Identification of Cortical Pathology in Multiple Sclerosis with 7T MRI

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TARGET AUDIENT: Radiologists, neurologist, physicians, MR physicists.

PURPOSE:

Limited resolution and contrast make it difficult for conventional MRI techniques to detect the millimeter to sub-millimeter scale pathological changes occurring with neocortical lesions (NLs) in multiple sclerosis (MS). In the present study we performed high resolution R2* mapping at 7T to: (1) visualize NLs in MS brain; and (2) assess the sensitivity of ME-GRE in detecting NLs compared to myelin and iron staining.

METHODS:

MRI: Brain slices of two donors who died at the stage of secondary progressive MS were imaged in specially fabricated tissue containers with 4% formalin solution. Scans were acquired using a whole body GE Sigma 7T MRI scanner using a dedicated 24-channel receive-only array. 3D T2*-w ME-GRE was performed with echo times = 8.7, 25.2, 41.7, and 58.2 ms; repetition time = 200 ms; spatial resolution = 0.21mm isotropic; flip angle = 20º, and bandwidth = 62.5 kHz. Quantitative R2* maps were obtained using single exponential fitting to the TE-dependent signal level.

Histology: After scanning, immunohistochemical staining for myelin (PLP) and Turnbull blue staining for iron were performed on 16 tissue sections and results were compared with MRI. Areas of demyelination were manually outlined and color-coded with green (complete WM demyelination) or blue (incomplete WM demyelination) or pink (complete GM demyelination) or yellow (incomplete GM demyelination). Iron densitometry was performed on the slides stained for non-heme iron. NLs were identified and classified on both MRI and histology according to their locations[1]: Type-I (leukocortical NL) involves both GM and WM; Type-II (intracortical NL) lies entirely in the cortical GM, without touching the pial surface; Type-III (subpial NL) lies entirely in GM, and touching the pial surface.

RESULTS:

Excellent MRI contrast between GM and WM and across the cortex was observed in R2* maps (Fig 1, inset shows intensity profile across cortex outlined with yellow box). A total of 93 NLs were identified on the two brain samples with 45 Type-I (48%), 37 Type-II (40%) and 11 Type-III (12%) NLs. Fig 2 shows examples of NLs identified by R2* prospectively (red arrow) and retrospectively (blue arrow). Generally, the PLP staining showed more extensive demyelination, an example of which can be seen in the areas indicated by black arrow and rectangle point in Figs 2A and B respectively. In the two brains we studied, MRI reached a retrospective sensitivity of 66% in detecting NLs compared to PLP staining. No MRI signal changes suggesting elevated iron (i.e., focal R2* increases) were observed. Quantitative analyses by optical densitometry showed iron content to be lower in demyelinated NLs than the adjacent normal appearing gray matter (NAGM) in both brains (Fig 3).

DISCUSSION:

Our data suggested that detection of cortical lesions might be improved substantially with susceptibility contrast at high field as compared with conventional (T1, T2) contrast at low field. A previous study performed at lower field strength found a detection sensitivity of 18%[2], substantially lower than the 66% found in our study. Our observations further indicate that lesion size may not be the main factor contributing to the difference in ability of histology and MRI to detect lesions. For several subpial NLs extending over relatively large surfaces of the cortex, we observed MRI maps successfully identifying only a very small portion of these areas. This limited sensitivity may have a variety of causes. Importantly, laminar R2* contrast varies considerably across functional regions[3], which compromises the detection of changes associated with large NLs that bridge these functional regions. . In addition, it may be that R2* loss in some NLs by be limited due to lingering presence of remaining breakdown products of myelin[4]. The fact that no iron increases were seen in any of the NLs is somewhat surprising considering the widely reported association of iron with MS lesions in WM[5]. This may point to a different disease mechanism, or a more efficient removal of myelin associated iron from the tissue following breakdown of myelin in GM versus WM.

CONCLUSION:

Post mortem studies of two brains from progressive MS patients show that, compared to myelin histology, R2* contrast at high field allows moderate to good (66%) sensitivity for the detection of NLs but often underestimates their spatial extent. Although this contrast may offer improved detection sensitivity compared to conventional contrasts, it continues to underestimate the full extent of the disease.

REFERENCES: [1] Peterson JW et al. Ann Neurol. 2001 50:389-400; [2] Seewann A et al. Neurology. 2012 78:302-8; [3] Fukunaga M et al. PNAS 2010 107:3834-9; [4] He X, et al. PNAS 2009 106:13558-63; [5] Forge JK et al. Life Sci. 1998 63:2271-84; [5] Yao B et al. Radiology 2012 262:206-15.

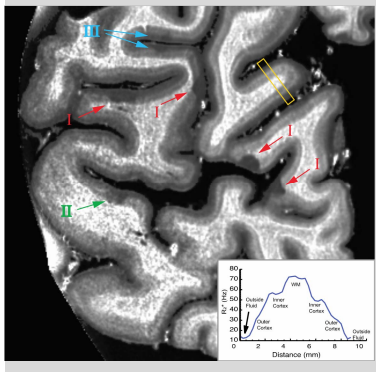

Fig 1: *Examples of NLs on R2*. Red arrow: type-I NL; Green: type-II NL; Cyan: type-III NL.*

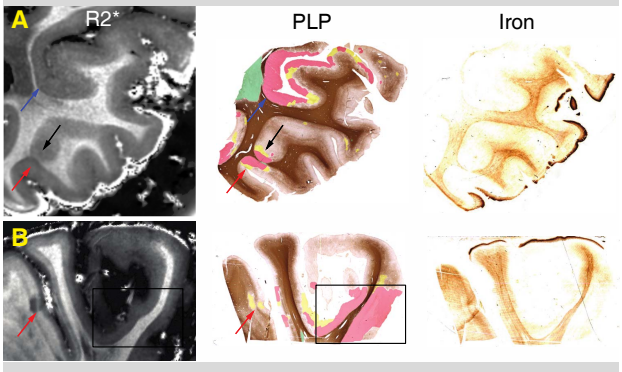

Fig 2: *Examples showing NLs identified by R2* prospectively (red arrow) and retrospectively (blue arrow) or barely visible (black arrow or rectangle).*

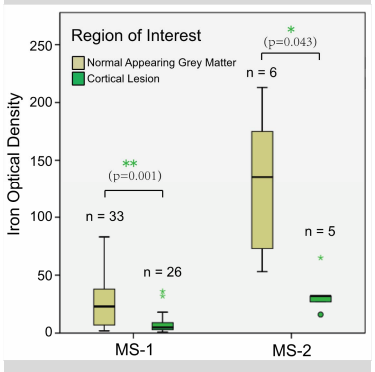

Fig 3: *Differences in iron content between NLs and NAGM in two MS brain cases.*