

Introduction

- Gadolinium (Gd)-based meningeal enhancement (ME) on post-contrast FLAIR MRI is an investigational biomarker in multiple sclerosis (MS), possibly linked to meningeal inflammation or glymphatic/lymphatic drainage.^{1,2} Leptomeningeal enhancement (LME) is associated with cortical thinning,³ suggesting a pathologic link between the two.
- Initial studies in MS on 3T MRI showed that LME is not present when evaluated using 2D acquisitions,³ but with a 3D acquisition and a time delay after contrast administration, Gd+ LME is seen in ~ 25% of participants with MS.¹
- Our group and others have subsequently shown that 7T MRI protocols visualize LME in up to 60 – 90% of people with MS,^{3,5} in addition to nearly all those imaged having evidence of regions of perivascular or dural enhancement (PDE).⁶
- Put together, these studies suggest that the ideal protocol for visualization of ME in MS may be use of both 7T MRI and a time delay after contrast administration. In this study, we aimed to evaluate this hypothesis by directly comparing magnetic field strengths and time delays after Gd administration in a cohort of MS subjects.

Methods

- Participants with MS were recruited from the University of Maryland Center for MS treatment and research.
- MRI of the whole brain was performed on a 7T Philips Achieva scanner equipped with a multi-channel transmit/32 channel receive head coil (NovaMedical, Wilmington MA). Within 2 weeks of the 7T scan, another MRI of the whole brain was performed on a 3T Siemens Magnetom Prisma^{FI}T scanner equipped with a 64-channel head/neck receive only coil and a body coil for transmission.
- A 3D FLAIR image was acquired on the 7T machine with the following parameters: TR 3000 ms, TI delay 2200 ms, TE 300 ms, FA 70 degrees, SENSE 2.5 x 3.0, 0.50 x 0.49 x 0.49 mm³ reconstructed resolution, 9:04 min:sec.
- For post-contrast imaging on the 7T scanner, FLAIR was again initiated within 1 minute of injection of 0.1 mmol/kg of gadolinium (Gd+ Early 7T FLAIR) and again starting ~22 minutes after Gd injection (Gd+ Delayed 7T FLAIR).
- A 3D FLAIR image was acquired on the 3T machine with the following parameters: TR 5000 ms, TI 1800 ms, TE 390 ms, variable FA, GRAPPA 2, 0.5 x 0.5 x 1.0 mm³ reconstructed resolution, 7:27 min:sec.
- For post-contrast imaging on the 3T scanner, FLAIR was again repeated ~21 minutes after Gd injection (Gd+ Delayed 3T FLAIR).
- All images were co-registered to a separately acquired T1-weighted 7T MP2RAGE image.
- Subtraction maps were created as [Gd+ FLAIR intensity - Gd- FLAIR intensity] at each voxel.
- Each image protocol for each subject was reviewed independently for ME in a random order. See Figures 1 and 2 for examples of the process. Hyperintensities noted on subtraction maps were confirmed as enhancing on pre- and post-contrast images. Enhancement at the pial surface or subarachnoid space was labelled as LME. Perivascular enhancement surrounding cortical/dural vessels and nodular areas of enhancement within the dura or around dural sinuses were all labelled as PDE.

- Counts and proportions of each foci type were calculated. Counts and proportions compared between groups using paired t-test.

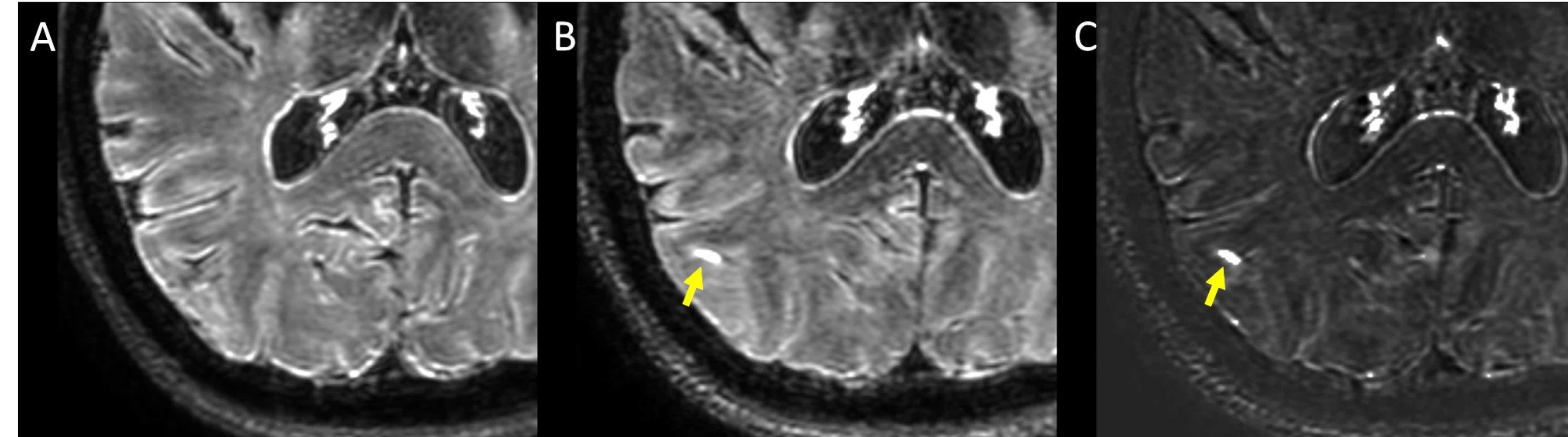


Figure 1: Process for identification of LME. Shown is an example of leptomeningeal enhancement (LME, yellow arrow). To identify such foci, co-registered pre-Gd FLAIR (A), Gd+ FLAIR (B), and subtraction (Gd+ minus Gd- (C)) were reviewed. Regions of hyperintensity on subtraction maps were confirmed on anatomic images and labelled as LME if present in the leptomeninges (pia, subarachnoid).

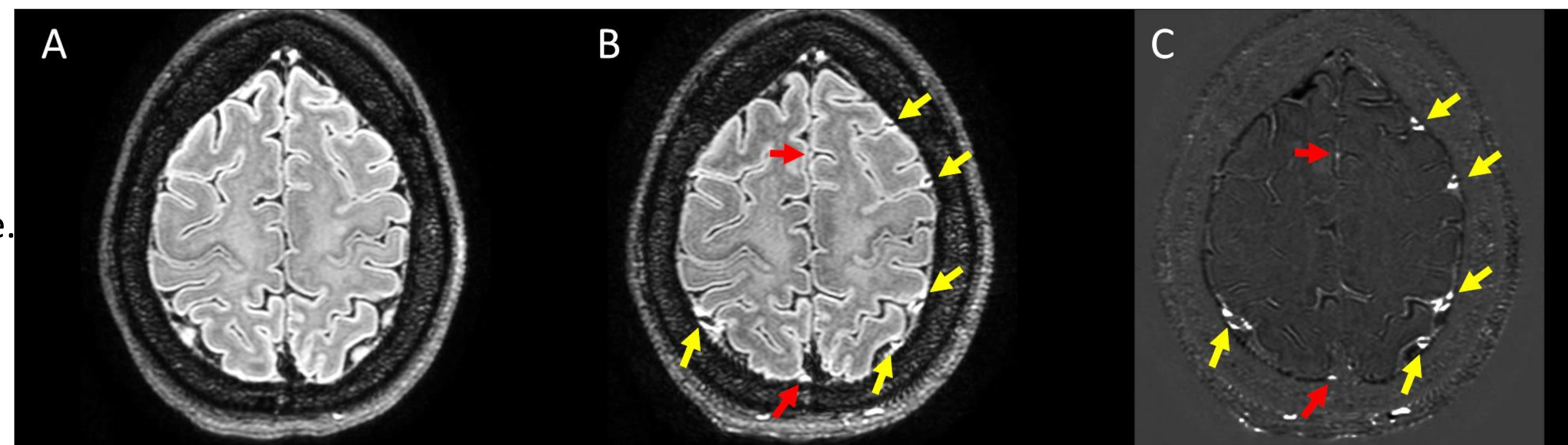


Figure 2: Process for identification of PDE. Shown are an examples of perivascular/dural enhancement (PDE). To identify such foci, co-registered pre-Gd FLAIR (A), Gd+ FLAIR (B), and subtraction (Gd+ minus Gd- (C)) were reviewed. Regions of hyperintensity on subtraction maps were confirmed on anatomic images. Hyperintensities surrounding large dural/cortical veins (as visualized by a central flow void) were labelled as perivascular (yellow arrows). Nodule-like hyperintensities in dura or adjacent to dural sinuses (red arrows) were labelled as dural enhancement. Together, these two foci were categorized as PDE.

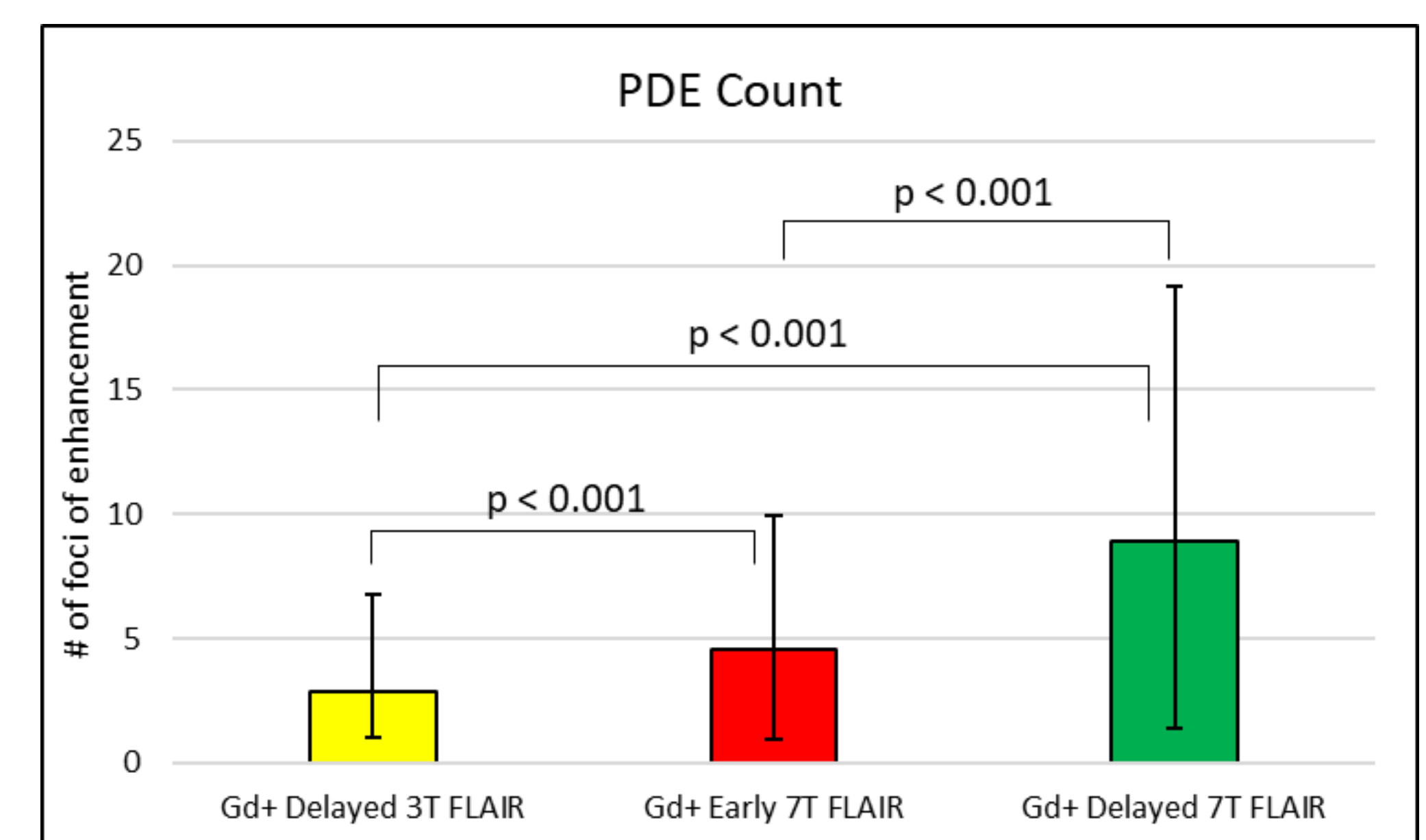
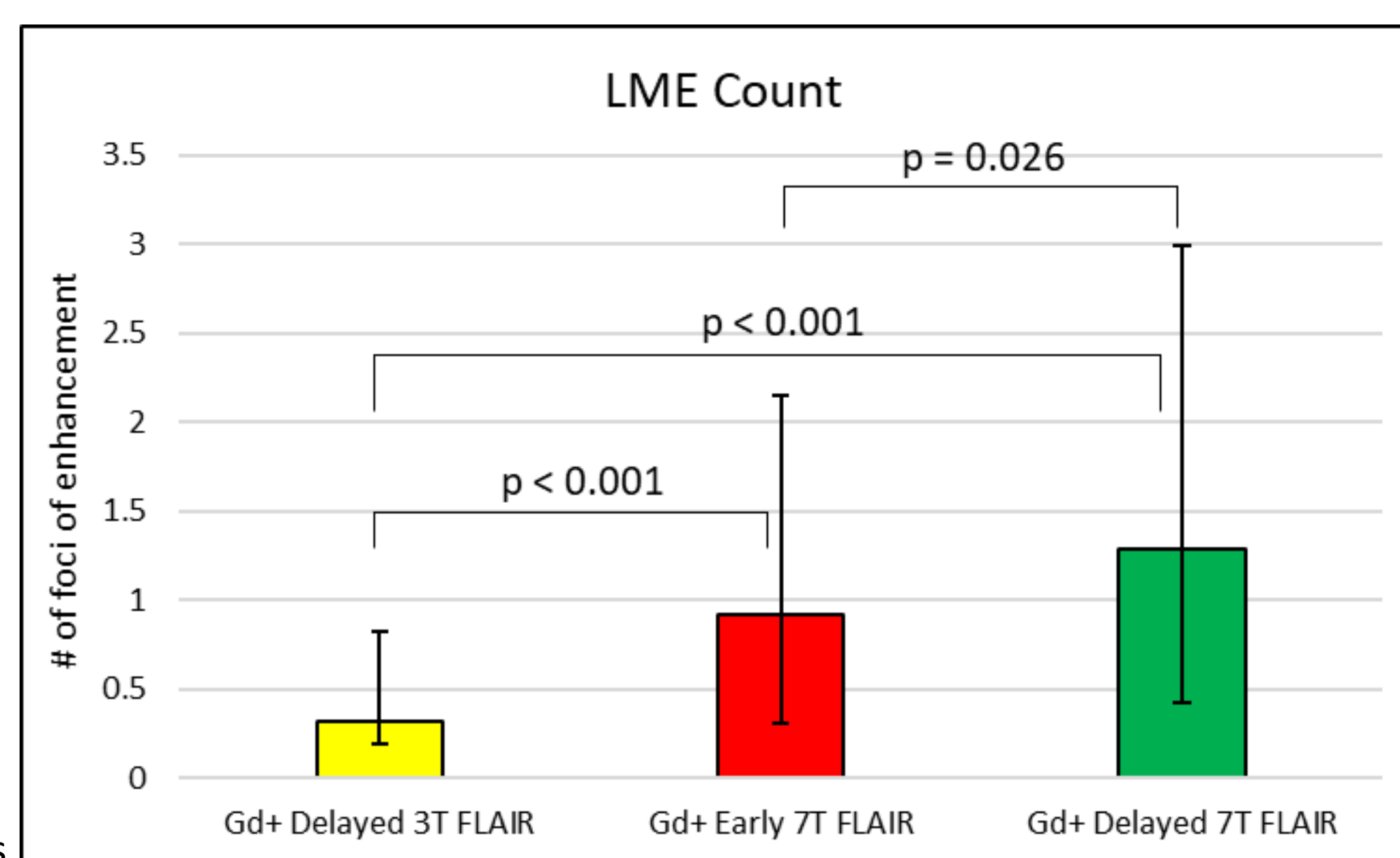
Results

Characteristic	MS Participants (n = 84)
Age, mean (SD)	45.8 (10.1) years
Sex	
Female (%)	59 (70.2%)
Male (%)	25 (29.8%)
MS Subtype	
RRMS (%)	69 (82.1%)
SPMS (%)	8 (9.5%)
PPMS (%)	7 (8.3%)
On MS treatment (%)	67 (79.8%)
# relapses in prior 12 months, median (range)	0 (0 – 3)
EDSS score, median (range)	2.75 (0 – 6.5)
SDMT # correct, mean (SD)	54.7 (15.3)

Table 1: Demographic and clinical characteristics of study population. SD = standard deviation. RRMS = relapsing-remitting MS. SPMS = secondary progressive MS. PPMS = primary progressive MS. EDSS = Expanded Disability Status Scale, SDMT = Symbol Digit Modalities Test. Note: only 51 participants had paired 3T scans, so, 3T vs. 7T comparisons are restricted to those subjects.

Protocol	LME + (n, (%))	PDE + (n, (%))
Gd+ Delayed 3T FLAIR	10 (19.6%)*†	32 (62.8%)*†
Gd+ Early 7T FLAIR	38 (45.2%)*	72 (85.7%)*
Gd+ Delayed 7T FLAIR	46 (54.8%)	83 (98.9%)

Table 2 (left): Proportion of participants with LME or PDE per imaging protocol. Shown is the number and % of participants with at least one focus of LME or PDE seen on the Gd+ Delayed 3T FLAIR, Gd+ Early 7T FLAIR, and Gd+ Delayed 7T FLAIR protocols. * = p < 0.001 compared to Gd+ Delayed 7T FLAIR † = p < 0.01 compared to Gd+ Early 7T FLAIR. Gd+ = gadolinium enhanced, LME = leptomeningeal enhancement, PDE = perivascular or dural enhancement



Figures 3 and 4 (above): Number of participants with LME or PDE per imaging protocol. Shown are the results of paired t-test comparisons between the number of enhancing foci Gd+ Delayed 3T FLAIR or Gd+ Early 7T FLAIR with Gd+ Delayed 7T FLAIR.

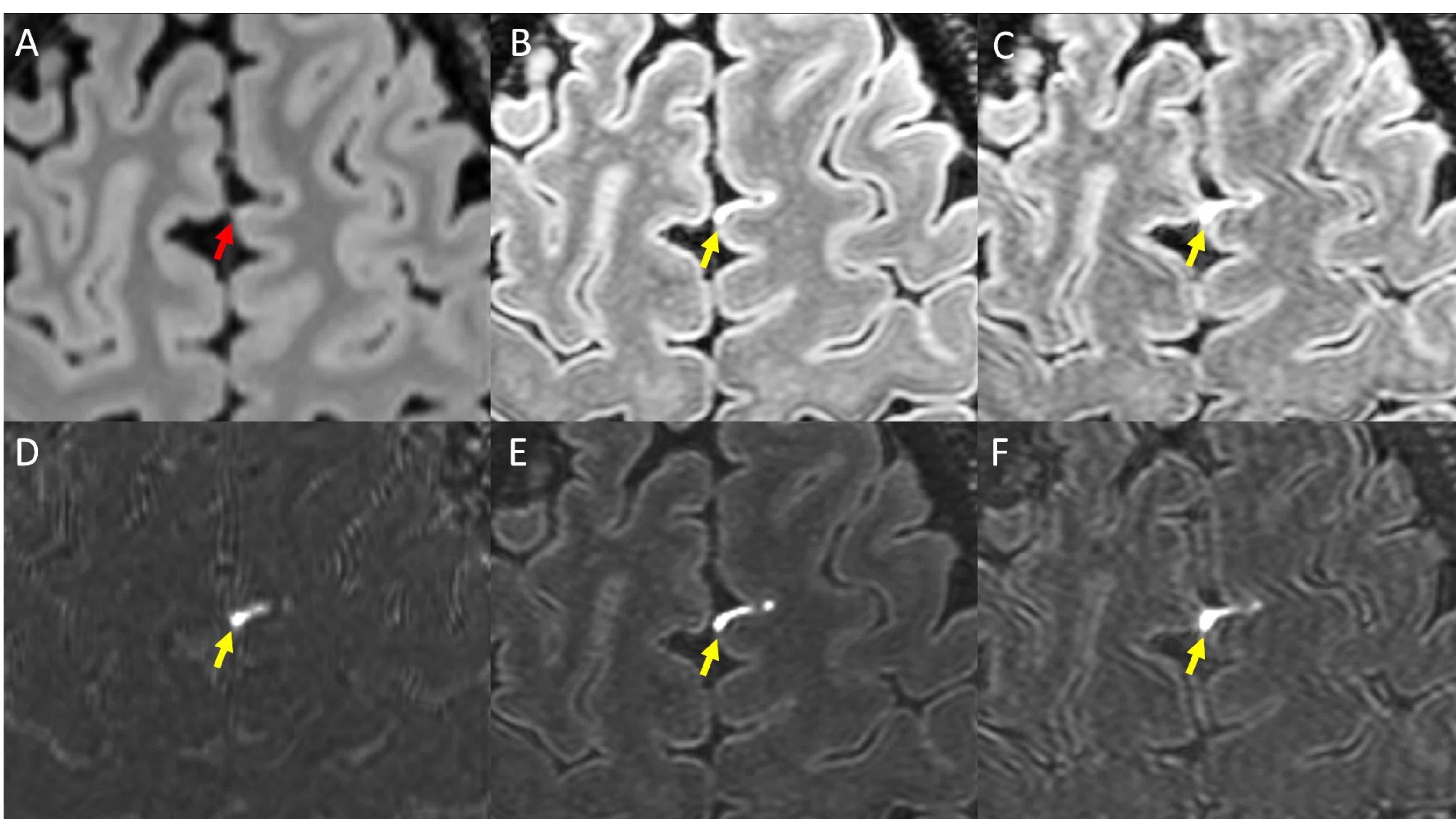


Figure 5: Example of LME as visualized on various Gd+ imaging protocols. Shown is Gd+ Delayed 3T FLAIR (A), Gd+ Early 7T FLAIR (B), and Gd+ Delayed 7T FLAIR (C). Also shown are subtraction maps associated with each (D, E, F, respectively). Yellow arrows indicate a focus of LME readily visible, but which is barely visible on Gd+ Delayed 3T FLAIR (red arrow). Note that although the focus is seen on Gd+ Early 7T FLAIR (B, E), it is thicker/more prominent on Gd+ Delayed FLAIR (C, F).

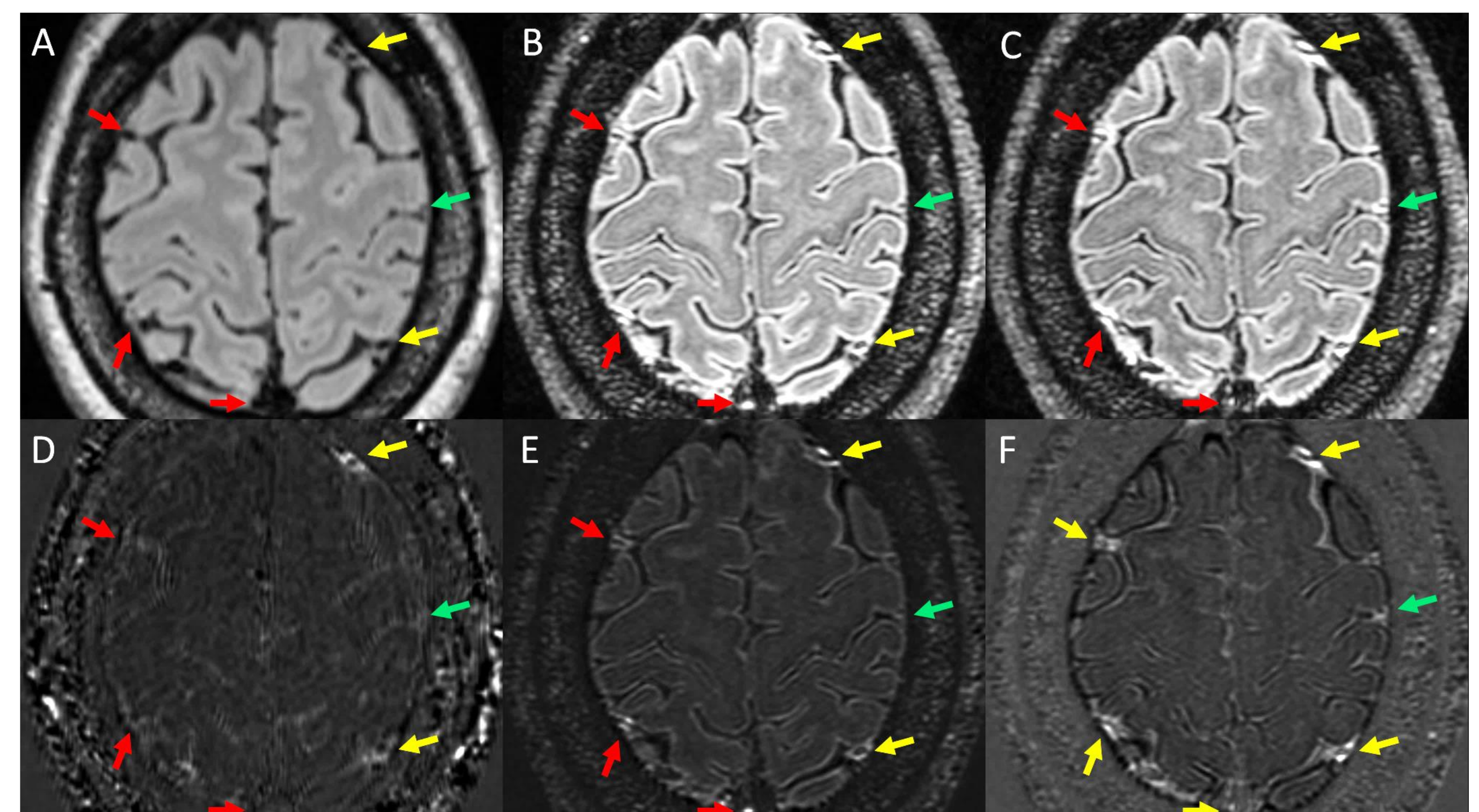


Figure 6: Examples of PDE as visualized on various Gd+ imaging protocols. Shown is Gd+ Delayed 3T FLAIR (A), Gd+ Early 7T FLAIR (B), and Gd+ Delayed 7T FLAIR (C). Also shown are subtraction maps associated with each (D, E, F, respectively). Yellow arrows indicate foci of PDE seen on all 3 protocols. Red arrows indicate regions where PDE was seen on both 7T protocols but not on Gd+ Delayed 3T FLAIR. Green arrows indicates a region where PDE was seen on Gd+ Delayed 7T FLAIR but could not be seen on Gd+ Delayed 3T FLAIR or Gd+ Early 7T FLAIR.

Conclusions

- Compared to Gd+ Delayed 3T FLAIR and Gd+ Early 7T FLAIR, Gd+ Delayed 7T FLAIR had the greatest sensitivity for visualization and quantification of both LME and PDE.
- These results suggest that ME in MS is sensitive to both field strength and the timing of acquisition after contrast administration.
- Thus, Gd+ Delayed 7T FLAIR should be the 'gold standard' for studies hoping to better understand the pathologic and clinical implications of ME in MS and evaluate for potential treatment response.

References

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