

Volumetrics on Multiple Sclerosis and Aging

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Introduction

Until very recently, it was difficult to quantify changes in brain volume with any precision. The development of methods that can use conventional MR images to provide sensitive and reproducible assessments of brain volumes has changed this picture. In this context, the ability of measuring cerebral tissue loss (atrophy) from conventional MR images with methods that can be easily implemented at any MR centre has increased the interest in brain atrophy as an index to accurately assess and monitoring the pathological evolution of a number of neurological conditions.

Using these methods of computed quantitative analysis, diffuse brain volume loss has been found in a number of neurological disorders [1-4]. We review here the most recent results on MRI-based quantitative brain atrophy and the clinical relevance of this measure in progressive neurological disorders such as multiple sclerosis (MS) and dementia.

Multiple Sclerosis

Cerebral atrophy occurs in most neurodegenerative disorders with a mechanism that is mostly driven by neuronal and axonal loss. However, in neurological disorders such as MS, the pathological correlates of brain atrophy can be more complex and loss of brain tissues such as myelin and glial cells might contribute significantly to the total loss of tissue volume occurring in MS brains [1; 5]. Thus, brain atrophy should be considered in this disease as an expression of a generalized process that involves various brain tissue components.

Diffuse Brain atrophy in MS

It has been long recognised that late stage multiple sclerosis is associated with a substantial atrophy of the brain with marked ventriculomegaly. With the advent of high quality MRI and digital signal processing methods, it also has become possible to measure even very small changes in brain volume occurring over relatively short periods *in vivo* (e.g., 6 months to 1 year or longer).

Serial MRI studies have concluded consistently that brain volume loss occurs at a faster rate in patients with MS than in age-matched, healthy controls. Depending on the measuring method used, studies have reported reductions in brain volume by 0.5-1% per year in MS patients [6; 7] (while brain volume in healthy controls is estimated to decrease about 0.1-0.3% per year) [8; 9]. Atrophy appears to proceed inexorably through the course of MS and changes in brain volume MS occur from the earliest stages of the disease [6], even from the time of first presentation [10].[11]

While interpretations of brain atrophy measures can reasonably be framed in terms of neuronal and axonal loss, the brain substance also includes a substantial extracellular compartment. Direct histopathological measures confirm an expansion of the extracellular space over the course of the disease. Thus, brain volume change does not provide a direct, quantitative index of axonal loss. Similar observations have been made in a study focusing on the corticospinal tracts in the spinal cord [12]. The area of these tracts and their axon density were reduced at all levels in MS indicating that axon loss occurs throughout the length of the neuraxis

Grey matter and white matter make similar contributions to total brain volume. There are differences in the relative contributions from different cell types whose loss could contribute to atrophy in these compartments, however. Myelin loss could make a greater contribution to white matter volume loss than to that of grey matter, for example. Neuronal or dendritic atrophy would make a large contribution to grey matter volume loss specifically.

Brain Atrophy of different tissue compartments in MS

The relative contributions of the different tissue compartments to brain atrophy and, in particular, the importance of neocortical pathology in such a process can be investigate by selectively assessing GM

volumes in MS patients [13-17]. Thus, a number of computational methods for measurements of regional brain volumes have been used successfully in several recent clinical studies to measure GM volume in a range of patients with different forms of MS. Using these methods, many studies have consistently demonstrated that GM atrophy is prominent in MS from the earliest disease stages [15; 16]. Neocortical volume decreases were found, for example [15], in both relapsing remitting (RR) and primary progressive (PP) MS patients even when patients were grouped for short disease duration (< 5 years) or for low cerebral lesion load (< 5cc of T₂-weighted [T₂-W] lesions) suggesting that neocortical pathology not only occurs at the earliest MS stages, but also appears to be significant even with minimal WM lesion accumulation.

The concept that, in a demyelinating disorder such as MS, a cortical pathology can be not only prominent from early disease stages, but can be at least partially independent of white matter lesion genesis is new and important. Indeed, this is strongly suggested by all GM volumetric MR studies so far reported [13-16]. In these studies, the modest relationship found between T₂-W lesion volume and GM volume measures in RR MS patients (which explained, in some cases, no more than the 25% of the variance in the neocortical measure [15]) and the complete absence of this relationship in PP MS patients [15] lend support to the hypothesis that GM atrophy is not necessarily dependent on cerebral white matter changes. In addition, recently, Sailer and coworker [18], by using a novel approach to image analysis that allows highly precise measurements of thickness all across the cortex, demonstrated about 30% decrease in cortical thickness in MS patients relative to age-matched healthy controls. In their elegant work, they also showed that cortical thinning can be predominant in the superior temporal gyrus and the superior and middle frontal gyri in MS patients with short disease course, low disability and low white matter lesions. Thus, these and more recent [19] results [20] provide evidence that there are specific brain GM regions that can be earlier and deeper involved than others in the pathological process and provide new evidence of the high relevance of a primary cortical pathology from the earliest stages of MS.

These conclusions rely on accurate segmentation of grey and white matter in the MR images. A methodological concern is that apparent decreases in GM volumes might be related to the presence of occult neocortical inflammatory lesions. Such lesions can be seen consistently in post-mortem studies [21; 22], but are rarely detected on MRI using conventional sequences [23; 24]. Thus, subtle changes in MR signal intensity due to MR undetectable neocortical lesions could affect segmentation between the cortex and CSF such that the cortex appears to decrease in volume. However, as the presence of significant GM volume decreases was found in several studies in patients with minimal T₂-W white matter lesion accumulation [14; 15; 18], it is very unlikely that the detected decrease in GM volumes could be due primarily to a neocortical lesion burden. MR data more likely suggest that, while there is a significant portion of neuro-axonal damage that is dependent on focal white matter changes, the GM pathology occurring in MS can be due also to mechanisms independent of lesion genesis.

Clinical Relevance of GM Atrophy in MS

Clinical-pathological correlations have been investigated intensively in MS by using different MR techniques. However, the results have been often disappointing. This is surely due to more than one factor [25], but it may have been contributed also the almost exclusive focus on pathological changes in the white matter of the previous studies [22]. Focal white matter lesions do not lead to disability progression in a simple way. A specific illustrative example of this can be coming from the PP form of MS, which is usually characterised by high disability with low white matter lesion load. Another example can come from the cognitive dysfunction, which is present in about 40-60% of MS patients and cannot be fully explained with white matter lesions alone [26].

The changes occurring in the GM can probably better elucidate both previous points. The results of GM volumetric studies showed that, whereas in RR MS patients the amount of GM atrophy seems to correlate moderately with T₂-W brain lesions and (somehow more weakly) with disease duration, GM volume loss does not seem to contribute significantly to extent of clinical disability in this form of the disease [13-16]. In contrast, a very close relationship can be found in PP MS patients, who do not show, instead, significant correlations between measures of clinical disability and those of T₂-W lesion volume or disease duration [15]. Thus, MR data support the hypothesis of potential clinical-pathological differences between the two forms of the disease [27-30] and suggest that in the PP more than in the RR form of MS, neocortical atrophy might be due to a pathological process that is mostly dominated by neurodegeneration and that, regardless of the mechanisms, seems to be very relevant to clinical disability.

As mentioned above, cognitive impairment can be demonstrated in a great number of MS patients, even including a proportion of those with very early disease stage [26; 31]. This has been considered generally to be strictly dependent on white matter changes and, eventually, subcortical pathology [32].

However, although increasing cognitive impairment may sometimes proceed in parallel with increasing T₂-W MR lesion load, the magnitude of the correlation between neuropsychological scores and T₂-W lesions has been generally modest [33; 34]. As MRI visible T₂-W lesions represent only part of the MS pathology and brain tissue apparently normal on conventional MR seems to have a great pathological relevance in the disease, pathology occurring in normal appearing brain tissue may be relevant to understanding the process underlying cognitive dysfunction in MS [34]. In agreement with this, cognitive impairment has been associated in many MR studies with measures of cerebral atrophy and the importance of decreasing brain volumes, rather than increasing lesion load, to MS-related cognitive impairment has been demonstrated even in early RR MS patients [35]. More recently, the specific contribution of the neocortical pathology to MS-related cognitive impairment has been assessed by selectively measuring neocortical volumes in RR MS patients with mild cognitive impairment [36]. In this study, after grouping patients with cognitive impairment and patients with preserved cognition accordingly to their performance on neuropsychological tests, significant decreases in neocortical volume were exclusively found in the former patient group. In addition, only cognitively impaired MS patients showed a close relationship between measures of neocortical atrophy and both global measures of the degree of cognitive impairment and selective measures of cognitive dysfunction such as defects in verbal and spatial memory, sustained attention and concentration and verbal fluency. This suggests that the measure of cortical volume may be a sensitive indicator of even mild cognitive impairment and, most of all, implies that neocortical pathology is relevant to cognitive impairment in MS.

Aging and Dementia

Early diagnosis of Alzheimer's disease

The concept of mild cognitive impairment (MCI) is aimed to capture patients in the transition from normality to Alzheimer's dementia. The diagnosis of MCI is clinically unhelpful as many MCI patients have AD but many do not. Pathological and clinical data indicate that some biological indicators of AD (the neurobiological "signature" or "fingerprint", including imaging indicators) might be used to distinguish those MCI patients who will progress (i.e. those who already have Alzheimer's) from those who will not (i.e. those who do not have Alzheimer's).

Biological indicators are hippocampal atrophy (due to early plaque and tangle deposition in the medial temporal lobe), high concentrations of tau protein in the CSF (due to neuronal/axonal damage following neurofibrillary tangle deposition), and functional defects in the temporoparietal and posterior cingulate cortex (due to deafferentation from medial temporal damage). Indeed, when compared to non progressors, MCI patients who will progress to dementia feature lower hippocampal volume measured through high resolution structural magnetic resonance imaging [37] high levels of tau protein in the CSF, and perfusion and metabolic defects (PET and SPECT) [38; 39]

Jack et coll. have tested the hypothesis that MRI-based measurements of hippocampal volume are related to the risk of future conversion to Alzheimer's disease in older patients with mild cognitive impairment [37]. Eighty consecutive patients who met criteria for the diagnosis of mild cognitive impairment were recruited from the Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry. At entry subjects enrolled underwent an MRI examination of the head, in order to obtain the volumes of both hippocampi to measure, and for a period of time were also followed longitudinally, on average 32.6 months, with approximately annual clinical/cognitive assessments. During the period of observation 27 of the 80 mild cognitive impairment patients became demented, and hippocampal atrophy at baseline was associated with crossover from mild cognitive impairment to Alzheimer's disease. The conclusions of Jack and coll. were that mild cognitive impairment patients who will progress to dementia feature lower hippocampal volume measured through high resolution structural magnetic resonance imaging.

Voxel-based morphometry analysis in mild cognitive impairment have shown a significant agreement showing that patients had highly significant gray matter loss predominantly affecting the medial temporal lobe, the hippocampal regions, the thalamus, the cingulate gyrus and extending also into the temporal neocortex [40-43]

A few studies have tried to compound more than one AD biomarker to discriminate MCI progressors from non progressors El Fakhri and colleagues [44] have studied 17 healthy controls, 56 nondemented patients with memory problems who did not develop AD during 3 to 5 years of follow-up, and 27 nondemented patients with memory problems who developed AD during follow-up. Combining information coming from SPET and structural MR at baseline allowed to correctly classify 94% of patients.

Tracking biological changes of Alzheimer's disease

Rates of global brain atrophy based on the brain-boundary shift integral are substantially higher in 18 patients with Alzheimer's disease (AD) than in 31 age-matched controls with a scan interval as short as 1 year [45]. Good separation was seen between the groups; patients with AD had annual rates of atrophy of 2.8% (SD 0.9) and controls had rates of 0.2% (0.3). Power calculations have been done to estimate sample sizes required to monitor treatment effects in clinical trials of drugs aimed to slow the progression of neurodegenerative diseases. These calculations have shown that atrophy rates derived from the brain-boundary shift integral would require smaller numbers (18 patients per treatment group with a magnitude of treatment effect of 50%) than would other techniques relying on segmentation of regional structures (42–187 patients). However, since rates of total brain atrophy are not specific for a particular degenerative disease (eg, AD and frontotemporal dementia have similar global atrophy rates) these rates have limited application in the differential diagnosis of dementia. With voxel-compression methods, characteristic patterns have been shown in the different dementias, with AD featuring diffuse atrophy, in contrast to the focal anterior atrophy of frontotemporal dementia. These patterns are consistent with the clinical symptoms of the disease, as well as postmortem evidence [46]. This technique is sensitive to early change and can identify regional brain atrophy before clinical diagnosis in AD and frontotemporal dementia [3].

Although not originally devised for prospective analyses, Ashburner and Friston's method and cortical pattern matching can also be used to analyse serially acquired images. In each case, registration is done on the baseline images rather than the template, and the registered time series from individual patients are subsequently aligned to a common template. In a study of 17 patients with Alzheimer's disease assessed by prospective methods, cortical pattern matching showed progression of atrophy from the medial temporal to the temporoparietal and frontal grey matter, whereas sensorimotor regions were generally spared. The region of deficits spread centrifugally from cingulate and other limbic regions into frontal cortices, with greatest neocortical atrophy detected in the left hemisphere. This progression occurred over a 2.5-year period in which Mini-Mental State Examination scores declined from 18 to 13. The extent of local grey-matter loss correlated with patients' declining cognitive scores. Moreover, different brain structures had different rates of change. Although the cortex loses grey matter at a rate of 4–5% per year locally, the inferior ventricular horns have greatest dynamic change rates (15–16% per year). In these regions, expansion rates are bilaterally significant even in controls (2–4% per year).

Conclusions

Measurements of brain atrophy can be used as a surrogate marker of pathology in MS and dementia. As brain atrophy includes contributions from changes in both white and grey matter, the pathological substrate (and therefore the precise interpretation) can change in different disease and in different stages of the same disease. However, widespread loss in GM tissue seems to occur consistently in both MS and dementia and appears to begin at early disease stages. To the extent that this damage is irreversible, it must be associated with irreversible neurological dysfunction. Mechanisms of cortical adaptation may be able to maintain normal function and minimise disability from axon injury in the early stages, but can no longer compensate in the later stages of the disease when a threshold of axonal loss is reached and compensatory resources of the CNS are exhausted. Such a hypothetical model argues for early therapeutic interventions, regardless of disability status in both neurological conditions. Measures of total and regional brain atrophy appear to be important for evaluating strategies for repair and/or neuroprotection in both dementia and MS. Longitudinal studies using quantitative approaches to imaging analysis should be carried out to better clarify these aspects.

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