The measurement and clinical relevance of brain atrophy in multiple sclerosis

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Brain atrophy has emerged as a clinically relevant component of disease progression in multiple sclerosis. Progressive loss of brain tissue bulk can be detected in vivo in a sensitive and reproducible manner by MRI. Clinical studies have shown that brain atrophy begins early in the disease course. The increasing amount of data linking brain atrophy to clinical impairments suggest that irreversible tissue destruction is an important determinant of disease progression to a greater extent than can be explained by conventional lesion assessments. In this review, we will summarise the proposed mechanisms contributing to brain atrophy in patients with multiple sclerosis. We will critically discuss the wide range of MRI-based methods used to quantify regional and whole-brain-volume loss. Based on a review of current information, we will summarise the rate of atrophy among phenotypes for multiple sclerosis, the clinical relevance of brain atrophy, and the effect of disease-modifying treatments on its progression.

Historical background

Brain-volume loss was reported as a component of multiple sclerosis in early descriptions of the pathology. In 1938, Robert Carswell discussed multiple sclerosis in an article on atrophy in his *Atlas of Pathology*.[1] In 1963, German pathologist Eduard Rindfleisch reported focal atrophy of brain tissue in his description of the perivascular nature of multiple sclerosis lesions.[2] With advances in technology,[3] structural neuroimaging provides increasingly sensitive methods of monitoring brain atrophy in vivo. In this review we will focus on brain atrophy, referring the readers to separate reviews on atrophy of the optic nerve and spinal cord in multiple sclerosis.[4–8]

Pathogenesis

Although brain atrophy is probably an endpoint of irreversible tissue loss in multiple sclerosis, it is not pathologically specific. The underlying mechanisms for brain atrophy are diverse and complex. Some proposed mechanisms are directly related to the multifocal inflammatory disease process, whereas others are indirectly related to or are independent from traditional measures of overt lesions.[9]

Overt lesions

Multiple sclerosis lesions are dynamic and progress through distinct stages on MRI scans. Lesions that are enhanced with intravenous-gadolinium contrast on T1-weighted images represent active areas of inflammation and dysfunction of the blood–brain barrier.[10,11] Most gadolinium-enhancing lesions become permanent hyperintense lesions on T2-weighted images and represent a range of pathological changes (eg, oedema, gliosis, inflammation, demyelination, remyelination, and axonal loss). About half of gadolinium-enhancing lesions will ultimately persist as severe hypointensity on T1-weighted images (T1 black holes).[11] These persistent

Focal-tissue loss within overt white-matter lesions is probably a major contributor to brain atrophy due to loss of myelin and axonal density.[10,14] But is there a relation between lesion load and brain atrophy, even remote to lesion development? One group studied 29 patients with a clinically isolated demyelinating syndrome over 14 years.[15] Progression of T2-hyperintense lesion load in the first 5 years after disease onset was the best predictor of whole-brain atrophy 14 years later, suggesting that lesions partly contribute to the development of global atrophy. However, most studies examining the relation between T2-hyperintense lesions and whole-brain atrophy reported that lesion load accounts for at most 10% of the variance in atrophy in patients with relapsing-remitting multiple sclerosis, and has limited predictive value for the subsequent development of atrophy.[16–18] An increasing amount of data show that whole-brain grey-matter volume is moderately correlated with lesion volume, suggesting that remote effects of white-matter lesions are partly responsible for grey-matter degeneration.[16,19–23] However, this association might not extend to atrophy in deep grey-matter nuclei, in which atrophy is poorly related to such lesions.[24]

Gadolinium-enhancing lesions partly predict the development of whole-brain atrophy in early relapsing-remitting multiple sclerosis in some studies.[14,25–33] One study[26] reported that the number of enhancing lesions was moderately correlated with ventricular enlargement in 16 patients with relapsing-remitting multiple sclerosis. Three other studies of patients with similar characteristics lend support to this association.[27–29] Two groups showed that ring-enhancing lesions might be particularly predictive of brain atrophy.[26,30] However, results from two studies[17,31] suggest that gadolinium-enhancing lesions do not predict whole-brain atrophy. Overall, the relation between enhancing lesion volume and brain atrophy seems to disappear in later disease

patients with secondary progressive multiple sclerosis, brain atrophy continues to progress.[33]

The association between T1-black holes and brain atrophy however, is unclear.[14,17,34,35] One study[34] recorded a relation between T1-black holes and supratentorial brain atrophy (r=0·48) in a cross-sectional study of patients with relapsing-remitting multiple sclerosis (n=55). Results from our group supported this finding in 78 patients with multiple sclerosis (r=0·35),[35] and we also reported an association between subcortical atrophy and volume of T1-black holes.[36] This finding contrasts with studies showing that the volume of T1-black holes at baseline does not predict the development of longitudinal whole-brain atrophy in relapsing-remitting multiple sclerosis.[17]

Are multiple sclerosis lesions and brain atrophy linked, or are they unique results of different pathological processes? On the basis of the above results, there seems to be a partial link between lesions and brain atrophy. One key mechanism linking MRI lesion load to brain atrophy is the remote effect of axonal injury on neuronal loss (Wallerian degeneration). A study of the pathology[37] has shown the abundance of transected axons in the brain of patients with multiple sclerosis (more than 11 000 per mm^3 of lesional tissue). Wallerian degeneration can be detected at the earliest stage of multiple sclerosis (in patients with a clinically isolated demyelinating syndrome).[38] However, the slight predictive value of lesion volumes suggests that other mechanisms might be contributing to volume loss.[14] There has been a recent effort to correlate diffuse damage in the normal-appearing brain tissue with brain atrophy. One group used MR spectroscopy to quantify N-acetyl aspartate as a marker of neuronal integrity and showed that decreased whole-brain N-acetyl aspartate preceded global-parenchymal loss in 42 patients with relapsing-remitting multiple sclerosis.[39] Another group, measuring whole-brain N-acetyl aspartate and diffusivity, showed these markers (but not any lesion-load volumes) were associated with whole-brain atrophy.[40] These studies provide evidence to show that in addition to overt lesion formation, global dysfunction or degeneration of neurons might be occuring, and perhaps preceding brain atrophy.

Alternative mechanisms

The absence of a strong association between lesion load and brain atrophy suggests that other mechanisms contribute to atrophy. There has been evidence of a genetic predisposition to brain atrophy or neurodegeneration in multiple sclerosis. Specifically, patients who carry the *APOE* ϵ4 allele have up to five times greater annual rate of brain atrophy than do patients who do not have the allele.[41] Patients with this genotype are also at risk for developing persistent T1-black holes.[41] Brain atrophy has also been associated with damage in grey matter, as measured by T2 hypointensity of subcortical structures, and is thought to represent pathological iron deposition[18,42,43] (figure 1).

Localisation of brain atrophy

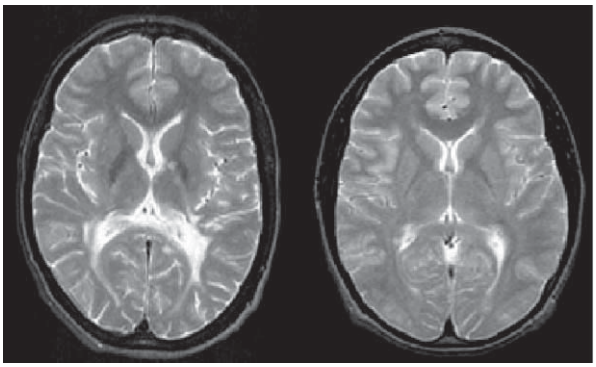
Brain atrophy seems to be widespread in multiple sclerosis, affecting all brain regions, including all the cerebral lobes, the compact white-matter tracts, brainstem, and cerebellum.[44] Both grey-matter and white-matter compartments are affected. Several groups have assessed grey-matter versus white-matter volume loss using various segmentation tools, and selective grey-matter atrophy has been documented in patients with a clinically isolated demyelinating syndrome or relapsing-remitting multiple sclerosis.[16,20,21,23,24,45–47]

Patient A

Baseline T2 intensity values:
Mean thalamus=0·44
Mean caudate=0·48
Left putamen=0·42
Right putamen=0·42
Left globus pallidus=0·28
Right globus pallidus=0·32
Mean red nucleus=0·39

Baseline BPF=0·82

Year 2 BPF=0·77



Patient B

Baseline T2 intensity values:
Mean thalamus=0·59
Mean caudate=0·63
Left putamen=0·59
Right putamen=0·59
Left globus pallidus=0·44
Right globus pallidus=0·44
Mean red nucleus=0·46

Baseline BPF=0·85

Year 2 BPF=0·85

Figure 1: **Midthalamic T2-weighted axial images from two placebo patients at baseline**
We did a post-hoc analysis of patients with MS from a 2-year clinical trial of interferon beta-1a (30μg IM weekly) or placebo.[18] We determined deep grey-matter T2 hypointensity, brain parenchymal fraction (BPF), and total T2-, gadolinium-enhancing-, and T1-lesion volumes. T2 hypointensity was chosen in regression modeling as the best predictor of BPF change at the 1 year (R^2=0·23, p=0·002) and 2 year (R^2=0·33, p<0·001) time points after accounting for all MRI variables. Mid-thalamic T2-weighted axial images from two placebo patients at baseline are shown, relating visual to quantitative findings, showing a range of T2 intensity and BPF values. Patient A (left) had relative baseline T2 hypointensity and atrophy, with marked atrophy progression. Patient B (right) had higher baseline T2 intensity and BPF values, with no atrophy progression. Thus, grey matter T2-hypointensity predicts the progression of brain atrophy in patients with early relapsing-remitting multiple

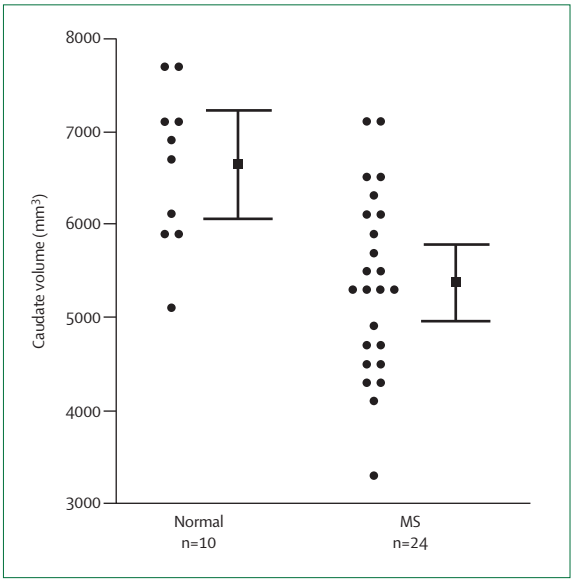


Figure 2: **Box plot of normalised caudate volumes**
We tested whether caudate atrophy occurs in MS, and whether it correlates with conventional MRI or clinical markers of disease progression. Caudate nuclei of 24 patients with MS and ten age-matched healthy controls were traced, normalised, reconstructed, and visualised from high-resolution MRI scans. Normalised bicaudate volume was 19% lower in MS *vs* controls ($p<0{\cdot}001$), an effect that persisted after adjusting for whole-brain atrophy ($p<0{\cdot}008$). Caudate volume did not correlate with total brain T2 hyperintense or T1-hypointense lesion load (both $p>0{\cdot}05$). Reproduced with permission from Lippincott, Williams & Wilkins.[24]

Cortical atrophy happens early in the course of multiple sclerosis[45,48,49] and can be localised to specific regions of the brain. One group measured cortical thickness in 20 patients with multiple sclerosis and noted the presence of focal atrophy in the bilateral frontal and temporal cortices early in the disease course, and additionally in the motor cortex in patients with more advanced disease.[49] Evidence from other groups, however, suggests that atrophy similarly affects both grey and white-matter compartments[20,50] or preferentially affects the white-matter compartment.[19] The similarity of the patient populations, small sample sizes, and differences in techniques might explain, in part, the conflicting conclusions of these studies.

Data show that the grey matter, although affected by the disease, has relatively less inflammation[51] compared with white matter, which is more prominently affected. This process could potentially cause increases in white-matter volume and mask ongoing atrophy. Consistent with this hypothesis, in a 3 year longitudinal study,[16] patients with early-onset multiple sclerosis had large decreases in grey-matter volume but small increases in white-matter volume. Additionally, those with a clinically isolated demyelinating syndrome had loss of grey-matter volume, but there were no changes in white-matter volume. Both groups of patients had large matter volume loss, which could have been the result of atrophy, was offset by inflammation or oedema-related increases in tissue bulk. These data suggest that decreases in grey-matter volume can identify progressive neurodegeneration more sensitively than can decreases in white matter or whole-brain volumes.

Atrophy of the deep grey nuclei also seems to happen in multiple sclerosis (figures 2 and 3). Tissue loss from the thalamus[52,53] and the caudate nucleus[24] has been measured with MRI segmentation. There was substantial neuron loss, with neuronal density decreased by 22%, in the thalamus of patients with multiple sclerosis.[52] This pathological evidence for neurodegeneration in the grey matter highlights the underlying causes of damage detected non-invasively by imaging studies, such as hypometabolism,[54] decreased neuronal activation,[55,56] increased diffusivity,[57] and decreased N-acetyl aspartate.[52]

Methods used to measure brain atrophy

Qualitative measures

Clinically, brain atrophy can be identified from qualitative images by the recognition of an increase in cerebrospinal fluid spaces or a reduction in size of parenchymal structures compared with the normal appearance for age (figure 4). Upon review of serial studies, progressive atrophy can be detected by comparison of images (figure 5). Such relatively simple determinations are easy to implement in routine patient care or for semiquantitative analysis,[44] and can help to assess disease severity and disease progression.

Quantitative two-dimensional measures

Because of the limited reproducibility and precision of visually based atrophy measures, quantitative

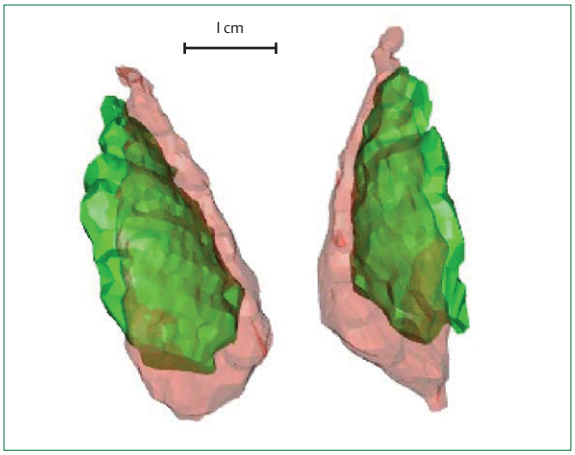


Figure 3: **Deep grey-matter damage might be an important component of the MS disease process**
Superior view of three-dimensional caudate reconstructions from a patient with MS (green) and a normal control (pink), both age 50 years old, normalised for head size. Surfaces were reconstructed from volume acquisition coronal MR

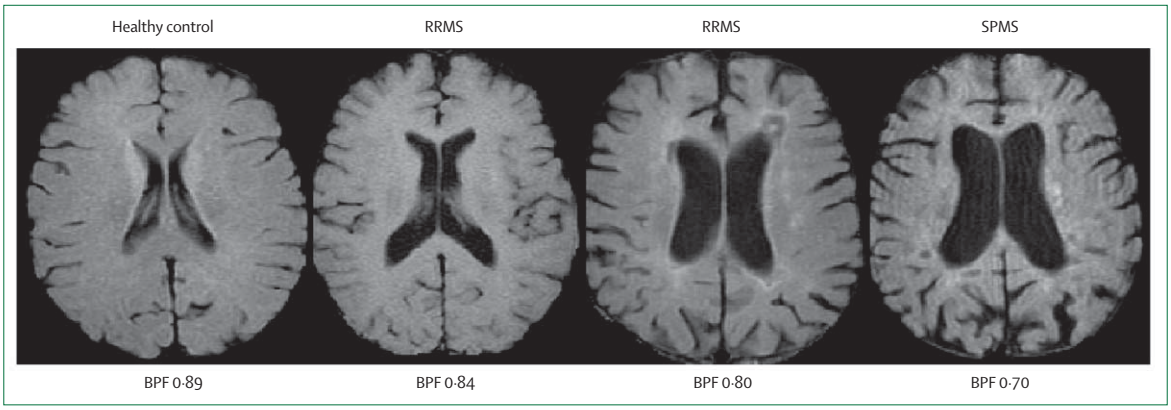


Figure 4: **Whole brain atrophy in MS as measured by a normalised proportional method**
Representative midventricular axial non-contrast T1-weighted MRI scans are shown from age-matched individuals in the sixth decade. Note the progressive decrease in brain parenchyma, increase in cerebrospinal fluid spaces, and decrease in brain parenchymal fraction (BPF) among the scans from left to right. The first patient with relapsing-remitting multiple sclerosis (RRMS) has an EDSS score of 1·5 and disease duration of 5 years. The next patient with relapsing-remitting multiple sclerosis has an EDSS score of 4·0 and disease duration of 10 years. The patient with secondary-progressive multiple sclerosis has an EDSS score of 6·5 and disease duration of 18 years. Reproduced with permission from the American Society for Experimental NeuroTherapeutics.[11]

techniques are preferred. Quantitative two-dimensional measures of atrophy include linear measures, which can be quantified on a single-image section with a distance tool on a computer workstation (or even a ruler on hardcopy films).[29,35,36,58–63] Although two-dimensional measures have the advantage of relative ease of implementation in the clinical setting, the main disadvantage is the absence of reproducibility compared

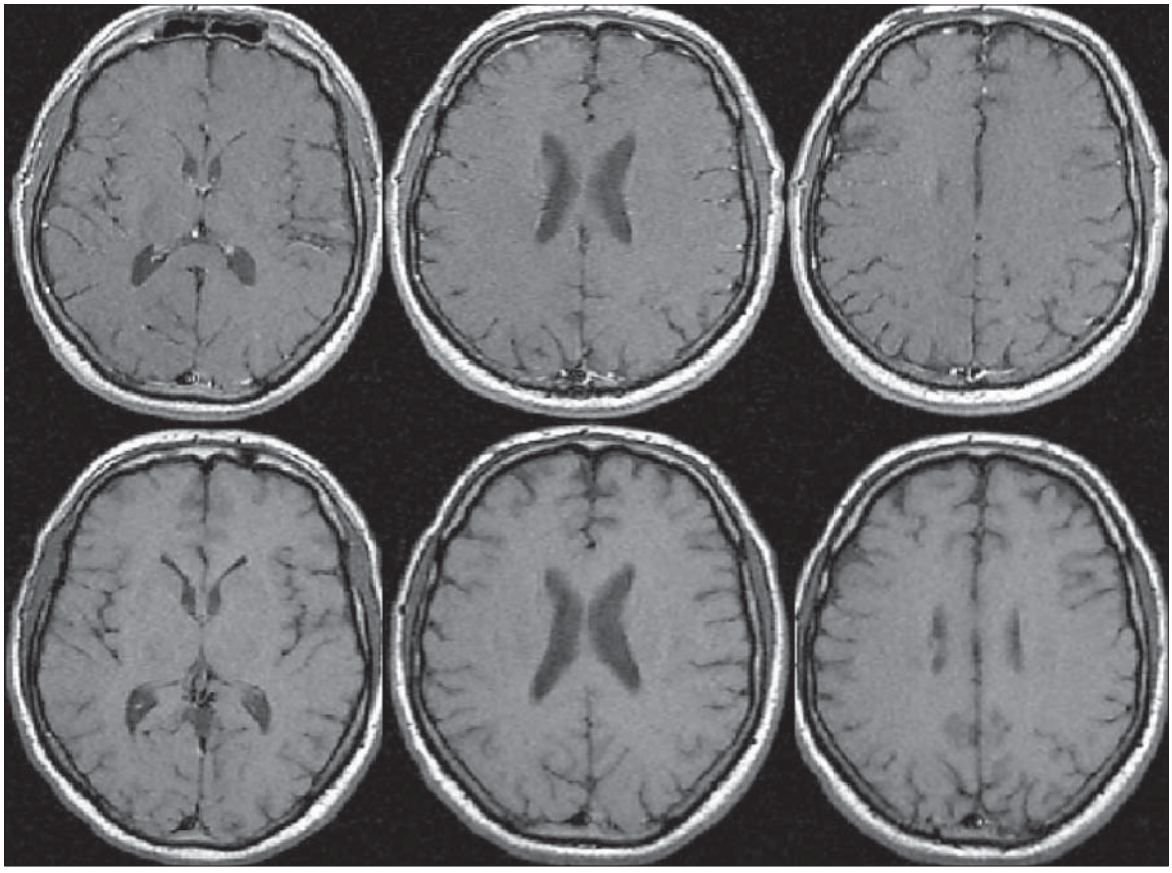


Figure 5: **Progressive brain atrophy in a 41-year-old man with RRMS imaged at baseline and 4 years later**

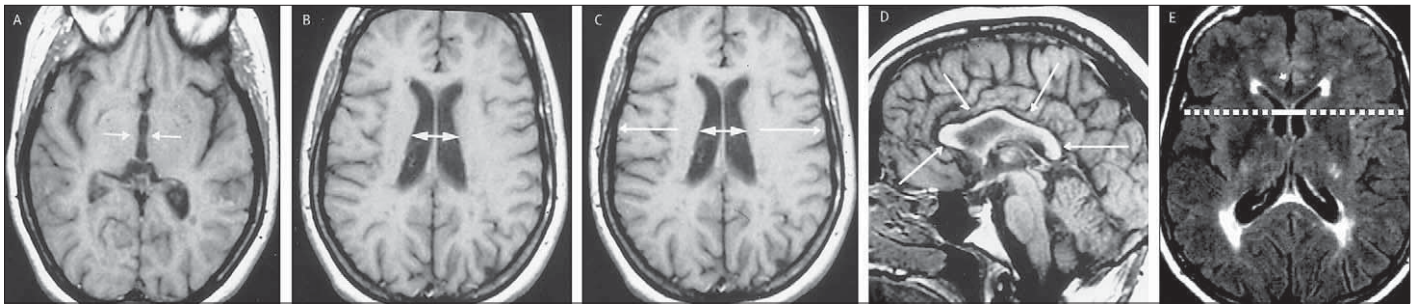


Figure 6: **Two-dimensional measures of brain atrophy**
Third ventricle width (A), maximum lateral ventricle width (B; arrows), brain width (C; arrows), corpus callosum area (D), and bicaudate ratio (E; minimum intercaudate distance [solid line] divided by the brain width along the same line [dashed line]). Measurement of third ventricular width is done by measuring the width along the anteriorposterior midpoint of the third ventricle. Lateral ventricular width is determined along a plane corresponding to the anteroposterior midpoint of the ventricle on an anatomical level from an axial slice at which the septum pellucidum remains thin. Brain width is the distance between two points on the cortical surface, measured at the same level and along the same line as the lateral ventricle width. Corpus callosum area is determined by outlining the margins of the structure from the best available midsagittal section The bicaudate ratio, also known as the intercaudate nucleus ratio, is measured from an axial section on which the heads of the caudate nuclei are most visible and closest together. These two dimensional measures of brain atrophy have shown longitudinal sensitivity to disease progression,[29] meaningful correlations with clinical findings,[29,36] and strong associations with three dimensional measures of whole brain atrophy.[64] Both the third ventricle width and bicaudate ratio show associations with cognitive impairment, even after accounting for other MRI biomarkers including whole-brain atrophy and lesion load.[36,60] A–D reproduced with permission from Lippincott, Williams & Wilkins[29]

with three-dimensional measures. Figure 6 shows examples of two-dimensional measures.

Quantitative three-dimensional measures

Quantitative measures of whole-brain atrophy, acquired by automated or semiautomated methods,[64] have become the most powerful methods for assessing patients with multiple sclerosis over time because of their reproducibility, sensitivity, and potential to capture global disease effects.[65,66]

Segmentation-based techniques include separation of intracranial contents into parenchymal and non-parenchymal classes, thereby arriving at an expression of what proportion of space is occupied by brain tissue at any given time. The most popular terminology for this "proportional method" is brain parenchymal fraction (BPF) (figures 4 and 7).[17,35,64,67,68] Other examples of techniques which use segmentation-based methods include 3DVIEWNIX,[69] SIENAX,[70], index of brain atrophy,[71] whole brain ratio,[72] brain to intracranial cavity ratio,[73] brain to intracranial volume ratio,[74] fuzzy connectedness,[75] the Alfano method,[76] MIDAS,[77] and ILAB4.[78] Segmentation-based techniques can also separately quantify the volume of grey matter, white matter, and cerebrospinal fluid compartments (figure 7).[23] The abnormal signal intensity of multiple sclerosis lesions presents a potential source of voxel misclassification. Lesions in the white matter tend to be misclassified as grey matter,[20] and misclassified volumes should be corrected to avoid confounding clinical correlations.[23]

Registration-based techniques are designed to follow patients longitudinally over time.[79] These methods align two serial scans from a patient and find areas of signal-intensity change after accounting for changes in head position or slice plane. The result is a number such as statistical parametric mapping (figure 7),[23,64,67,82,83] template-driven segmentation,[84] and brain boundry shift integral.[79] The advantages of registration-based methods are that they are sensitive to longitudinal changes and (because they are mostly automated) need little operator input and time. The main disadvantage is the need for additional steps in image processing.

Thus, there are a multitude of techniques now available to measure brain atrophy. However, the main limitation of the use of brain atrophy in clinical trials is that different measures can produce conflicting results. Differing results might be valid,[85] but as a result of the low specificity of brain atrophy, techniques can quantify different physiological observations.

Atrophy and disease course

Clinically isolated syndrome

There is increasing evidence that brain atrophy is not restricted to the later progressive stages, but begins in the earliest stages of multiple sclerosis.[6] In patients with clinically isolated demyelinating syndrome, whole-brain atrophy is detectable in those who go on to develop multiple sclerosis.[86,87] Patients who meet the international panel criteria for multiple sclerosis[88] (but who have had only a single demyelinating event) had detectable ventricular enlargement over the subsequent year (median enlargement=0·3 cm^3, n=27) compared with those who do not meet the criteria (median enlargement=0·05 cm^3, n=28, p=0·03).[77] In another study of patients with clinically isolated demyelinting syndrome followed up over 3 years, the group that developed multiple sclerosis during the study period had detectable grey-matter atrophy, but no white-matter atrophy.[16] In the placebo group of a randomised controlled trial of subcutaneous interferon beta-1a in clinically isolated demyelinating syndrome,

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