The neurologist's dilemma: MS is a grey matter disease that standard clinical and MRI measures cannot assess adequately – Yes

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The title statement contains two separate claims: 1. ‘MS is a grey matter disease’, and 2. ‘[the grey matter part of] MS cannot be adequately assessed by standard clinical and MRI measures’. The first claim might be understood in more than one sense. For example, ‘MS is a grey matter disease’ might simply mean ‘MS pathology is found in areas that are anatomically referred to as “grey matter”, such as the cortex or the basal ganglia’. Alternatively, it may indicate ‘MS (partly, largely or wholly) affects grey matter elements, such as neurons, axons, dendrites, synapses, spines, etc.’ And finally, the statement may imply ‘MS is a disease that *starts* in the grey matter’ (i.e. either in grey matter areas or in grey matter structures, as defined above). The first and second interpretations of the first claim have been supported by solid empirical evidence. Demyelination is found in many (if not all) neocortical areas, as well as in palaeo- and archicortical structures such as the insula and hippocampus, in the basal ganglia, hypothalamus, cerebellar cortex and in the spinal cord grey matter.^{1,2} Furthermore, in the grey matter of MS patients, neuronal and synapse densities were found to be reduced, and axons and neurites are transected.³ Whether MS *begins* in the grey matter is far more difficult to prove. Both white and grey matter demyelination are present from the earliest phases of the disease,^{2,4} and definitive conclusions cannot be drawn at present as to whether MS *primarily* targets neuronal or glial elements within the brain. Of course, it is intriguing that the classical hypothesis, which states that MS is caused by an auto-immune, inflammatory demyelinating process (with axonal damage as a secondary effect), leaves us with some important explanatory gaps. For example, it does not explain why even the most potent anti-inflammatory drugs, while near-totally abrogating inflammation, are largely incapable of halting disease progression. Moreover, fairly recent *in vitro* and animal work, as well as human post mortem studies investigating early/acute demyelinating pathologies have come up with interesting examples of oligodendrocyte and myelin degeneration without a concomitant local adaptive immune response,⁵ as well as axonal pathology without demyelination.⁶ Whether these preliminary findings will prove to be

serious, or even fatal, impediments to the classical immunopathogenic model of MS is a question that is currently being carefully contemplated by an increasing number of groups.

To go back to the question of whether MS can be considered a grey matter disease, and in light of the anatomical, pathological, and aetiopathogenic issues discussed above, I would suggest narrowing the claim for now. MS is *also* a grey matter disease. As said, both white and grey matter pathology are present in the MS central nervous system right from the start of the disease, and although grey matter disease tends to become the more dominant pathology in chronic MS,^{2,4} critically renaming the disease at this point in time would, perhaps, be overly zealous. Acceptance of the evidence that MS is no longer a prototypical white matter disease, but in fact a ‘pan-degenerative’ disorder, is already quite the paradigm shift.

Then, let us consider the second claim. Is it true that grey matter pathology cannot be adequately assessed by standard clinical and MRI measures? Here, I would say ‘yes’ with more conviction. Of course, it depends on which techniques one would consider to be ‘standard’, but in terms of imaging, widely available conventional T2-weighted sequences are notoriously insensitive to (cortical) grey matter MS lesions.⁷ More advanced techniques like double inversion recovery (DIR) have shown better results,⁸ but these images are often difficult to read and are still far from standard use in daily clinical or radiological practice. Moreover, although detection of cortical MS lesions has improved using, for example, DIR, and this technique has a high pathological specificity, overall sensitivity is still quite poor.⁹ In many MS studies, grey matter atrophy measures are used to assess ongoing (neuro)degeneration, and it was consistently reported that grey matter atrophy is already present in early disease and becomes more prominent with

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progression.⁴ But again, although this imaging method appears to be a reliable and informative one to assess disease and/or treatment effects, image post-processing and specific expertise are required, and as such, measuring grey matter atrophy, like imaging grey matter lesions, cannot yet be considered standard practice.

As with imaging, the neurologist's dilemma also holds concerning clinical measures of MS grey matter pathology. Grey matter damage has been related to clinical disability and especially to cognitive impairment. It was even shown that physical disability and cognitive impairment are better explained by grey matter than white matter damage.^{10,11} However, cognitive deficits generally present heterogeneously in the clinic. Specialists from different fields (neurologists, neuro-psychologists, radiologists, pathologists) have been trying to find a satisfactory solution to the problem of what exactly constitutes cognitive decline in MS and, importantly, how it should be measured. Neuropsychological examinations tend to be lengthy and exhausting (to both patients and health care professionals) and interpretation of test results is challenging without highly specialized knowledge or without carefully considering potential confounders like physical disability, fatigue and mood, which are also not routinely assessed, nor in a standardized fashion.

So to sum up: is MS a grey matter disease? I would say it is a pan-degenerative disorder, with both white matter and (extensive) grey matter involvement. Both pathologies may variably determine physical and cognitive decline. Is grey matter pathology difficult to assess with standard imaging and MRI techniques? It most definitely is. Future scientific work should therefore strive towards facilitated implementation and interpretation of more advanced MRI techniques. Neuro(psycho)logists face the challenge of designing a cognitive testing battery that is both sensitive and specific, comprehensive but not too long, and applicable outside the specialized MS research setting. A challenge

roughly comparable to herding cats, but when has that ever stopped us from trying?

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