A Corticocentric Model For Multiple Sclerosis Pathogenesis

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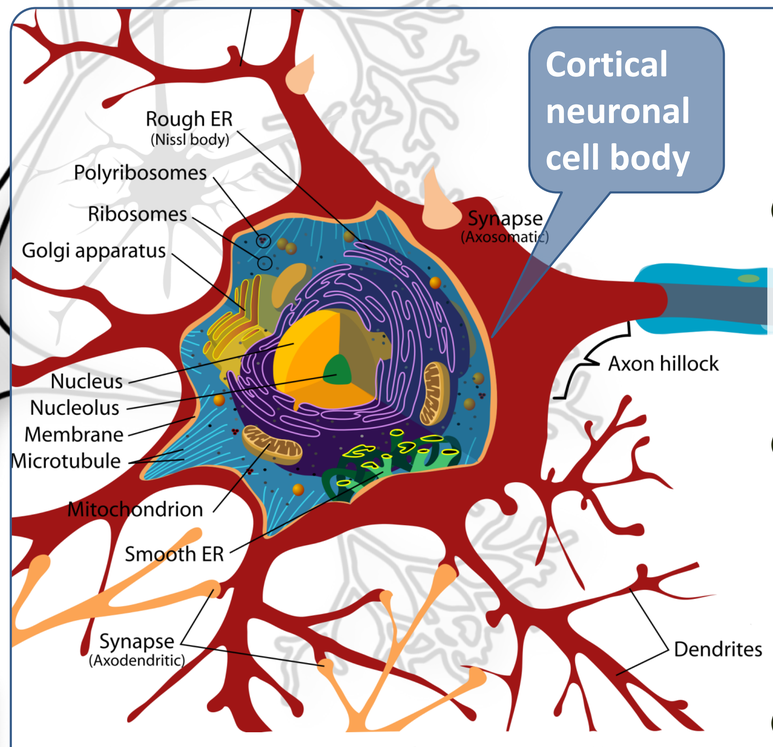
Cortical lesion load correlates with diffuse injury of normal appearing white matter

Background
Degeneration of central nervous system normal appearing white matter (NAWM) underlies disability and progression in multiple sclerosis (MS). Axon loss typifies NAWM degeneration.

Methods
Nineteen patients with MS underwent 7T magnetisation-prepared-rapid-acquisition-gradient-echo (MPRAGE), and magnetisation transfer ratio (MTR) brain MRI. Cortical lesions were identified using MPRAGE and MTR images of cortical ribbons (figures 1 and 2). White matter lesions (WMLs) were segmented using MPRAGE. WMLs were subtracted from white matter volumes to produce NAWM masks (figure 3). Pearson correlations were calculated for NAWM MTR vs. cortical lesion load, and WML load.

Results
Cortical lesion volumes and counts had significant correlation with NAWM mean MTR. The strongest correlation was with cortical lesion volumes obtained using MTR images ($r = -0.6874$, $p = 0.0006$; figure 4). WML volume had no significant correlation with NAWM mean MTR ($r = -0.08706$, $p = 0.3615$).

Conclusion
Our findings implicate cortical lesions in the pathogenesis of NAWM axon loss, which underpins long-term disability and progression in MS.

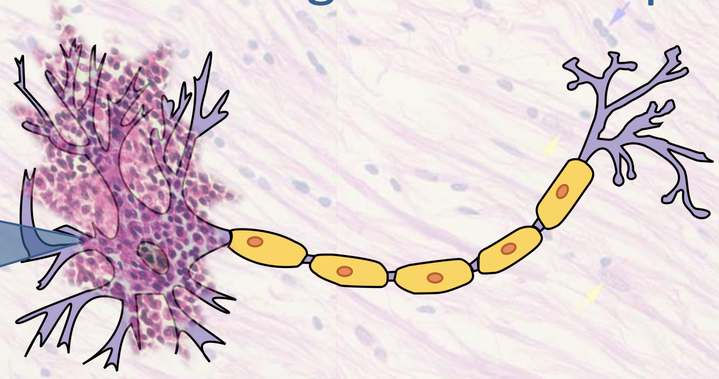


Effect of cortical lesion load

- Cortical lesions are less focally destructive than WMLs, but the remote effects could still be significant.
- Most central nervous system (CNS) neurons cannot divide mitotically and must therefore last a lifetime; this necessitates maintenance and repair.
- Most of the proteins, vesicles, and organelles (including all-important mitochondria) required for axon survival are synthesised in the cell body (housing the neuron's nucleus and ribosomes), and then transported along the axon as needed.
- The majority of CNS neurons' cell bodies reside in the cortex.
- Even if an inflammatory demyelinating cortical lesion only modestly impairs activity within a neuronal cell body, this could still lead to the eventual demise of its axon, if the rate of maintenance falls below that required.
- CNS neurons are among the most metabolically demanding cells in the body.
- The longest axons (e.g. corticospinal tract) maintain cellular processes up to a metre away from their cell bodies, and could be the worst affected if their cell bodies are perturbed by cortical lesions.

A "two-hit" mechanism might better explain severity of white matter lesion axon loss

First hit:
Cortical lesion impairing cellular processes and axonal resilience in those neurons that survived it.



Second hit:
White matter lesion more likely to transect those neurons that already endured cortical insult.

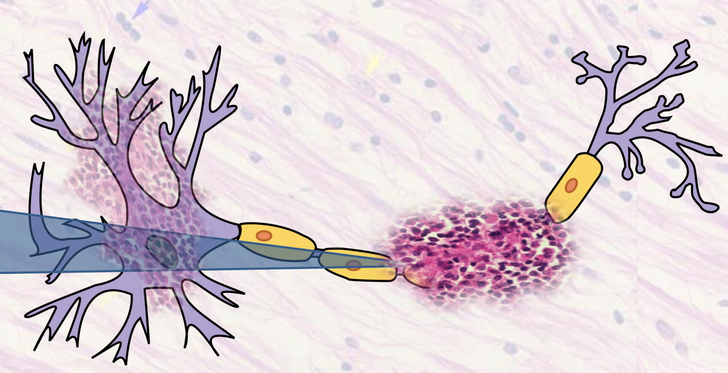


Figure 1. Examples of cortical lesions

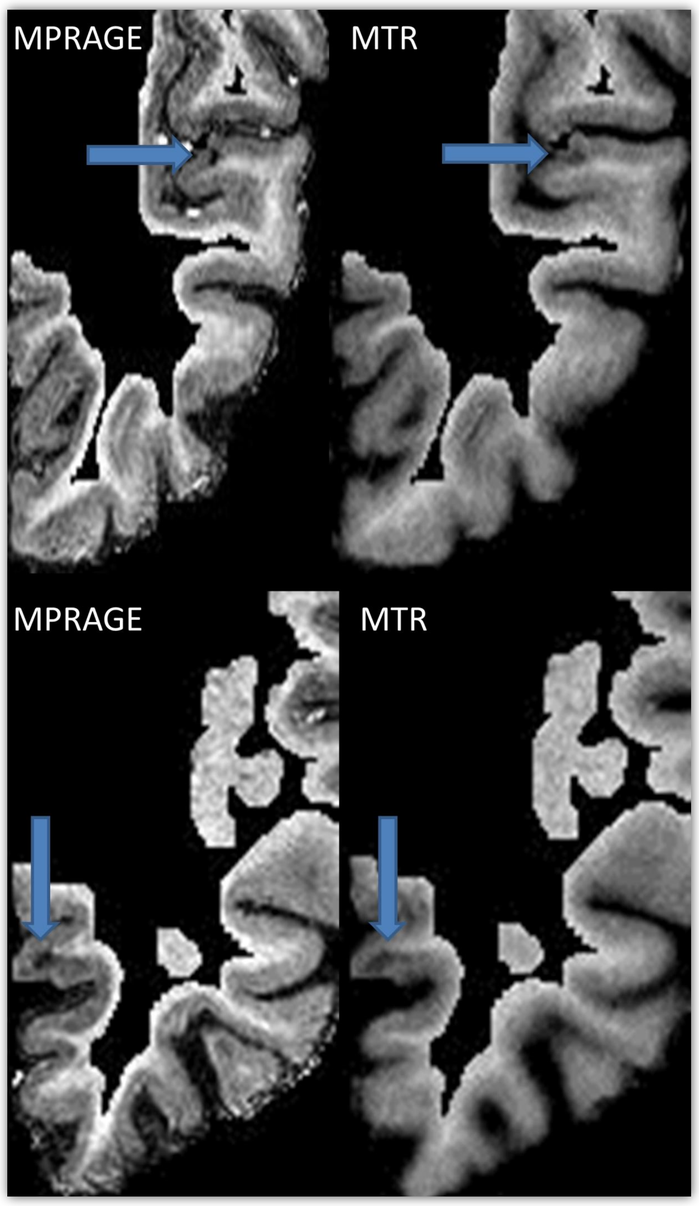


Figure 1 legend:
Two cortical lesions are shown, in each case using MPRAGE on the left, and MTR on the right.
MPRAGE = magnetisation prepared rapid acquisition gradient echo; MTR = magnetisation transfer ratio

Figure 2. MTR cortical lesion counts vs. MPRAGE cortical lesion counts

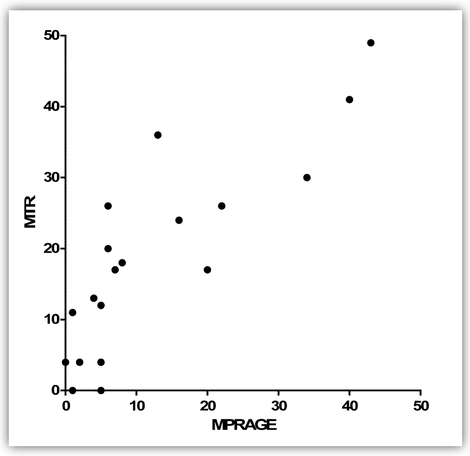


Figure 2 legend:
Often more cortical lesions were found using MTR than MPRAGE images. Whilst a difference in sensitivity is to be expected (since the contrast mechanisms of MTR and MPRAGE are independent), a plot of MTR vs. MPRAGE counts appears to intercept the origin. Therefore, though the sensitivity of MTR and MPRAGE for cortical lesions differs (and in neither case is likely to be 100%), they both yielded counts proportional to the true lesion load.

Figure 3. NAWM segmentation

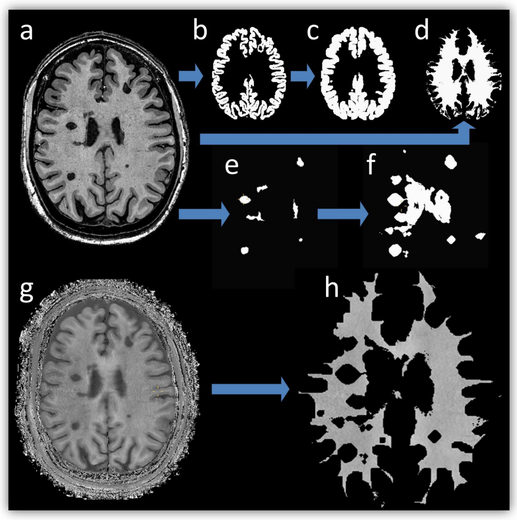


Figure 3 legend:
MPRAGE volumes (a) were automatically segmented to produce cortical ribbons (b) and white matter segments (d). Cortical ribbons were dilated to produce cortical masks (c), which were subtracted from MPRAGE images (a) prior to manual segmentation of WMLs (e). WML maps were 3D dilated by 5 voxel layers (f), to encompass beyond-edge-effects in proximity to lesions. White matter segment masks (d) were applied to the MTR volumes (g), which had been co-registered to the MPRAGE. The resultant MTR white matter volumes were pruned by subtracting dilated cortical masks (c) and dilated WML maps (f), yielding a NAWM MTR volume (h).

MPRAGE = magnetisation prepared rapid acquisition gradient echo; WML = white matter lesion; MTR = magnetisation transfer ratio; NAWM = normal appearing white matter

Figure 4. NAWM MTR vs. MTR cortical lesion load

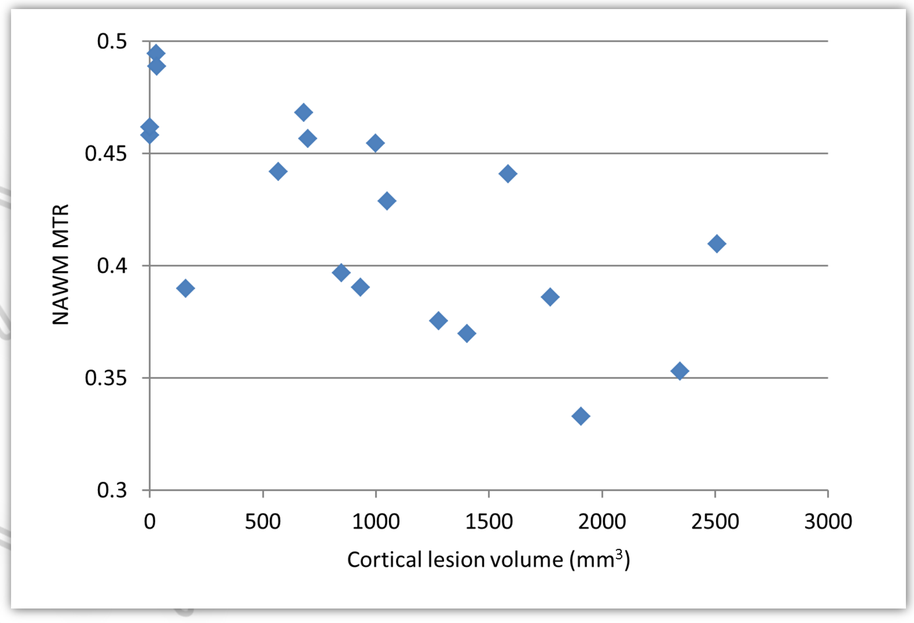


Figure 4 legend:
Scatter plot showing mean MTR of the NAWM vs. cortical lesion load (total cortical lesion volume).

MTR = magnetisation transfer ratio; NAWM = normal appearing white matter; MPRAGE = magnetisation prepared rapid acquisition gradient echo