This scientific commentary refers to ‘A gradient in cortical pathology in multiple sclerosis by in vivo quantitative 7 T imaging’, by Mainero et al. (doi:10.1093/brain/awv011).

Multiple sclerosis is widely regarded as an archetypal white matter disease. The early histopathological descriptions of grey matter involvement resurfaced only when MRI studies reiterated the frequent occurrence of cortical lesions in multiple sclerosis (Kidd et al., 1999). In fact, cortical demyelination is seen in very few other CNS diseases (Lassmann, 2012) and the occurrence of juxtacortical lesions is one of the main differentiating features for multiple sclerosis (Barkhof et al., 1997). Comparison of MRI and histopathology has been a humbling experience for radiologists, but also a learning opportunity for pathologists (Geurts and Barkhof, 2008). The use of sensitive immunohistochemical staining techniques (against major myelin proteins) has provided a wealth of data on the type and extent of cortical involvement in (progressive) multiple sclerosis. Subpial lesions in particular can be extensive (Kutzelnigg et al., 2005) and have triggered debate as to the underlying causal factors, which are believed by some to be found in the CSF or to be related to inflammation in overlying meninges.

One of the ‘grand challenges’ in imaging of cortical pathology is the in vivo detection of the most dominant cortical lesion type, the subpial lesion, by means of MRI techniques (Daams et al., 2013). Novel pulse sequences such as double inversion recovery and phase-sensitive inversion recovery, but also higher spatial resolution, through application of ultrahigh field scanners operating at 7 T, can be used for this purpose. In this issue of Brain, Mainero and colleagues used a high-resolution T2*-weighted magnetic resonance sequence to examine quantitative differences across cortical layers through the use of quantitative T2* (the inverse of the T1* relaxation rate) from a multi-echo gradient-echo pulse sequence (Mainero et al., 2015). The in-plane resolution (0.25 mm) allowed the investigators to examine signal intensity and T2*-relaxation rates at 25%, 50% and 75% depths of the cortical mantle inward from the pial surface based on segmentation of anatomical magnetic resonance images. Data were analysed within focal lesions, and according to sulcal vis-à-vis gyral location.

The resulting signal intensities in 41 patients with multiple sclerosis were analysed on a pixel-by-pixel basis for deviation from normality based on a reference group of 17 healthy volunteers. In the multiple sclerosis group, widespread cortical increases in T2* were found, which differed between disease stages. In the early relapsing-remitting subgroup, longer T2* was detected mostly in focal lesions and at the 25% depth within sulci; in progressive patients, by contrast, deeper layers (50% and 75% from the pial surface) were affected, and changes also occurred outside visible lesions and on the gyral surface. Thus, the pattern of T2* changes involves deeper layers of the cortex and becomes more diffuse in the progressive phase of the disease. The T2* findings were associated more strongly with disability scores than was the case for cortical thickness/volume, perhaps because of the small sample size; notably, regional cortical thinning was not found in multiple sclerosis when compared to controls, suggesting that cortical T2* changes may be more sensitive in detecting multiple sclerosis-related pathological abnormalities than cortical thickness. Cortical T2* changes were related to the extent of white matter lesions, perhaps because both accumulate as a function of disease duration.

The main finding of these comprehensive studies by Mainero et al. using T2* mapping at 7 T is the suggestion that outer cortical layers are the most severely affected in multiple sclerosis. This corroborates the frequent occurrence of subpial lesions in histopathological studies (Kutzelnigg et al., 2005) and magnetic resonance studies looking at magnetization transfer ratio (MTR) (Derakhshan et al., 2014; Samson et al., 2014). One intriguing finding is that cortical changes were more prominent within sulci than at the gyral surface. Similar observations have been made in histopathological studies and could point to differences in CSF dynamics (more static) within deeper sulci, allowing dif fusible factors to exert stronger effects locally, or the localization of inflammation in the leptomeninges.

While the spatial distribution patterns are intriguing and largely consistent with patterns of histopathological damage in (progressive) multiple sclerosis, the nature of the T2* changes can only be speculated upon. T2* is a magnetic resonance contrast that is complex and affected by various biophysical processes, including myelin density, iron accumulation and other factors that affect
susceptibility. In fact, if one were to choose a magnetic resonance parameter to examine myelin, several other magnetic resonance parameters might be preferred to $T_2^*$, e.g. MTR or short-component $T_2$ (myelin-water) relaxation time. However, $T_2^*$ is one of the simplest pulse-sequences to implement at 7 T and provides a relatively good spatial resolution. Studies comparing $T_2^*$ relaxation rate at 7 T and histopathology are, however, urgently needed to study the true underlying tissue pathological component(s) and move beyond the current rather general interpretation of ‘cortical damage’. Provocative as the findings of Mainiero and colleagues may be, several caveats should be kept in mind. While the $T_2^*$ images were acquired at 7 T, the cortical segmentation was done based on 3 T anatomical images with a lower (0.95 mm in-plane) resolution. If one adds the possible inaccuracy of the registration of the 7 T to the 3 T images (the quality of which will be spatially varying due to differences in susceptibility) it is obvious that one should interpret the assignment of $T_2^*$ changes to cortical layers with some caution. Detection of focal lesions was performed using $T_2^*$ images, which are less sensitive for detecting (cortical) lesions than for example fluid-attenuated inversion recovery (FLAIR) images, hence the distinction between lesion and ‘normal-appearing’ cortex may have been inaccurate. This may not be a major issue, as focal lesions form the tip of the iceberg of more widespread changes of a similar nature (Seewann et al., 2011).

With these caveats in mind, the proposed quantitative $T_2^*$ measurements at 7 T seem to provide a plausible and easy-to-implement measure to study the gradient of changes in cortical pathology in multiple sclerosis in vivo. Longitudinal studies are now needed to examine the spread of pathology through the cortex in individual subjects in relation to other inflammatory and neurodegenerative changes and to establish their relevance to, for example, cognitive impairment. Ultra-high field MRI is an enrichment of our armamentarium for studying cortical involvement in multiple sclerosis, including its gradient of laminar involvement.

Frederik Barkhof and Jeroen J. G. Geurts VU University Medical Center, Amsterdam, NL

Correspondence to: Frederik Barkhof E-mail: f.barkhof@vumc.nl

doi:10.1093/brain/awv031

References


Could the serotonin theory give rise to a treatment for levodopa-induced dyskinesia in Parkinson’s disease?

This scientific commentary refers to ‘Eltoprazine counteracts l-DOPA-induced dyskinesias in Parkinson’s disease: a dose-finding study’, by Svenningsson et al. (doi:10.1093/brain/awu409).

Involuntary movements, or dyskinesias, are a debilitating complication of levodopa therapy for Parkinson’s disease, and are ultimately experienced by the vast majority of patients. In this issue of Brain, Svenningsson et al. provide evidence that oral treatment with eltoprazine, a 5-HT1A/1B receptor agonist, has beneficial antidyskinetic effects together with a favourable risk-benefit profile in Parkinson’s disease (Svenningsson et al., 2015).

Currently, the only recommended add-on antidyskinetic agent is amantadine, a multi-target drug with antagonistic activity at the N-methyl D-aspartate receptor (Fox et al., 2011), initially thought to produce only