Brain Atrophy Assessment in Multiple Sclerosis: Importance and Limitations

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KEYWORDS

• Brain atrophy • Multiple sclerosis • Tissue damage

The recent development of computational methods that, using conventional magnetic resonance (MR) images, are able to provide sensitive and reproducible measures of brain volumes has allowed an indirect quantification of cerebral tissue loss in many neurologic disorders. These methods can be easily implemented at any MR center and have been extensively used in the study of multiple sclerosis (MS), increasing the interest in cerebral tissue loss (brain atrophy) as a marker to accurately assess and monitor the pathologic evolution of the disease.[1–4] Brain volume loss has been recognized as an important feature of MS from the earliest disease stages and, in this complex disease, is the expression of a generalized process involving various tissue components of the brain.

This article reviews the most recent literature on the use of brain atrophy as a measure of disease progression in MS. Particular attention is paid to the methods used for these assessments, the clinical relevance of global and regional volume loss, and the potential limitations of these measurements.

MEASURING BRAIN VOLUMES

There are many valid approaches to obtaining MR imaging–based measures of brain volume changes. On the basis of the amount of operator intervention, they can be grouped into manual, semi-manual, and fully automated. Clearly, when compared with manual ones, automated analysis methods provide better reproducibility and reduce reliance on time-consuming user intervention. More generally, methods for measuring brain volumes can be broadly divided into two categories depending on whether brain volumes are measured cross-sectionally or longitudinally (**Table 1**).

Cross-Sectional Methods

These methods need a single image as input and measure the current atrophy state. They are generally based on segmentation of the brain tissues.

The first of these approaches to assess global brain atrophy is based on the measurement of the brain parenchymal fraction (BPF).[5] The brain volume is calculated by measuring the difference in volumes inside a mesh over the exterior surface of the brain and inside the ventricles. A partial volume correction is employed to limit the impact of cerebrospinal fluid (CSF) within the cerebral sulci. Differences in the field of interest and segmentation partially cancel out because only one segmentation is performed to obtain the ratio of volume of parenchymal brain tissue to the total volume within the outer surface of the brain. This method is highly

Table 1
Methods used for measuring brain atrophy

Type of Method	Features
Cross-sectional	
BPF[5]	Calculation of the ratio of brain parenchyma volume to the total volume within the outer surface of the brain
BICCR[6]	Brain tissue volume measured with respect to the volume of the inner table of the skull
Fuzzy connectedness algorithm[7]	Each brain compartment considered a fuzzy connected set
Alfano's method[8]	Brain volumes obtained automatically with a multispectral relaxometry approach
TDS[9]	Brain volumes segmented by using a digital brain atlas
SABRE[10]	Individualized Talairach brain maps used for different brain regions in each hemisphere
Free Surfer[11,12]	Calculation of cortical thickness after inflation of the folded cortical surface
SIENAX[14]	Global and regional brain volume measurements normalized for subject head size
VBM[16,18,19]	Assessment of voxelwise brain tissue "concentrations"
Longitudinal	
BBSI[20]	Volume changes measured by subtracting baseline and follow-up scans
SIENA and SIENAr[21,23]	Volume changes assessed by estimating the local shift in brain edges across the brain and its voxelwise extension for regional assessments

Abbreviations: BBSI, brain boundary shift integral; BICCR, brain to intracranial capacity ratio; BPF, brain parenchymal fraction; SABRE, semiautomatic brain region extraction; SIENAX, structural image evaluation, using normalization, of atrophy; TDS, template-driven segmentation; VBM, voxel-based morphometry.

accurate, and the results are highly reproducible across different images from the same brain acquired over a short period of time (1 week), with a coefficient of variation less than 0.2%.[5]

A similar method has been proposed by Collins and colleagues.[6] With the brain to intracranial capacity ratio (BICCR), brain tissue is segmented as a primary step. The volume of brain tissue (or of any compartment) is measured with respect to the volume of the inner table of the skull.

Another method uses the fuzzy connectedness algorithm[7] on dual-echo, fast spin-echo MR images for segmenting and estimating the volume of the white matter (WM), grey matter (GM), and CSF, each one detected as a fuzzy connected set.

Additional methods for measuring brain volumes in different brain compartments are the one described by Alfano and colleagues[8] and the template-driven segmentation method (TDS).[9] In the first method, WM, GM, and CSF volumes are obtained with an unsupervised, automated segmentation of the brain using a multispectral relaxometric MR approach. In TDS, the initial signal intensity–based statistical tissue classification is subsequently refined using a digital brain atlas as an anatomic template. This template, which is subdivided into over 120 anatomic labels, is matched to a given subject's image using a combination of automated linear and nonlinear registration algorithms. Similarly, a more recent technique[10] (SABRE) provides a semiautomatic brain region extraction and uses individualized Talairach brain maps for each subject to delineate and quantify different brain regions in each hemisphere. In this context, certainly interesting is an image analysis technique (Free Surfer) that segments out the cortex from the brain, avoiding the confound coming from gyral folding by inflating the folded cortical surface.[11,12] This approach has allowed highly accurate measurements not only of overall cortical thickness but also of local cortical thickness in different regions.[13]

The cross-sectional version of the structural image evaluation using the normalization of atrophy (SIENA) method (SIENAX[14] (part of the FMRIB Software Library [FSL]; www.fmrib.ox.ac.uk) is an increasingly used method that estimates global

and regional brain tissue volumes normalized for subject head size. It starts by extracting brain and skull images from the single whole-head input data.[15] The brain image is then affine-registered to a canonical image (MNI152 image) in a standardized space (using the skull image to provide the scaling cue), a procedure that provides a spatial normalization (scaling) factor for each subject. Next, tissue-type segmentation with partial volume estimation is performed[15] to calculate the total volume of brain tissue, including separate estimates of volumes of GM, WM and ventricular CSF. As is true for other methods, this calculation can be extended to include selective measures of multiple brain regions by using standard-space masks. This cross-sectional version of the SIENA longitudinal method gives a test-retest reproducibility of brain volume measures of about 0.5%.

Specific regional measures of volume changes can also be obtained more indirectly by using the voxel-based morphometry (VBM) approach.[16] This method is widely used for characterizing regional volume and tissue "concentration" differences in conventional MR images. Mainly, it is used to make voxelwise comparisons of the local concentration of GM regions between two groups of subjects. The procedure is relatively straightforward and involves a spatial normalization of high-resolution images from all subjects in a study into the same stereotactic space. This normalization is followed by a segmentation of the GM from the spatially normalized images and then a smoothing of the GM segments. Voxelwise parametric statistical tests which compare the smoothed GM images from the two groups are performed. Corrections for multiple comparisons are most frequently made using the theory of Gaussian random fields. VBM is most commonly performed using the statistical parametric mapping (SPM) software package. A VBM-style

analysis is also straightforward to carry out with FSL tools.[16,17] In this situation, a voxelwise general linear model is applied using permutation-based nonparametric testing.[18] The comparison of the classical VBM approach and the FSL-VBM approach on the same data set shows similar changes in cortical GM areas (**Fig. 1**).[19]

Longitudinal Methods

Longitudinal methods need two sets of MR images acquired at different times as input. They measure the atrophy rate. Each of the previously described cross-sectional methods can give a measure of the atrophy rate by assessing the differences of measurement results at different time points; however, a more precise measurement is obtained when serial scans from an individual are accurately registered and the cerebral volume changes are derived directly.[2] Explicit examples of registration-based methods that can be used for this purpose are brain boundary shift integral (BBSI)[20] and SIENA.[21]

In BBSI,[20] volume changes over time are measured by subtracting baseline and follow-up scans. The method defines a region that lies near the borders of the baseline and registered follow-up brains. The BBSI technique is based on integrating the differences in intensities over this region. Scan intensities are normalized by dividing each scan by its respective mean, calculated over the interior region. The intensities are bounded by a clipping function based on a predefined upper and lower intensity for each scan. Dividing the integrated differences by the span of the clipping function provides a measure of the global brain volume loss.

Another increasingly popular approach to measuring total brain volume change directly is the SIENA method,[21] also part of FSL. This method assesses brain volume changes by estimating
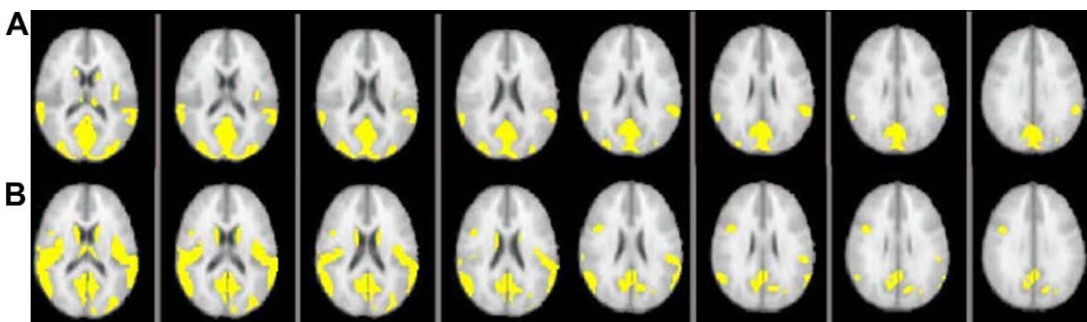

Fig. 1. VBM analysis performed by using FSL (*A*) and SPM05 (*B*). Data are from a group of patients with relapsing-remitting MS compared with a group of normal controls. The color overlay is created on top of the MNI152 standard brain. Brain voxels with significant GM loss in MS patients are shown in yellow (*P* < .05, corrected). Note how the two methods show similar local GM atrophy.

directly the local shifts in brain edges across the entire brain. SIENA starts by extracting brain and skull images from the two time point whole-head input data.[15] The two brain images are then aligned to each other[15] (using the skull images to constrain the registration scaling). Both brain images are re-sampled into the space halfway between the two, avoiding bias in atrophy estimation due to asymmetric interpolation blurring. Next, tissue-type segmentation is performed[15] to find brain/nonbrain edge points, and then perpendicular edge displacement (between the two time points) is estimated at these edge points. The displacement is estimated by aligning the peaks of the spatial derivatives of the intensity profiles of the two images to subvoxel accuracy. The mean edge displacement is converted into a global estimate of percentage brain volume change (PBVC) between the two time points. SIENA has been extended to allow the voxelwise statistical analysis of atrophy across subjects.[22,23] This approach takes a SIENA-derived edge "flow image" (edge displacement between the time points) for each subject and warps this to align with a standard space edge image. The resulting images from all subjects are fed into voxelwise statistical analysis to find statistically significant localized difference in atrophy between the two groups of subjects.

In a recent study,[24] the BBSI and SIENA methods were compared using the same data set. The two methods were in excellent agreement with each other. There was close correlation between the two measures (r = 0.87, $P < .0001$, median absolute difference = 0.25%), and even the absolute scaling of the two measures was close. With both methods, the measurements had an error of less than 0.2%, in agreement with previously published estimations of the overall error rate. Furthermore, another recent study[25] has shown that registration-based techniques appear to be more precise and sensitive than segmentation-based methods in measuring brain atrophy, with BBSI and SIENA providing comparable results. Despite this finding, measures made with different techniques usually cannot be compared directly (although their measurements of change may be correlated), and sensitivities to change may be different.

GLOBAL BRAIN ATROPHY

Since the earliest MR imaging studies in MS, marked atrophy of the brain has been recognized as an important feature of the late disease stages. Today, the availability of high-quality MR images and cutting-edge signal post-processing methods has allowed us to measure even small changes in brain volume occurring over relatively short periods of time (months). Serial MR imaging studies have demonstrated that brain volume loss occurs at a rate of around 0.5% to 1% per year in MS patients[4,26] compared with a rate of about 0.1% to 0.3% per year in healthy subjects.[27,28]

Brain atrophy appears to proceed relentlessly throughout the course of MS even at the earliest stages.[2–4] In subjects at presentation with clinically isolated syndrome (CIS) suggestive of MS, it has been demonstrated that significantly greater ventricular enlargement occurs in persons in whom MS develops when compared with persons who remain stable.[29,30] Several cross-sectional studies have shown that brain volume also is significantly reduced in relapsing-remitting (RR) MS subjects when compared with age-matched controls.[5,20,31,32] Similarly, significant and diffuse brain atrophy is reported in patients with the secondary progressive (SP) and primary progressive (PP) forms of the disease.[20,33–39] In a mixed population of MS patients (benign MS, RRMS, SPMS, and PPMS), a significant brain volume loss in each patient group was found, as well as a greater ventricle enlargement in patients than in normal controls[20]; however, in general, the rate of brain atrophy progression seems to be substantially independent of the MS subtype.[40]

BRAIN ATROPHY IN GREY AND WHITE MATTER

Several MR[41–44] and histologic[45–49] studies have suggested that, even though MS is a demyelinating disorder, cortical GM pathology is also present. Many of the previously mentioned computational methods for measurement of brain volumes have been used successfully to selectively measure GM volumes in MS patients.

Several studies have demonstrated that GM volume loss is consistently present in MS patients from the earliest disease stages. For example, a decrease of GM fractional volume has been detected in CIS patients in whom clinically definite MS developed 3 years later,[50] and cortical GM loss has been found in early RRMS patients.[31,51–53] Other studies have tried to gain insights into the temporal evolution of GM atrophy in the early course of the disease. In particular, it has been demonstrated that GM volume loss may evolve over time periods as short as 1.5 to 2 years[54,55] or less than 1 year[56] in RRMS patients.

One of the most intriguing observations of MR studies assessing brain atrophy in MS has been that the pathology underlying cerebral volume loss seems to have a different impact in different GM regions. Overall, the studies have agreed in finding the frontal, temporal, and parietal lobes as the most involved (atrophic) cortical GM regions

in MS patients.[2,57–62] Although global measures have generically found a diffuse reduction of brain volumes in MS patients without major differences between clinical phenotypes and disease stages, selective regional measures have demonstrated differences in brain regional involvement in the progressive and relapsing forms of MS,[63] or a progressive involvement of the cortical regions in patients with long disease duration or increasing disability.[13,61,62,64] Atrophy seems to start in frontotemporal areas, specifically involving the superior temporal gyrus and superior and middle frontal gyri, and to extend to other clinically relevant areas (eg, the motor cortex) in more advanced disease phases.[13]

Atrophy of the deep GM also occurs in MS. Normalized bicaudate volume has been found to be lower in MS patients than in normal controls,[65] with no correlation with whole-brain atrophy or lesion volume. Thalamic volume reduction up to 25% in RRMS patients and up to 35% in SPMS patients has been observed in several recent cross-sectional and longitudinal studies.[58,66–69] A longitudinal study of early PPMS patients[59] found bilateral atrophy of the thalamus at baseline, which also extended to the putamen, caudate, and other cortical and infratentorial areas after 1 year. The thalamus seemed to be the only GM compartment involved in pediatric MS.[70] All of these studies, demonstrating that there are specific deep GM regions (eg, thalamus and caudate nuclei) that can be involved earlier and more strongly than other regions in the pathologic process, provide additional evidence of the high relevance of GM pathology from the earliest stages of MS. Two of these studies bring the most relevant support to this hypothesis. By combining histopathologic methods and quantitative MR measures, they have elegantly shown that both RRMS[66] and SPMS[69] patients have comparable ex vivo loss of thalamic neurons and in vivo thalamic volume decrease.

Interestingly, when compared with GM volumes, decreases of WM volumes in MS are much less frequently reported. No WM atrophy has been found in CIS patients in whom clinically definite MS developed 3 years later[50] and in early RRMS over an 18-month[55] or 2-year[54] follow-up. Nevertheless, decreases of WM volume have been reported in other studies of relapsing[31,52,71] and progressive[59,71] MS patients. Moreover, in a 9-year longitudinal study of a group of MS patients with a wide range of disease duration, the midsagittal corpus callosum size decreased independently of the disease course at the rate of about 1.8% per year.[72] This decrease adds to the significant atrophy of central brain regions (ie, lateral ventricles) that also largely progresses over time in all MS stages and subtypes.[2,29,30,62,73,74]

CLINICAL RELEVANCE OF BRAIN ATROPHY

In the last decade or so, many studies have investigated whether robust MR correlates of clinical change do exist in MS. The results have often been disappointing, probably explained by the fact that attention has been mostly focused on focal pathologic damage (ie, lesions) in WM. Focal WM lesions do not lead to disability progression in a simple way, and focal demyelination alone cannot explain entirely the pathologic process leading to clinical disability.[75–78] Brain atrophy measures, by reflecting tissue loss (mostly myelin and axonal damage or loss) in both abnormal and normal appearing brain, may correlate with disability better than measures of focal demyelination or inflammation.

Both global brain[71,79–81] and selective GM[51,61,63,82] measures of volume loss have been closely associated with disability. Greater brain atrophy is generally found in CIS subjects in whom MS develops when compared with those in whom it does not[29,30] and, in established MS, brain atrophy is greater in patients who show sustained progression of disability than in those who are clinically stable.[32,38,83] In longitudinal studies of relapsing and progressive MS patients, brain volume at early stages seems to be a good predictor of disability status at follow-up, suggesting that atrophy is a relevant marker of disease progression and may even precede the development of measurable disability.[36,84]

Interestingly, specific aspects of clinical dysfunction have been linked to regional brain atrophy. For example, longitudinal studies have shown a persisting association between segmental callosal atrophy and disability status, even at early disease stages.[72,85] Also, the decline in ambulatory function (ie, Timed Walk Test) has been related to atrophy of periventricular and brainstem regions,[62] whereas a focal thinning of the precentral gyrus and primary visual cortex has been related to the motor and visual scores of the Expanded Disability Status Scale, respectively.[60]

Several MR studies have linked cognitive impairment to brain atrophy in MS. This impairment is an increasingly recognized clinical aspect of the disease observed in about 40% to 60% of patients, even including a proportion of those with early disease stage.[86,87] Although increasing cognitive impairment may sometimes proceed in parallel with increasing T2 MR imaging lesion load, the magnitude of the correlation between neuropsychologic scores and T2 lesion volume has been found to be weak or moderate.[88,89] By contrast, cognitive impairment has been found to be associated with measures of cerebral atrophy, and the

importance of decreasing brain volumes (rather than increasing lesion load) to MS-related cognitive impairment has been suggested in several studies.[68,90–92] In particular, cortical atrophy has been found to be significantly higher in cognitively impaired than in cognitively preserved RRMS patients[91] and, in both RRMS and SPMS patients, has been the best predictor of verbal memory impairment and neurobehavioral symptoms.[93] In other studies, the atrophy of the frontal cortex has been found to be related to reduced cognitive functions,[94] and right and left frontal atrophy has been associated with auditory/verbal memory and episodic and working memory deficits, respectively.[95]

The results of the previously mentioned studies strongly suggest the notion that brain atrophy (in particular, selective GM atrophy) is a good marker of unfavorable disease outcome in MS; however, its correlation with clinical disability is far from perfect. In a complex disease such as MS, several other factors (eg, spinal cord damage, cortical adaptation to injury, genetic predisposition to injury repair) can all contribute to weaken this relationship and should be considered when interpreting the clinical relevance of this and other MR imaging measures.[96,97]

USE OF BRAIN ATROPHY AS AN ENDPOINT IN CLINICAL TRIALS

After MR-derived measures of brain volume changes were established as a sensitive, reproducible, and accurate index of brain tissue damage, they were used in several clinical trials to assess treatment efficacy.[5,33,83,98–102] Nevertheless, only rarely has a treatment effect on brain atrophy been demonstrated.

Common characteristics of the studies using brain volume change as an endpoint are the relatively short follow-up period (mostly 2 to 3 years) and the increase of the atrophy rate occurring during the first period of treatment with anti-inflammatory agents. The latter finding is an important point that needs to be discussed.

Several lines of evidence suggest that the large brain atrophy rates found at the beginning of an anti-inflammatory therapy may be more a reflection of the resolution of inflammatory edema than a consequence of the irreversible loss of axons and myelin. In agreement with this, in many cases, the atrophy rate reduces after the first treatment period (ie, after the inflammatory edema is resolved), and, often, this lower rate is maintained over the remaining treatment period.[99,103] In patients who had severe and rapidly evolving MS who underwent autologous hematopoietic stem

cell transplantation,[104] this procedure was associated (in addition to an immediate and longstanding suppression of focal demyelination and inflammatory activity) with a large and progressive atrophy (about 1.4% per year) over the first 2 years after treatment and to a significant and sustained reduction of volume loss in the subsequent 3 years (about 0.4% per year).[105] Indeed, in CIS patients, in whom a minor resolution of inflammatory edema is expected, treatment with interferon beta-1a was shown to be effective in slowing progressive brain tissue loss.[101]

Against this background, it is evident that measures of brain volume changes are sensitive and accurate enough to provide a robust index of efficacy in clinical trials; however, it is also clear that in a complex disease such as MS in which inflammation, demyelination, and neurodegeneration contribute to chronic disease progression, brain atrophy can be considered a good index of clinical outcome only when the study design entails relatively long follow-up periods.

UNDERSTANDING AND INTERPRETING BRAIN ATROPHY

The pathologic correlates of brain atrophy are arguably more complex in MS than in many other neurodegenerative disorders. In the brain of a patient who has MS, demyelination and inflammation add to neurodegeneration, and, as a consequence, loss of brain components such as myelin and glial cells contributes with that of neurons and axons to the total loss of tissue volume. Nevertheless, the mechanisms leading to atrophy in MS are still inadequately understood.

Axonal damage may lead to retrograde neurodegeneration and cause brain atrophy.[106,107] Because the corticospinal tracts and frontal periventricular WM are preferential sites for MS lesions,[89] WM pathology in MS may lead to a selective retrograde injury to frontal, temporal, and motor areas of the cortex. This injury could explain, for example, the characteristic pattern of cortical atrophy found in the studies mentioned previously.[2,57–62]

Interestingly, although a significant proportion of neuroaxonal damage is dependent on focal WM changes,[108] other studies[13,51,107] have shown that widespread neocortical loss and thinning can be found even in patients with minimal cerebral lesion load. This observation suggests that retrograde changes from focal WM lesions cannot explain the full range of findings. Pathologic studies have shown that neuroaxonal damage and loss may occur via mechanisms that are independent of those causing demyelination and are likely

related to the presence of an abnormal glia-axonal interaction even with low or absent inflammation.[49,109] In agreement with this, apoptotic neuronal death unrelated to axonal transection has been found in the cortex of MS patients.[49] It is possible that factors that are not directly connected with lesion formation may also have a significant role in determining brain atrophy in MS.

Although the interpretation of brain atrophy measures can reasonably be framed in terms of a mutual contribution of demyelination, inflammation, and neurodegeneration, brain tissue also includes a significant extracellular compartment. MR studies have shown indirectly that, in the MS brain, water content is increased in inflammatory lesions[110] and normal-appearing tissue.[111] Direct histopathologic measures confirm the expansion of the extracellular space over the course of the disease.[112] In this context, dramatic changes in water content that can affect interpretation of brain volume measurements might also include dialysis (with volume increases up to 3%)[113] and acute dehydration or rehydration.[114] Similarly, as discussed previously, the short-term decreases in brain volume reported (eg, in anti-inflammatory treatments[83,99,103,115,116]) should be accounted for a decrease in water content (ie, "pseudoatrophy") rather than for a real "atrophy" arising from myelin loss and neuroaxonal degeneration.

Generic factors such as life habits, genetic load, and concomitant paraphysiologic conditions may affect brain volume measurements and need to be taken into account when interpreting brain atrophy in MS patients. For example, alcohol abuse is associated with changes in water content and structural brain damage leading to brain volume changes that can partially recover after therapeutic sobriety.[22] Also, there is some evidence that the ApoE genotype, by influencing the ability to respond to injury, may have a significant role in tissue damage leading to atrophy.[117,118] Similarly, although it is known that brain atrophy progresses with age, this seems to be more pronounced when aging is complicated by the presence of smoking, diabetes, and other cardiovascular risk factors.[119]

PITFALLS AND LIMITATIONS OF MR IMAGING–DERIVED MEASURES OF BRAIN ATROPHY

Despite the accuracy of MR imaging–derived measures of brain atrophy, various sources of error can affect the estimation of brain volume changes. Clearly, the quality of image acquisition (ie, image resolution, signal-to-noise ratio) has a crucial role. For example, poor contrast in images may cause suboptimal tissue classification when intensity-based tissue segmentation is used. Also, artifacts due to head motion and inhomogeneities in radio frequency can cause intensity variations in the image and problems in threshold-based segmentation, particularly in methods that rely on high-resolution data to perform accurate regional analysis.[11,12] Additional problems may arise in the presence of partial head acquisition. In this situation, the differences in the amount of brain image acquired at two time points might be erroneously confounded with brain volume changes. This issue can be overcome in registration-based methods by using standard-space–based limits for the bottom and top slices of the brain.[15]

In interpreting the brain atrophy occurring in MS, the decrease in cortical GM volumes might be overestimated owing to the fact that cerebral cortical lesions, which appear to be common in MS,[49,120] are virtually invisible with conventional MR sequences. Such lesions, which have been detected recently by using specific MR imaging sequences,[44,121,122] may affect segmentation between the cortex and the CSF, such that the former may be erroneously decreased in volume.

Although image segmentation is usually aided by multiple-contrast acquisitions, most segmentation methods produce the best results on T1-weighted acquisitions.[123] In this context, less reliable results are usually obtained when post-gadolinium, T1-weighted images are used to estimate brain volume changes. This characteristic is particularly important for data derived from multicenter trials, because, in these studies, post-gadolinium images (used to assess brain MR imaging lesion activity) are often the only T1-weighted data available. Practically, the presence of the contrast agent in the central nervous system causes both poor contrast MR images and suboptimal brain extraction. For example, in a data set on 55 RRMS patients who underwent identical pre- and post-gadolinium T1-weighted MR imaging at baseline and 1 year later, the correlation between the two sets of T1-weighted images was limited (Pearson correlation = 0.71; M. Battaglini and N. De Stefano, personal observation, 2008). The measurements of global brain volume changes could be improved by using a more accurate approach for brain extraction[124] (the Pearson correlation on the previous set of data was 0.86; **Fig. 2**); however, with post-gadolinium, T1-weighted images, an accurate classification of GM and WM is not possible.

Although most of the methods for assessing brain volume changes tend to be largely automated, they hide several complexities that should be appreciated to understand the possible sources of measurement errors. For example, the removal of non-brain tissue may be imperfect
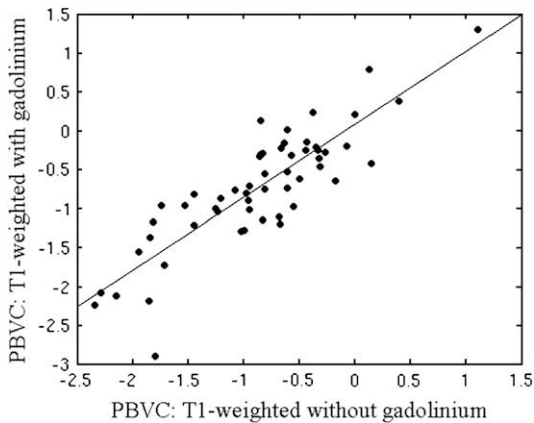
Fig. 2. The correlation between percentage brain volume changes (PBVC) obtained by using T1-weighted MR images with and without injection of gadolinium (Pearson's correlation = 0.86, P < .001). Data are from a group of 55 patients with RRMS who underwent the acquisition of both T1-weighted sequences at baseline and after 1 year.

(eg, incorrect inclusion of eyes, periorbital fat, and other non-brain structures). In this case, manual editing[125] or a more accurate brain extraction procedure[124] may decrease volume overestimation and reduce variability. Also, all registration-based methods suffer from the well-known issue of ambiguity of interpretation (eg, apparent changes due to tissue loss or systematic alignment changes), which easily can occur with poor imaging resolution or large anatomic variation across subjects.[126] When serial changes in brain volume are measured using technically demanding approaches, such as voxel-based assessments or model-based parcellation techniques, high-quality MR image acquisition is mandatory. In this context, measures of brain atrophy should take advantage of the continuous development of image acquisition (eg, high MR fields, new sequences) and post-processing procedures (eg, intensity normalization, segmentation, and coregistration) that can significantly improve the final output.

SUMMARY

Despite the important issues that still need to be solved, the meaning of brain atrophy in MS has a great potential and represents one of the most interesting and promising in vivo measures of unfavorable disease outcome. Future studies are warranted to answer important questions such as when and at what rate atrophy starts to develop in MS, how exactly atrophy relates to the complex MS pathology, how it relates to prognosis, whether atrophy distribution is clinically important, and

whether an "atrophy threshold" exists. Long follow-up studies and combined histologic and MR imaging studies can provide an answer to at least some of these questions.

REFERENCES

1. Zivadinov R. Can imaging techniques measure neuroprotection and remyelination in multiple sclerosis? Neurology 2007;68:S72–82 [discussion: S91–76].
2. De Stefano N, Battaglini M, Smith SM. Measuring brain atrophy in multiple sclerosis. J Neuroimaging 2007;17(Suppl 1):10S–5S.
3. Simon JH. Brain atrophy in multiple sclerosis: what we know and would like to know. Mult Scler 2006; 12:679–87.
4. Bermel RA, Bakshi R. The measurement and clinical relevance of brain atrophy in multiple sclerosis. Lancet Neurol 2006;5:158–70.
5. Rudick RA, Fisher E, Lee JC, et al. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. Multiple Sclerosis Collaborative Research Group. Neurology 1999; 53:1698–704.
6. Collins DL, Montagnat J, Zijdenbos AP, et al. Automated estimation of brain volume in multiple sclerosis with BICCR. Lect Notes Comput Sci 2001;2082: 141–7.
7. Udupa JK, Wei L, Samarasekera S, et al. Multiple sclerosis lesion quantification using fuzzy-connectedness principles. IEEE Trans Med Imaging 1997; 16:598–609.
8. Alfano B, Brunetti A, Covelli EM, et al. Unsupervised, automated segmentation of the normal brain using a multispectral relaxometric magnetic resonance approach. Magn Reson Med 1997;37: 84–93.
9. Guttmann CR, Benson R, Warfield SK, et al. White matter abnormalities in mobility-impaired older persons. Neurology 2000;54:1277–83.
10. Dade LA, Gao FQ, Kovacevic N, et al. Semiautomatic brain region extraction: a method of parcellating brain regions from structural magnetic resonance images. Neuroimage 2004;22: 1492–502.
11. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II. Inflation, flattening, and a surface-based coordinate system. Neuroimage 1999; 9:195–207.
12. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 1999;9:179–94.
13. Sailer M, Fischl B, Salat D, et al. Focal thinning of the cerebral cortex in multiple sclerosis. Brain 2003;126:1734–44.

14. Smith SM, Zhang Y, Jenkinson M, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. Neuroimage 2002;17:479–89.

15. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23(Suppl 1):S208–219.

16. Ashburner J, Friston KJ. Voxel-based morphometry–the methods. Neuroimage 2000;11:805–21.

17. Good CD, Johnsrude IS, Ashburner J, et al. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21–36.

18. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. Hum Brain Mapp 2002;15:1–25.

19. Battaglini M, Smith SM, Douad G, et al. Voxel-based analysis of global and neocortical progression of brain atrophy in RRMS [abstract]. ISMRM 2007.

20. Fox NC, Jenkins R, Leary SM, et al. Progressive cerebral atrophy in MS: a serial study using registered, volumetric MRI. Neurology 2000;54:807–12.

21. Smith SM, De Stefano N, Jenkinson M, et al. Normalized accurate measurement of longitudinal brain change. J Comput Assist Tomogr 2001;25:466–75.

22. Bartsch AJ, Homola G, Biller A, et al. Manifestations of early brain recovery associated with abstinence from alcoholism. Brain 2007;130:36–47.

23. De Stefano N, Jenkinson M, Guidi L, et al. Voxel-level cross-subject statistical analysis of brain atrophy in early relapsing remitting MS patients. Int Soc Magn Reson Med [book of abstracts]. 2003;2:2625.

24. Smith SM, Rao A, De Stefano N, et al. Longitudinal and cross-sectional analysis of atrophy in Alzheimer's disease: cross-validation of BSI, SIENA and SIENAX. Neuroimage 2007;36:1200–6.

25. Anderson VM, Fernando KT, Davies GR, et al. Cerebral atrophy measurement in clinically isolated syndromes and relapsing remitting multiple sclerosis: a comparison of registration-based methods. J Neuroimaging 2007;17:61–8.

26. Anderson VM, Fox NC, Miller DH. Magnetic resonance imaging measures of brain atrophy in multiple sclerosis. J Magn Reson Imaging 2006;23:605–18.

27. Coffey CE, Wilkinson WE, Parashos IA, et al. Quantitative cerebral anatomy of the aging human brain: a cross-sectional study using magnetic resonance imaging. Neurology 1992;42:527–36.

28. Pfefferbaum A, Mathalon DH, Sullivan EV, et al. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. Arch Neurol 1994;51:874–87.

29. Brex PA, Jenkins R, Fox NC, et al. Detection of ventricular enlargement in patients at the earliest clinical stage of MS. Neurology 2000;54:1689–91.

30. Dalton CM, Brex PA, Jenkins R, et al. Progressive ventricular enlargement in patients with clinically isolated syndromes is associated with the early development of multiple sclerosis. J Neurol Neurosurg Psychiatry 2002;73:141–7.

31. Chard DT, Griffin CM, Parker GJ, et al. Brain atrophy in clinically early relapsing-remitting multiple sclerosis. Brain 2002;125:327–37.

32. Rudick RA, Fisher E, Lee JC, et al. Brain atrophy in relapsing multiple sclerosis: relationship to relapses, EDSS, and treatment with interferon beta-1a. Mult Scler 2000;6:365–72.

33. Turner B, Lin X, Calmon G, et al. Cerebral atrophy and disability in relapsing-remitting and secondary progressive multiple sclerosis over four years. Mult Scler 2003;9:21–7.

34. Stevenson VL, Miller DH, Leary SM, et al. One year follow up study of primary and transitional progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 2000;68:713–8.

35. Rovaris M, Judica E, Gallo A, et al. Grey matter damage predicts the evolution of primary progressive multiple sclerosis at 5 years. Brain 2006;129:2628–34.

36. Sastre-Garriga J, Ingle GT, Chard DT, et al. Grey and white matter volume changes in early primary progressive multiple sclerosis: a longitudinal study. Brain 2005;128:1454–60.

37. Leary SM, Miller DH, Stevenson VL, et al. Interferon beta-1a in primary progressive MS: an exploratory, randomized, controlled trial. Neurology 2003;60:44–51.

38. Ingle GT, Stevenson VL, Miller DH, et al. Two-year follow-up study of primary and transitional progressive multiple sclerosis. Mult Scler 2002;8:108–14.

39. Filippi M, Rovaris M, Iannucci G, et al. Whole brain volume changes in patients with progressive MS treated with cladribine. Neurology 2000;55:1714–8.

40. Kalkers NF, Ameziane N, Bot JC, et al. Longitudinal brain volume measurement in multiple sclerosis: rate of brain atrophy is independent of the disease subtype. Arch Neurol 2002;59:1572–6.

41. Matthews PM, De Stefano N, Narayanan S, et al. Putting magnetic resonance spectroscopy studies in context: axonal damage and disability in multiple sclerosis. Semin Neurol 1998;18:327–36.

42. Filippi M, Inglese M. Overview of diffusion-weighted magnetic resonance studies in multiple sclerosis. J Neurol Sci 2001;186(Suppl 1):S37–43.

43. Chard DT, Griffin CM, McLean MA, et al. Brain metabolite changes in cortical grey and normal-appearing white matter in clinically early relapsing-remitting multiple sclerosis. Brain 2002;125:2342–52.

44. Calabrese M, De Stefano N, Atzori M, et al. Detection of cortical inflammatory lesions by double inversion recovery magnetic resonance imaging in patients with multiple sclerosis. Arch Neurol 2007; 64:1416–22.

45. Bjartmar C, Trapp BD. Axonal and neuronal degeneration in multiple sclerosis: mechanisms and functional consequences. Curr Opin Neurol 2001;14: 271–8.

46. Lucchinetti CF, Bruck W, Lassmann H. Evidence for pathogenic heterogeneity in multiple sclerosis. Ann Neurol 2004;56:308.

47. Bruck W. Inflammatory demyelination is not central to the pathogenesis of multiple sclerosis. J Neurol 2005;252(Suppl 5):v10–15.

48. Wegner C, Esiri MM, Chance SA, et al. Neocortical neuronal, synaptic, and glial loss in multiple sclerosis. Neurology 2006;67:960–7.

49. Peterson JW, Bo L, Mork S, et al. Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. Ann Neurol 2001;50:389–400.

50. Dalton CM, Chard DT, Davies GR, et al. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. Brain 2004;127: 1101–7.

51. De Stefano N, Matthews PM, Filippi M, et al. Evidence of early cortical atrophy in MS: relevance to white matter changes and disability. Neurology 2003;60:1157–62.

52. Ge Y, Grossman RI, Udupa JK, et al. Brain atrophy in relapsing-remitting multiple sclerosis: fractional volumetric analysis of gray matter and white matter. Radiology 2001;220:606–10.

53. Quarantelli M, Ciarmiello A, Morra VB, et al. Brain tissue volume changes in relapsing-remitting multiple sclerosis: correlation with lesion load. Neuroimage 2003;18:360–6.

54. Tiberio M, Chard DT, Altmann DR, et al. Gray and white matter volume changes in early RRMS: a 2-year longitudinal study. Neurology 2005;64: 1001–7.

55. Chard DT, Griffin CM, Rashid W, et al. Progressive grey matter atrophy in clinically early relapsing-remitting multiple sclerosis. Mult Scler 2004;10: 387–91.

56. Valsasina P, Benedetti B, Rovaris M, et al. Evidence for progressive gray matter loss in patients with relapsing-remitting MS. Neurology 2005;65:1126–8.

57. Prinster A, Quarantelli M, Orefice G, et al. Grey matter loss in relapsing-remitting multiple sclerosis: a voxel-based morphometry study. Neuroimage 2006;29:859–67.

58. Carone DA, Benedict RH, Dwyer MG, et al. Semi-automatic brain region extraction (SABRE) reveals superior cortical and deep gray matter atrophy in MS. Neuroimage 2006;29:505–14.

59. Sepulcre J, Sastre-Garriga J, Cercignani M, et al. Regional gray matter atrophy in early primary progressive multiple sclerosis: a voxel-based morphometry study. Arch Neurol 2006;63:1175–80.

60. Calabrese M, Atzori M, Bernardi V, et al. Cortical atrophy is relevant in multiple sclerosis at clinical onset. J Neurol 2007;254:1212–20.

61. Charil A, Dagher A, Lerch JP, et al. Focal cortical atrophy in multiple sclerosis: relation to lesion load and disability. Neuroimage 2007;34:509–17.

62. Jasperse B, Vrenken H, Sanz-Arigita E, et al. Regional brain atrophy development is related to specific aspects of clinical dysfunction in multiple sclerosis. Neuroimage 2007;38:529–37.

63. Pagani E, Rocca MA, Gallo A, et al. Regional brain atrophy evolves differently in patients with multiple sclerosis according to clinical phenotype. AJNR Am J Neuroradiol 2005;26:341–6.

64. Chen JT, Narayanan S, Collins DL, et al. Relating neocortical pathology to disability progression in multiple sclerosis using MRI. Neuroimage 2004; 23:1168–75.

65. Bermel RA, Innus MD, Tjoa CW, et al. Selective caudate atrophy in multiple sclerosis: a 3D MRI parcellation study. Neuroreport 2003;14:335–9.

66. Wylezinska M, Cifelli A, Jezzard P, et al. Thalamic neurodegeneration in relapsing-remitting multiple sclerosis. Neurology 2003;60:1949–54.

67. Audoin B, Davies GR, Finisku L, et al. Localization of grey matter atrophy in early RRMS: a longitudinal study. J Neurol 2006;253:1495–501.

68. Houtchens MK, Benedict RH, Killiany R, et al. Thalamic atrophy and cognition in multiple sclerosis. Neurology 2007;69:1213–23.

69. Cifelli A, Arridge M, Jezzard P, et al. Thalamic neurodegeneration in multiple sclerosis. Ann Neurol 2002;52:650–3.

70. Mesaros S, Rocca MA, Absinta M, et al. Evidence of thalamic gray matter loss in pediatric multiple sclerosis. Neurology 2008;70:1107–12.

71. Tedeschi G, Lavorgna L, Russo P, et al. Brain atrophy and lesion load in a large population of patients with multiple sclerosis. Neurology 2005; 65:280–5.

72. Martola J, Stawiarz L, Fredrikson S, et al. Progression of non–age-related callosal brain atrophy in multiple sclerosis: a 9-year longitudinal MRI study representing four decades of disease development. J Neurol Neurosurg Psychiatry 2007;78: 375–80.

73. Luks TL, Goodkin DE, Nelson SJ, et al. A longitudinal study of ventricular volume in early relapsing-remitting multiple sclerosis. Mult Scler 2000;6: 332–7.

74. Dalton CM, Miszkiel KA, O'Connor PW, et al. Ventricular enlargement in MS: one-year change at various stages of disease. Neurology 2006;66:693–8.

75. McDonald WI, Miller DH, Thompson AJ. Are magnetic resonance findings predictive of clinical outcome in therapeutic trials in multiple sclerosis? The dilemma of interferon-beta. Ann Neurol 1994; 36:14–8.

76. McDonald WI. Rachelle Fishman-Matthew Moore Lecture. The pathological and clinical dynamics of multiple sclerosis. J Neuropathol Exp Neurol 1994;53:338–43.

77. Trapp BD, Ransohoff R, Rudick R. Axonal pathology in multiple sclerosis: relationship to neurologic disability. Curr Opin Neurol 1999;12:295–302.

78. Trapp BD, Bo L, Mork S, et al. Pathogenesis of tissue injury in MS lesions. J Neuroimmunol 1999;98: 49–56.

79. Sanfilipo MP, Benedict RH, Sharma J, et al. The relationship between whole brain volume and disability in multiple sclerosis: a comparison of normalized gray vs. white matter with misclassification correction. Neuroimage 2005;26:1068–77.

80. Losseff NA, Wang L, Lai HM, et al. Progressive cerebral atrophy in multiple sclerosis: a serial MRI study. Brain 1996;119(Pt 6):2009–19.

81. Ge Y, Grossman RI, Udupa JK, et al. Brain atrophy in relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis: longitudinal quantitative analysis. Radiology 2000;214:665–70.

82. Bakshi R, Benedict RH, Bermel RA, et al. Regional brain atrophy is associated with physical disability in multiple sclerosis: semiquantitative magnetic resonance imaging and relationship to clinical findings. J Neuroimaging 2001;11:129–36.

83. Molyneux PD, Kappos L, Polman C, et al. The effect of interferon beta-1b treatment on MRI measures of cerebral atrophy in secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive multiple sclerosis. Brain 2000;123(Pt 11):2256–63.

84. Fisher E, Rudick RA, Simon JH, et al. Eight-year follow-up study of brain atrophy in patients with MS. Neurology 2002;59:1412–20.

85. Pelletier J, Suchet L, Witjas T, et al. A longitudinal study of callosal atrophy and interhemispheric dysfunction in relapsing-remitting multiple sclerosis. Arch Neurol 2001;58:105–11.

86. Feinstein A, Kartsounis LD, Miller DH, et al. Clinically isolated lesions of the type seen in multiple sclerosis: a cognitive, psychiatric, and MRI follow up study. J Neurol Neurosurg Psychiatry 1992;55:869–76.

87. Amato MP, Ponziani G, Pracucci G, et al. Cognitive impairment in early-onset multiple sclerosis: pattern, predictors, and impact on everyday life in a 4-year follow-up. Arch Neurol 1995;52:168–72.

88. Rovaris M, Filippi M, Falautano M, et al. Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis. Neurology 1998;50:1601–8.

89. Filippi M, Tortorella C, Rovaris M, et al. Changes in the normal appearing brain tissue and cognitive impairment in multiple sclerosis. J Neurol Neurosurg Psychiatry 2000;68:157–61.

90. Zivadinov R, De Masi R, Nasuelli D, et al. MRI techniques and cognitive impairment in the early phase of relapsing-remitting multiple sclerosis. Neuroradiology 2001;43:272–8.

91. Amato MP, Bartolozzi ML, Zipoli V, et al. Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. Neurology 2004;63:89–93.

92. Benedict RH, Zivadinov R. Predicting neuropsychological abnormalities in multiple sclerosis. J Neurol Sci 2006;245:67–72.

93. Sanfilipo MP, Benedict RH, Weinstock-Guttman B, et al. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. Neurology 2006;66:685–92.

94. Locatelli L, Zivadinov R, Grop A, et al. Frontal parenchymal atrophy measures in multiple sclerosis. Mult Scler 2004;10:562–8.

95. Tekok-Kilic A, Benedict RH, Weinstock-Guttman B, et al. Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis. Neuroimage 2007;36:1294–300.

96. Matthews PM, Arnold DL. Magnetic resonance imaging of multiple sclerosis: new insights linking pathology to clinical evolution. Curr Opin Neurol 2001;14:279–87.

97. Mainero C, De Stefano N, Iannucci G, et al. Correlates of MS disability assessed in vivo using aggregates of MR quantities. Neurology 2001;56:1331–4.

98. Frank JA, Richert N, Bash C, et al. Interferon-beta-1b slows progression of atrophy in RRMS: three-year follow-up in NAb− and NAb+ patients. Neurology 2004;62:719–25.

99. Hardmeier M, Wagenpfeil S, Freitag P, et al. Rate of brain atrophy in relapsing MS decreases during treatment with IFNbeta-1a. Neurology 2005;64:236–40.

100. Gasperini C, Paolillo A, Giugni E, et al. MRI brain volume changes in relapsing-remitting multiple sclerosis patients treated with interferon beta-1a. Mult Scler 2002;8:119–23.

101. Filippi M, Rovaris M, Inglese M, et al. Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet 2004;364:1489–96.

102. Rovaris M, Comi G, Rocca MA, et al. Short-term brain volume change in relapsing-remitting

multiple sclerosis: effect of glatiramer acetate and implications. Brain 2001;124:1803–12.

103. Miller DH, Soon D, Fernando KT, et al. MRI outcomes in a placebo-controlled trial of natalizumab in relapsing MS. Neurology 2007;68:1390–401.

104. Mancardi GL, Saccardi R, Filippi M, et al. Autologous hematopoietic stem cell transplantation suppresses Gd-enhanced MRI activity in MS. Neurology 2001;57:62–8.

105. Roccatagliata L, Rocca M, Valsasina P, et al. The long-term effect of AHSCT on MRI measures of MS evolution: a five-year follow-up study. Mult Scler 2007;13:1068–70.

106. Trapp BD, Peterson J, Ransohoff RM, et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998;338:278–85.

107. Evangelou N, Konz D, Esiri MM, et al. Size-selective neuronal changes in the anterior optic pathways suggest a differential susceptibility to injury in multiple sclerosis. Brain 2001;124:1813–20.

108. Arnold DL. Changes observed in multiple sclerosis using magnetic resonance imaging reflect a focal pathology distributed along axonal pathways. J Neurol 2005;252(Suppl 5):v25–29.

109. Garbern JY, Yool DA, Moore GJ, et al. Patients lacking the major CNS myelin protein, proteolipid protein 1, develop length-dependent axonal degeneration in the absence of demyelination and inflammation. Brain 2002;125:551–61.

110. Helms G. T2-based segmentation of periventricular paragraph sign volumes for quantification of proton magnetic paragraph sign resonance spectra of multiple sclerosis lesions. MAGMA 2003;16:10–6.

111. Whittall KP, MacKay AL, Li DK, et al. Normal-appearing white matter in multiple sclerosis has heterogeneous, diffusely prolonged T(2). Magn Reson Med 2002;47:403–8.

112. Evangelou N, Esiri MM, Smith S, et al. Quantitative pathological evidence for axonal loss in normal appearing white matter in multiple sclerosis. Ann Neurol 2000;47:391–5.

113. Walters RJ, Fox NC, Crum WR, et al. Haemodialysis and cerebral oedema. Nephron 2001;87:143–7.

114. Mellanby AR, Reveley MA. Effects of acute dehydration on computerized tomographic assessment of cerebral density and ventricular volume. Lancet 1982;2:874.

115. Rao AB, Richert N, Howard T, et al. Methylprednisolone effect on brain volume and enhancing lesions in MS before and during IFNbeta-1b. Neurology 2002;59:688–94.

116. Zivadinov R, Rudick RA, De Masi R, et al. Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS. Neurology 2001;57:1239–47.

117. De Stefano N, Bartolozzi ML, Nacmias B, et al. Influence of apolipoprotein E epsilon4 genotype on brain tissue integrity in relapsing-remitting multiple sclerosis. Arch Neurol 2004;61:536–40.

118. Enzinger C, Ropele S, Smith S, et al. Accelerated evolution of brain atrophy and "black holes" in MS patients with APOE-epsilon 4. Ann Neurol 2004;55:563–9.

119. Enzinger C, Fazekas F, Matthews PM, et al. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. Neurology 2005;64:1704–11.

120. Kidd D, Barkhof F, McConnell R, et al. Cortical lesions in multiple sclerosis. Brain 1999;122(Pt 1):17–26.

121. Geurts JJ, Pouwels PJ, Uitdehaag BM, et al. Intracortical lesions in multiple sclerosis: improved detection with 3D double inversion-recovery MR imaging. Radiology 2005;236:254–60.

122. Kangarlu A, Bourekas EC, Ray-Chaudhury A, et al. Cerebral cortical lesions in multiple sclerosis detected by MR imaging at 8 Tesla. AJNR Am J Neuroradiol 2007;28:262–6.

123. Miller DH, Barkhof F, Frank JA, et al. Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. Brain 2002;125:1676–95.

124. Battaglini M, Smith SM, Brogi S, et al. Enhanced brain extraction improves the accuracy of brain atrophy estimation. Neuroimage 2008;40:583–9.

125. Jasperse B, Valsasina P, Neacsu V, et al. Intercenter agreement of brain atrophy measurement in multiple sclerosis patients using manually-edited SIENA and SIENAX. J Magn Reson Imaging 2007;26:881–5.

126. Bookstein FL. "Voxel-based morphometry" should not be used with imperfectly registered images. Neuroimage 2001;14:1454–62.