinical phenotype.²⁰ A 7.5-year longitudinal study tried to provide specific cutoff values to discriminate physiologic and pathologic brain atrophy rates in patients with MS, which might be of great value in a clinical setting.²¹ An annualized percentage brain volume change of -0.4% had a specificity of 80% and a sensitivity of 65% for discriminating the presence or absence of pathologic brain atrophy. Further studies, on different cohorts of patients, with different duration of follow-up and using different methods of acquisition and analysis, are needed to confirm the clinical relevance of such a cutoff.

Measuring atrophy progression provides clinically relevant information. More pronounced ventricular enlargement occurs in patients with CIS who evolve to MS compared to those who do not.¹ Greater brain atrophy develops in patients with worsening disability than

Table 2 The main sources of error in image acquisition and processing affecting quantification of atrophy from MRI scans

Acquisition	
Image artifacts due to head motion, radiofrequency intensity nonuniformity and geometric distortion, phase-encode ghosting (wrap-around artifact)	
Poor signal-to-noise ratio or contrast in images	
Partial head coverage	
Image acquisition with nonidentical scan parameters or imperfect patient repositioning in a longitudinal framework	
Processing	
Imperfect removal of nonbrain tissue (e.g., eyes, periorbital fat) during image processing	
Misclassification of T1-hypointense lesions as gray matter or CSF	
Errors in interpretation (e.g., apparent tissue loss due to systematic alignment changes) with registration-based methods due to poor image resolution or large anatomical variation across patients	

Figure 3 Longitudinal changes in gray matter (GM) and white matter (WM) atrophy in multiple sclerosis (MS) phenotypes



Plot of the mean annualized rates of change for WM fraction (WMF), GM fraction (GMF), and brain parenchymal fraction (BPF) in patients with MS with different disease clinical phenotypes, including healthy controls (HCs; white bars; $n = 17$), patients with clinically isolated syndromes (CIS; gray bars) throughout the 4-year study ($n = 7$), patients who started the study with a diagnosis of CIS and converted to relapsing-remitting MS (CIS→RRMS; light yellow bars; $n = 8$), patients with RRMS throughout the study (RRMS; dark yellow bars; $n = 28$), patients who started the study with a diagnosis of RRMS and progressed to secondary progressive MS (RRMS→SPMS; light orange bars; $n = 7$), and patients with SPMS (orange bars) throughout the study ($n = 19$). Error bars indicate SEM. From Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. *Ann Neurol* 2008;64:255-265,⁴ by permission of Wiley-Liss, Inc., © 2008 American Neurological Association.

in those who are clinically stable.² Whole brain atrophy correlates with cognitive dysfunction²² and mood disturbances.²³ Finally, quantification of brain volume on early scans provides prognostic measures of clinical status not only for medium and long-term follow-up,²⁴ but also for short-term (over 6 months) decline.²⁵

Cross-sectional and longitudinal studies have investigated the mechanisms driving brain atrophy development. T2-hyperintense lesion volume correlates with brain atrophy at a given timepoint and over time.²⁶ A 14-year longitudinal study suggested that this relationship might be dynamic, since early rather than later T2 focal lesion accumulation was related to the subsequent long-term atrophy.²⁷ Correlative studies with MRI-detected disease activity (new T2 or gadolinium-enhancing lesions) have shown that inflammation can result in a transient increase in brain volume, which can dramatically resolve (pseudotrophy) following steroid treatment.²⁸ While some authors have suggested faster brain volume reduction in *APOE* $\epsilon 4$ MS carriers,²⁹ others did not confirm these findings.³⁰

There is recent evidence of more severe brain atrophy in patients with MS harboring one or more cardiovascular risk factors.³¹ Accumulation of damage in sites directly connected to the brain, such as the optic nerves and spinal cord, may also influence brain atrophy

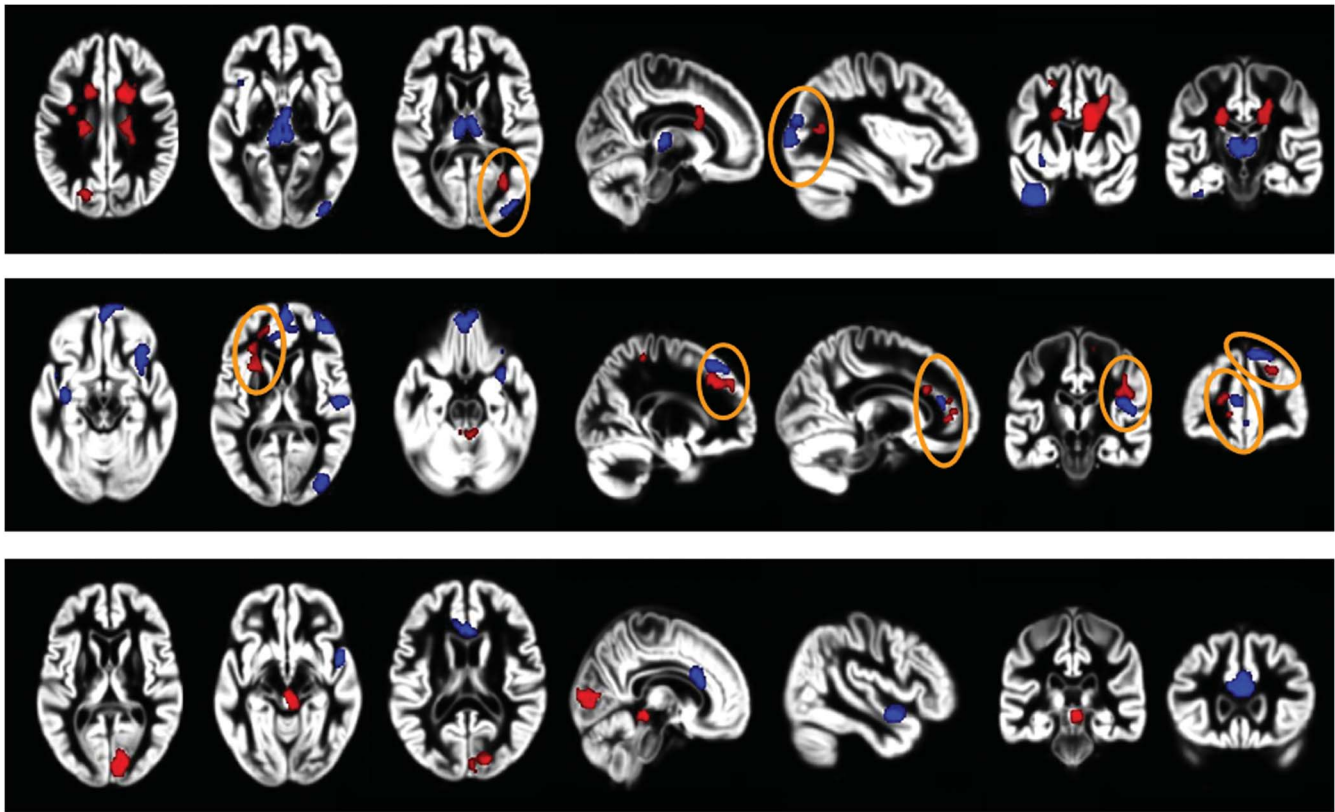
through secondary degeneration. For instance, a 4-year study showed an association between retinal layer abnormalities and brain atrophy progression.³² Other studies³³ found a correlation between brain atrophy and imaging measures of cervical cord damage.

GM and WM atrophy. The ability to analyze brain WM and GM involvement separately has been one of the main advances in atrophy quantification. Although atrophy involves both these compartments, GM atrophy assessment provides more clinically relevant information than does WM atrophy. Significant GM fraction reduction was found in patients with CIS who developed MS over the subsequent 3 years.³⁴ Confirming several smaller studies, in a large ($n = 927$) cross-sectional cohort, GM atrophy helped to distinguish the different disease forms (being more severe in SPMS) and was correlated with disability and cognitive impairment.³ Even though these results need to be confirmed on a larger dataset, expressed as an increase relative to controls, GM atrophy over a 4-year period accumulated with disease stage, being 8.1 times greater in patients with relapsing-remitting MS (RRMS), 12.4 times greater in patients converting from RRMS to SPMS, and 14 times greater in patients with SPMS (figure 3).⁴ In contrast, WM atrophy rates were constant across all MS disease stages.⁴ Reduced GM volume explains deteriorating cognitive function³⁵ and impairment in selected cognitive domains. A 13-year study in relapse-onset patients with MS demonstrated that baseline GM atrophy was the only imaging predictor of disability worsening.⁶

GM atrophy is unevenly distributed across the brain. At the beginning of the disease (i.e., CIS and pediatric³⁶ MS), GM involvement might start from deep GM (DGM) nuclei and then progressively extend to cortical GM regions.³⁷ In PPMS, early involvement of the cingulate cortex occurred, which continued at a steady rate over a 5-year period, contributing to clinical deterioration.³⁸

Atrophy of selected GM regions helps to explain specific clinical deficits or variability between clinical phenotypes. A well-characterized pattern of regional GM atrophy involving several frontal, parietal, and temporal regions distinguishes cognitively impaired patients with MS (figure 4)³⁹; patients with MS with longstanding disease or severe disability show focal thinning of the primary sensorimotor cortex⁴⁰; atrophy of the hippocampus and its subfield correlates with cognitive deficits.⁴¹ Applying radial mapping analysis (measured as the distance from hippocampal medial core to the surface), an expansion of the dentate gyrus of the hippocampus has been described, mostly in patients with RRMS, which may represent an inflammation-induced neurogenic process.⁴² In

Figure 4 T2 lesions, gray matter (GM) atrophy, and cognitive impairment in multiple sclerosis (MS)



Distribution of regions of significant GM atrophy (blue) and T2-visible lesions (red) in cognitively impaired vs cognitively preserved patients with MS according to the clinical phenotype. Top row: relapsing-remitting MS; middle row: secondary progressive MS; bottom row: primary progressive MS. Orange circles identify regions with a correspondence between presence of T2-visible lesions and GM atrophy. Images are oriented with neurologic convention. From Riccitelli G, Rocca MA, Pagani E, et al. Cognitive impairment in multiple sclerosis is associated to different patterns of gray matter atrophy according to clinical phenotype. *Hum Brain Mapp* 2011;32:1535-1543,³⁹ by permission of Wiley-Liss, Inc., © 2010.

patients with CIS, inflammation may cause an early, paradoxical increase of GM volume.⁴³

Several mechanisms drive GM atrophy. WM lesion accumulation influences GM atrophy, as suggested by cross-sectional⁴⁴ and longitudinal studies that found a correlation between atrophy of selected GM regions over time and WM lesion progression.⁴⁵ A 2-year study found that halting new T2 lesion formation may result in less GM atrophy, with no effect on cognitive deterioration.⁴⁶ Another study described an association between increased periventricular T2 lesion volume and decreased cortical thickness in RRMS, but not in CIS,⁴⁷ suggesting that common CSF-mediated factors might play a role in GM and WM damage accumulation. Studies that have assessed the anatomical correspondence between regional GM and WM damage found only a partial correspondence between damaging processes occurring in these 2 brain compartments.⁴⁸ In early PPMS, cortical damage over a 2-year period was mostly a sequela of NAWM pathology, which, in turn, was predicted by abnormalities within WM lesions.⁴⁹

Cortical atrophy can also occur as a result of focal GM lesions. However, the use of voxel-wise measures

has shown that regional GM atrophy and cortical lesions are not spatially coupled.⁵⁰

A 2-year longitudinal study demonstrated that fluctuations in inflammatory WM lesion activity can profoundly influence WM volume changes (pseudoatrophy), whereas it does not affect GM volume changes.⁵¹

Deep GM nuclei. In early work, 3rd ventricle width (TVW) correlated with performance on many cognitive tests.⁵ A postmortem/MRI correlative study showed increased TVW (105%) and decreased thalamic volume (17%) in 10 patients, with a 22% reduction of neuronal density.⁵² In 86 patients with MS,⁵³ volume was reduced in caudate, putamen, pallidum, nucleus accumbens, and thalamus. The effect on the thalamus was nearly twice that of any other DGM structure. In 120 patients,⁵⁴ MRI/clinical correlations were again between thalamus and measures of cognitive processing speed and executive function, and between caudate and tests emphasizing working memory and verbal memory.

The thalamus is an assembly of multiple interconnected nuclei, with unique efferents of the cerebral

cortex. The next research goal is to identify tracts emanating from specific thalamic nuclei or subregions and measure the correlation between microstructural tract injury and associated seed nuclei. Recent multi-center work⁵⁵ performed a diffusion tractography-based parcellation of the thalamus and its WM connections and found that cognitive impairment in RRMS was associated with increased fractional anisotropy in most thalamic regions, atrophy of the frontal subregion that includes the anterior nucleus, and abnormal fractional anisotropy of all cortico-thalamic tracts.

In a longitudinal study,⁵⁶ the rate of atrophy over 3 years was modest in patients with MS when compared to healthy controls, and was more pronounced in patients with low cognitive reserve. In another investigation, decreased cognitive processing speed over 3 years was related to localized atrophy of the anterior and superior surface of the left thalamus.⁵⁷

Measuring DGM nuclei atrophy may provide important prognostic information, as suggested by patients with CIS, in whom decreased thalamic volume over a 2-year period was associated with development of MS,⁵⁸ or in relapse-onset patients with MS, in whom baseline thalamic atrophy was associated with the accumulation of disability after an 8-year follow-up.⁵⁹

The mechanisms influencing DGM tissue loss are those previously described for the whole GM, although a significant regional effect of T2 lesions has been described early in the disease course.⁶⁰

DISCUSSION Many technical improvements have occurred that have enhanced the quantification of brain atrophy, and there is an increased understanding of the clinical relevance of atrophy and its underlying substrates in patients with MS. Multiple physiologic and disease-related factors are now recognized as potential modifiers of brain atrophy estimates, which suggests that caution is needed when moving atrophy measures into clinical practice. The choice of the analysis method and target tissue area should be guided by clinical questions (i.e., monitoring of disease course, obtaining prognostic information, explaining specific symptoms). At present, it seems that a global measure of brain volume or a simple measure of GM volume may be sufficient for clarifying many of the processes at work in MS. To move atrophy quantification definitively into clinical practice, effort should be devoted to creating a worldwide standardized protocol for image acquisition not only for research studies, but also for individual patient management. As is the case for many other paraclinical diagnostic tools, specialized analysis by expert laboratories may be the future.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified through searches of PubMed with the search terms atrophy, multiple sclerosis, tissue loss, white matter, lesions, gray matter, brain, phenotype/s, disability, prognosis, and cognitive impairment from 1979 until September 2016. Articles were also identified through searches of the authors' own files. Only articles published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

AUTHOR CONTRIBUTIONS

M.F. drafted the introduction and conclusions as well as the global measurement section. M.A.R. drafted the gray matter and white matter atrophy section. J.J.G.G. drafted the pathologic basis section. M.A.H., R.G.H., M.J., and E.P. drafted the methodologic issues section. N.D.S. and M.B. drafted the pitfalls and limitations section. R.H.B.B. drafted the deep gray matter nuclei section. The complete article was commented on, revised, and approved by all authors.

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