

Brain, Cognition and MRI in MS: An Ongoing Refinement Process

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The frequency and importance of cognitive impairment in multiple sclerosis (MS) is well recognised¹. Domains of cognition most frequently affected are: episodic and working memory, attention, and speed of information processing. In this issue of the Journal, Feinstein et al describe their findings in a cohort of 62 MS patients evaluated for the relative importance of diffusion tensor imaging (DTI) derived indices of normal appearing white matter (NAWM) and grey matter (NAGM) on determining cognitive impairment². Their main finding is that fractional anisotropy (FA) of NAWM emerged as a significant predictor of cognitive impairment, adding to the variance derived from lesion and atrophy data. This means that cognitive impairment cannot be entirely explained by brain atrophy and T1 and T2 lesion volumes.

The authors explain in part their low percentage (18%) of cognitive impairment by a higher education level. A more common yield is 40%, but we are attaining similar low numbers in our MS population. This might reflect the fact that there is a trend towards a more benign course of MS, as has been the case in recent therapeutic trials. Feinstein's cohort includes early MS patients, in whom the ability to predict cognitive deficits by MRI parameters is of particular importance because of the profound impact of cognitive impairments on employment, autonomy, quality of life, and relationships¹, especially at a young age.

This work adds to an increasing amount of data showing that images obtained by magnetisation transfer ratio (MTR) can detect early damage even outside established lesions. A low MTR reflects several structural abnormalities, including diffuse astrocytic hyperplasia, patchy oedema, perivascular cellular infiltrates, abnormally thin myelin, and axonal damage, which reduce the mobility of protons³. Several studies³⁻¹² demonstrate the unique role of MTR as a marker of cognitive impairment.

Diffusion tensor imaging includes measures of mean diffusivity, which is affected by cell size and integrity, and of fractional anisotropy which indicates the degree of structural integrity and structural alignment within fibre tracts⁶. Several studies report an association between cognitive impairment (specific or global) and FA in the parenchyma¹³, the NAWM¹⁴, the fronto-lateral area¹⁵ and within the normal appearing corpus callosum¹⁶. The association between cognitive deficits and mean diffusivity in the NAGM¹⁷ and within the parenchyma¹⁸ has also been described. Most studies show a correlation between DTI indices and cognition^{19,20}. Other parameters, including the apparent diffusivity coefficient (ADC)^{15,21} and entropy¹⁸ were also associated with cognition. Another study has documented the role of cortical lesions in cognition impairment. Double inversion recovery allows visualization of cortical lesions. Cognitively impaired patients have a higher cortical lesion volume and decreased normalized neocortical gray matter volume, when compared with cognitively unimpaired patients²². Regional analysis revealed significant cortical thinning in frontal and temporal regions of RRMS patients without cognitive

impairment compared to normal controls, while a widespread pattern of cortical thinning was observed in patients with cognitive impairment²³. Decreased FA has been reported in the splenium of the corpus callosum²⁴.

The first attempts at correlating brain function and MRI concerned crude brain volumes: brain parenchymal fraction, third ventricle width, and T2 and T1 lesion volumes. It is now possible, by segmentation procedures, to image and measure separately and longitudinally, important structures involved in cognitive processes, such as the cerebral lobes, the thalamus, the hippocampus, the grey and white matter, and the corpus callosum, allowing for further refinement of correlating function and anatomy. In addition, tractography allows the following of axonal tracts that interconnect these structures¹⁴. Actual brain function can also be imaged by functional MRI. Spectroscopy can evaluate the degree of neuroaxonal integrity, by measuring levels of N-acetyl aspartate. Functional MRI has revealed that brain plasticity allows for compensatory mechanisms to lost functions. In short, MRI advances can now address the complexity of brain functioning. Cognitive impairment in MS results both from lesions to discrete areas, such as the hippocampus and thalamus, and from more diffuse lesions of GM and WM.

Recent pathological and MRI studies have unravelled the dynamics of tissue damage. The classical acute plaque is a stage of an evolving process. It is unknown at this time whether the initial damage is inflammatory or degenerative in nature. The primal lesions could involve the white or the grey matter. In subsequent stages, multiple components of both the innate and acquired immune response concur to damage not only myelin and oligodendrocytes, but axons and neurons as well. In the fully constituted plaque, macrophages invade tissue to phagocytise the cellular debris. In the more chronic phases, astrocytes proliferate, and fibrin is deposited. The plaque goes through cycles of activation and quiescence, inflammation spreading from the plaque rim. In the late progressive phases, diffuse microglial proliferation has been observed. The mechanisms of grey matter damage are still obscure. There is a plaque-like type of cortical lesion (types 1 and 2), and a more diffuse type which has been attributed to humoral factors (antibodies, cytokines, and chemokines) seeping down from the sub-arachnoid space into the superficial layers²⁵.

Given the apparent diversity and randomness of MS lesions, one could expect a variety of cognitive deficits in patients. Although there are some disparities among patients, a common pattern emerges of impairment of memory, attention and speed of information processing. There is then more homogeneity than diversity in cognition impairment. This is possibly a reflection of an underlying systematic spread of lesions of the WM and GM, masked by the ostensible disorganisation of plaques. Most MR images of MS brains show subcortical and periventricular lesions; indeed, such distribution is required for diagnostic

criteria. We can infer that these lesions disrupt, to varying degrees, tracts, both intra and intercortical, and intra and interhemispheric involved in brain connectivity, thus explaining disturbances of memory, attention and information processing, which depend on such connectivity. Longitudinal MR studies show progressive atrophy of the GM, thalamus and hippocampus, incompletely related to T2 lesion volume (linked to inflammation), a possible indication that a degenerative process, distinct from inflammation, runs its course, in parallel with immunologically-induced pathology.

We can expect that this process of increasing refinement of correlating cognition with anatomical lesions will accelerate. It will be important to study early MS cases, so as to intervene rapidly in order to lessen the dire consequences of lesions involving structures subserving cognition.

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*Céline Jobin, Pierre Duquette
Montréal, Québec, Canada*

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