

Editorial

A new view of the cortex, new insights into multiple sclerosis

Clinical–pathological correlations have been investigated using magnetic resonance-based techniques in patients with multiple sclerosis arguably more intensively than for any other neurological disease. However, despite impressive accomplishments, consensus regarding a common pathology underlying clinical behaviours in patients with relapsing–remitting (RR), secondary progressive (SP) and primary progressive (PP) multiple sclerosis has been elusive. In part this may have been due to the singular focus on pathological changes in the white matter.

Attention has been directed to the multifocal inflammatory lesions in white matter because their pathology appeared to offer an explanation for the characteristic RR course of the earlier stages of the disease in most patients. However, focal white matter lesions do not lead to disability progression in a simple way, particularly for PP multiple sclerosis, which is characterised by a relatively low white matter lesion load. White matter lesions alone also do not easily explain cognitive dysfunction in multiple sclerosis, evidence of which can be found in 40–65% of patients, including even a proportion of those presenting with otherwise apparently clinically isolated focal syndromes (Feinstein *et al.*, 1992).

Pathological changes in grey matter provide an alternative basis for hypotheses concerning clinicopathological correlations in multiple sclerosis. Although recognised by early neuropathologists (Greenfield and King, 1936), the significance of inflammation and demyelination in grey matter was not widely appreciated. Recent histopathological studies have re-examined grey matter involvement and suggest that the extent of pathology is potentially substantial (Peterson *et al.*, 2001; Cifelli *et al.*, 2002). In theory, a powerful approach to understanding the clinical significance of this pathology would be to follow changes *in vivo*, when they can be related directly with symptoms and signs. While magnetic resonance imaging is relatively insensitive to focal lesions in grey matter, it can measure grey matter volumes to high precision. Relative atrophy has been demonstrated even early in the disease and can be related to disability (Chard *et al.*, 2002; Cifelli *et al.*, 2002). Magnetic resonance spectroscopy has confirmed that this atrophy is associated with loss of the neuronal marker, *N*-acetylaspartate (Kapeller *et al.*, 2001; Cifelli *et al.*, 2002).

In this issue of *Brain*, Sailer and colleagues take an important further step towards a better understanding of the cortical pathology of multiple sclerosis (Sailer *et al.*, 2003). After acquisition of high-resolution magnetic resonance imaging data, they use a novel approach to image analysis that allows highly precise measurements of thickness all across the cortex. The method first uses the contrast in signal intensities to distinguish cortex from white matter and cerebrospinal fluid. The cortex that is segmented out from the rest of the brain in this way is then electronically expanded to flatten the gyral folds, rather like blowing up a crumpled Chinese paper ball. The elegance of the approach (developed by Bruce Fischl and his colleagues at the Athinoula Martinos Imaging Centre at Massachusetts General Hospital) is that it effectively addresses a few analysis problems simultaneously. Measurement of cortical thickness for assessment of change is potentially more sensitive than measurement of cortical volume. Measuring cortical thickness also allows atrophy to be assessed regionally. By removing the confound of gyral folding with cortical flattening, alignment of brains between different individuals becomes easier. No information is lost in the unfolding, so information on regional changes in the unfolded representations can be related directly back to the original brain anatomy.

Using this method, Sailer *et al.* (2003) confirm that cortical atrophy can be substantial in multiple sclerosis. They report a ~30% decrease in cortical thickness in the patients relative to age-matched healthy controls. More important is their unequivocal demonstration that relative atrophy varies between brain regions in individual patients. The anatomical distribution of changes appears consistent. In patients with a shorter disease course, cortical thinning was found predominantly in the temporal and frontal areas, specifically involving the superior temporal gyrus and the superior and middle frontal gyri. Patients with more severe disability and a longer disease course displayed thinning of the motor cortex in addition to these changes. This suggests a relative hierarchy of changes over time, involving first frontal and temporal regions and later the pre-central gyrus.

Are the results valid? Given a mean cortical thickness of ~2.5 mm, the differences between patients and controls changes measured are on the order of 0.5 mm at maximum.

Such small changes would be difficult to measure accurately post-mortem, particularly with variable agonal tissue oedema and fixation-related volume changes. However, the measure of mean cortical thickness for healthy controls is in good agreement with literature values. The measure of relative thickness change over the whole brain also is generally similar to that reported for the whole cortical volume change measured using a different method (Chard *et al.*, 2002). Finally, an extension of a distinct, separately validated algorithm for brain size change (Smith *et al.*, 2002), which gives a continuous linear measure of cortical thickness, also found evidence for selective frontal and temporal atrophy in patients with RR multiple sclerosis, consistent with the new findings reported here (Chen *et al.*, 2002; J.Chen, S.Smith, P.M.Matthews, unpublished results). The Sailer *et al.* (2003) results therefore look attractively solid. The recognition that clear cortical thickness changes of this magnitude occur argues that pathological changes in the cortex make a significant contribution to total brain atrophy, especially early in the disease.

A major challenge raised by this and related studies is to understand the mechanism underlying this progressive cortical atrophy in multiple sclerosis. One hypothesis is that remote axonal damage may trigger retrograde neuroaxonal degeneration. Axotomy in the corticospinal tract in animal models is associated with death of as many as 40–50% of neurons in motor cortex (Bonatz *et al.*, 2000). Surviving neurons also may show secondary atrophy, in part as a consequence of changes in the extent and complexity of dendritic arborisation. Sailer *et al.* (2003) hypothesise that the characteristic pattern of white matter pathology in multiple sclerosis adequately explains selective retrograde injury to frontal, temporal and motor areas of the cortex. The corticospinal tract, including fibre connections of the precentral gyrus, and the frontal periventricular white matter, consisting of efferent and afferent fibres to frontal and superior temporal lobes, are preferential sites for white matter lesions of multiple sclerosis (Narayanan *et al.*, 1997).

However, retrograde changes from focal white matter lesions do not satisfactorily explain the full range of findings. The visual cortex is not preferentially affected, despite the involvement of the optic nerve and radiations by lesions and demonstration of lateral geniculate nucleus neuronal changes (Evangelou *et al.*, 2001). In addition, De Stefano *et al.* (2003) have provided evidence that, while there is a similar relationship between cortical atrophy and disability in patients with PP and RR multiple sclerosis, cortical atrophy and white matter lesion volumes are correlated in RR multiple sclerosis patients, but not in PP multiple sclerosis patients.

Cortical inflammatory pathology could itself cause cortical atrophy. In the influential early report by Lumsden (1970), the frequency of cortical lesions was found to be strikingly high in the frontal and the superior temporal lobe. Cortical inflammation in multiple sclerosis or experimental allergic encephalitis is associated with myelin loss, axonal transection

and neuronal apoptosis. A study combining magnetic resonance imaging, spectroscopy and histopathological techniques for analysis of the thalamus demonstrated similar degrees of neuronal loss and volume loss in the thalamus, suggesting that neuronal loss accounts for much of the thalamic atrophy (Cifelli *et al.*, 2002). It is also possible that metabolic impairment from neurotoxic factors or secondary degenerative changes with alterations in activity arising from, for example, loss of coherent excitatory input after demyelination at a distance, could contribute to atrophy. Trans-synaptic effects could amplify the consequences of direct injury. But for these types of changes to explain the relative focality of cortical thickness changes reported by Sailer *et al.* (2003), it is necessary to posit plausible mechanisms for selective targeting or vulnerability of specific cortical regions. Myelin content alone does not appear to be a reason for targeting, as selective changes were not found in the heavily myelinated occipital striate cortex or area V5. Less is known about factors that may contribute to vulnerability to injury. The potential for withstanding oxidative stress from inflammatory mediators such as nitric oxide might be one relevant variable between neurons, for example.

The paper by Sailer *et al.* (2003) is a stimulating application of innovative analysis that sets new challenges for neuroscience regarding multiple sclerosis pathology. It illustrates well the two major types of contributions that magnetic resonance techniques can make to understanding the pathology of multiple sclerosis. First, it illustrates how magnetic resonance methods contribute to the appreciation of the dynamics of the disease pathology and its relationship with clinical course. Secondly, the study emphasises the importance of quantitative pathology. It appears that *size does matter*. Providing a new marker for neuroaxonal degeneration with measurement of cortical change promises increased sensitivity for the evaluation of potential neuroprotective agents. It now becomes an urgent matter to define precisely the substrate for this atrophy in order to identify the most promising candidate therapies.

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