Appendix

The data required to apply our techniques on a scan are the following:

1) A T1-weighted brain image (1.5T or 3T)
2) A T2-weighted brain image registered to the T1-weighted image
3) A T2-weighted FLAIR brain image registered to the T1-weighted image
4) A brain mask that discriminates between cerebral and extracerebral voxels (from a skull-stripping algorithm such as that described in Carass et al[13]).

The first step of our algorithm is normalization. We denote the voxel intensities by $T_{1,RAW}(v)$, $T_{2,RAW}(v)$, and $T_{2F,RAW}(v)$ from the raw T1-weighted, T2-weighted, and FLAIR images, respectively, for voxels $v = 1, \ldots, V$ in the brain. The normalized intensities are calculated as

$$T_1(v) = \frac{(T_{1,RAW}(v) - \hat{\mu}_{1,RAW})}{\hat{\sigma}_{1,RAW}},$$

where

$$\hat{\mu}_{1,RAW} = \frac{1}{V} \sum_{v' \epsilon v} T_{1,RAW}(v'),$$

and

$$\hat{\sigma}_{1,RAW} = \frac{1}{V-1} \sum_{v' \epsilon v} (T_{1,RAW}(v') - \hat{\mu}_{1,\mathrm{RAW}})^2,$$

and

$$T_2(v) = \frac{(T_{2,RAW}(v) - \hat{\mu}_{2,RAW})}{\hat{\sigma}_{2,RAW}},$$

where

$$\hat{\mu}_{2,RAW} = \frac{1}{V_{2,TRIM}} \sum_{v' \epsilon v_{2,TRIM}} T_{2,RAW}(v'),$$

and

$$\hat{\sigma}_{2,RAW} = \frac{1}{V_{2,TRIM-1}} \sum_{v' \epsilon V_{2,TRIM}} (T_{2,RAW}(v') - \hat{\mu}_{2,RAW})^2,$$

and

$$V_{2,TRIM} = \{v' \epsilon V : v' < T^{0.95}_{2,RAW}\}$$

where $\mathrm{T}^{0.95}_{2,\mathrm{RAW}}$ is the 95th percentile of the observed $\mathrm{T}_{2,\mathrm{RAW}}$.

Similarly, we let the normalized FLAIR values be

$$T_{2F}(v) = \frac{(T_{2F,RAW}(v) - \hat{\mu}_{2F,RAW})}{\sigma_{2F,RAW}},$$

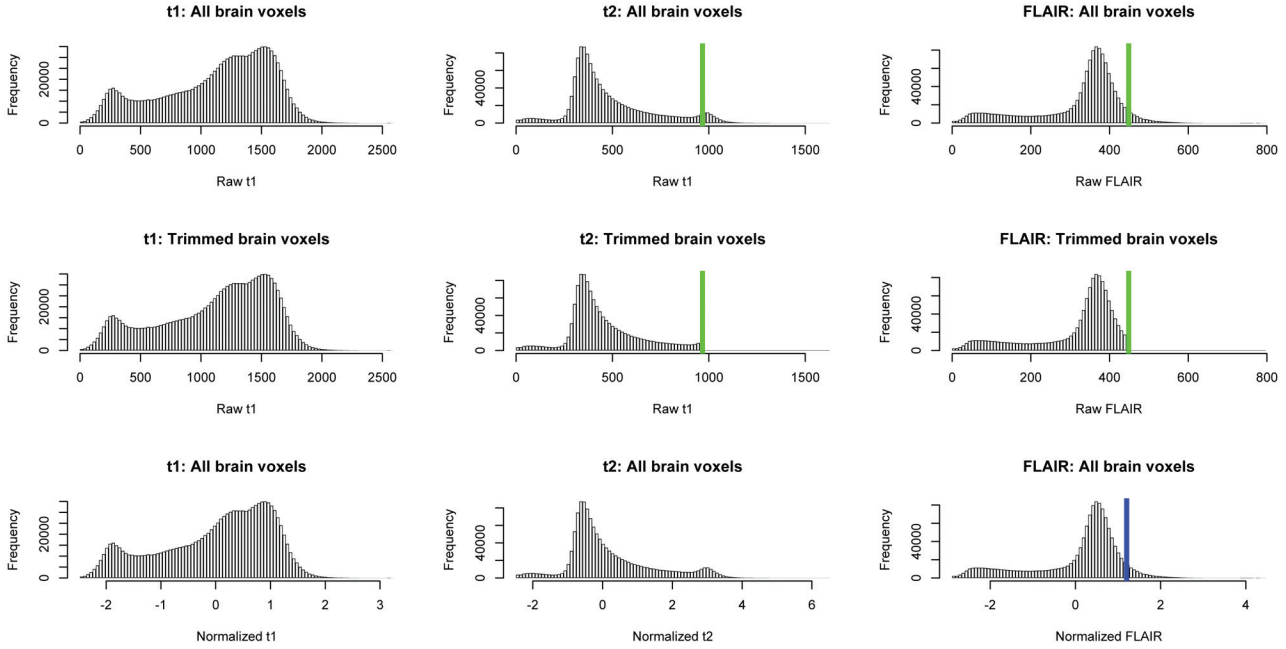
where

$$\hat{\mu}_{2F,RAW} = \frac{1}{V_{2,TRIM}} \sum_{v' \epsilon V_{2F,TRIM}} (T_{2F,RAW}(v') - \hat{\mu}_{2F,RAW})^2,$$

and

$$\hat{\sigma}_{2F,RAW} = \frac{1}{V_{2,TRIM-1}} \sum_{v' \epsilon V^{v}_{2F,TRIM}} (T_{2F,RAW}(v') - \hat{\mu}_{2F,RAW})^2,$$

and $\mathrm{V}_{2\mathrm{F,TRIM}} = (\mathrm{v}' \epsilon \mathrm{V} : \mathrm{v}' < \mathrm{T}^{0.95}_{2\mathrm{F,RAW}})$, where $\mathrm{T}^{0.95}_{2\mathrm{F,RAW}}$ is the 95$^{\mathrm{th}}$ percentile of the observed $T_{2F,RAW}$.



On-line Fig 1. Histograms of the raw and normalized T1-weighted, T2-weighted, and T2-weighted FLAIR intensities for 1 subject. The top rows show voxels from the whole brain, with green vertical lines indicating the trimming cut-points. The second row shows the data after trimming; the mean and SD of the trimmed data were used for normalization. The third row shows the normalized values. The blue vertical line corresponds to the 99th percentile of the FLAIR intensities, which was used to define candidate lesion voxels.