Supplementary materials for:Intensity warping for multisite MRI harmonization

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1. Schematic of *mica* method

Figure (1) shows a schematic of the *mica* process: images were bias corrected and skull-stripped, voxel-intensities were converted to CDFs, CDFs were

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aligned, and warping functions from CDF alignment were used to generate harmonized images.

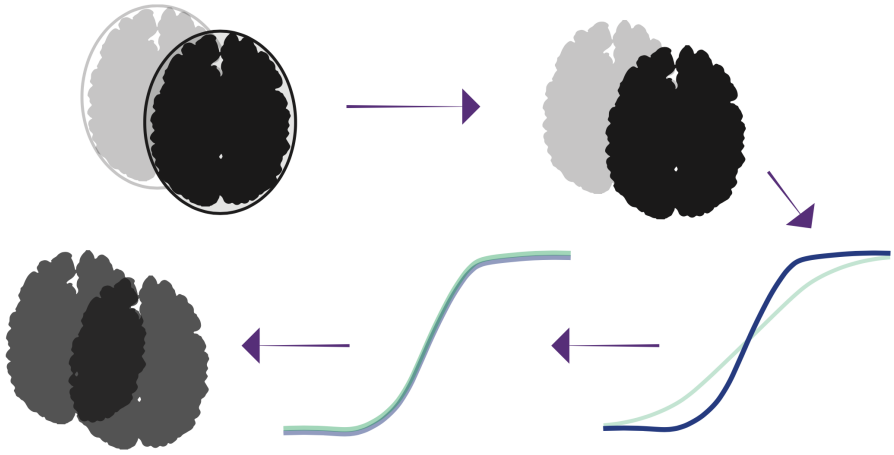

Figure 1: Harmonization pipeline. Raw images are N4 bias-corrected, skull-stripped, voxel intensities are converted to CDFs, CDFs are aligned by warping intensity values. The transformation of intensity values that produces this alignment is called a warping function, and the nonlinear transformation is applied to the raw images to produce harmonized images.

2. Expansion of manuscript Figure 1

Figure 2 adds two panels to Figure 1 in the manuscript: a panel showing the histograms after White Stripe only and a panel showing the histograms after *mica* without White Stripe or other intensity normalization. This Figure shows that both *mica* alone and White Stripe alone remove some scanner effects in the NAIMS data. With *mica* alone, the histograms are well aligned, but the final intensity domain depends on the scan chosen as the reference. With White Stripe alone, the intensities are in units of normal appearing white matter, but some areas of the histograms (lower intensity values, gray matter) are not well aligned. *mica* plus White Stripe combines the superior histogram alignment of *mica* with the voxel intensity unit interpretability of White Stripe.

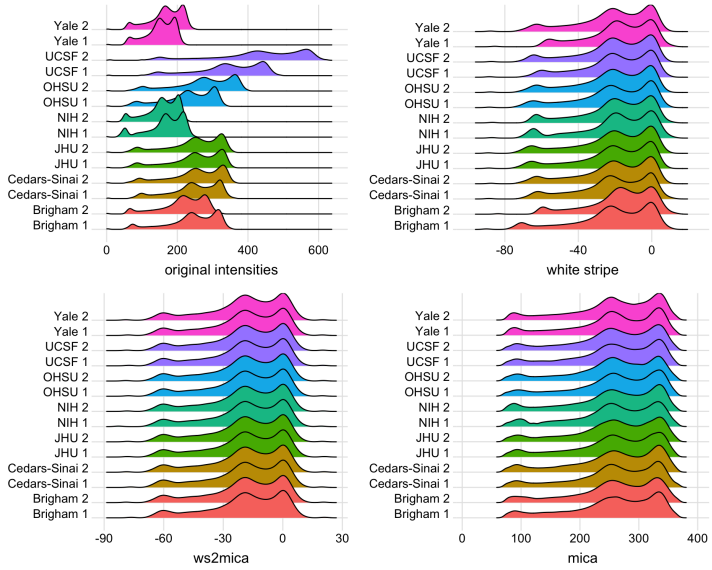

Figure 2: Histograms of NAIMS data for unnormalized and unharmonized images, White Stripe normalized images, *mica* harmonized images, and images that have been processed using White Stripe and *mica*.

3. PDFs of trio2prisma images across methods

Figure (3) shows probability distribution functions (PDFs) of voxel intensities under different image harmonization and intensity normalization scenarios.

4. Sensitivity of leave N scans out

In order to understand how quickly the intensity warping function used to account for scanner effects stabilizes as the number of scans, N, used to construct this warping function increases. To examine this in the context of the *trio2prisma* study, we performed the following experiment.

1. Select 1 of the 10 subjects from the *trio2prisma* dataset. For number of scans $n \in 1:9$:
   (a) Choose N subjects randomly from the remaining sample. For $N = 9$ this is the *mica-loso* process previously described.

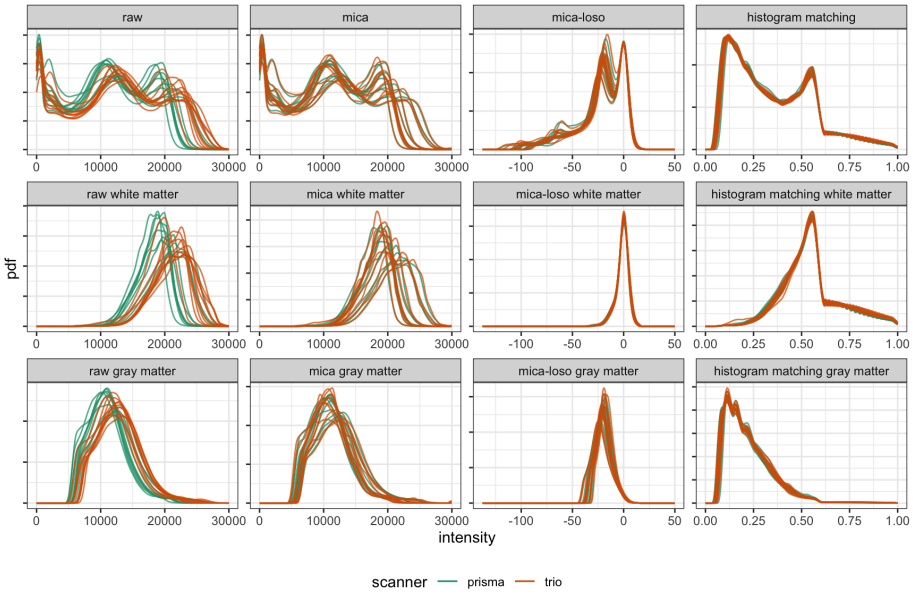

Figure 3: Histograms of intensities before and after harmonization by tissue type in the trio2prisma study. Rows indicate tissue type, with whole brain, white matter, and gray matter shown in rows 1, 2, and 3, respectively. Columns correspond to different harmonization methods.

(b) For each of the N subjects, calculate the warping function, $h_n^{-1}(x)$; $n \in 1 \ldots N$, that maps the Trio scan to the Prisma scan for that subject.

(c) Calculate the leave $10 - N$ scans out (lNso) intensity warping function, $h_{lNso}^{-1}(x)$, by averaging the *mica* warping function for the N selected subjects.

(d) For each N, calculate the root integrated square error (RISE) between the intensity warping function $h_n^{-1}(x)$ and the lNso warping function $h_{lNso}^{-1}(x)$ via

$$\sqrt{\int \left[\left(h_n^{-1}(x) - h_{lNso}^{-1}(x)\right) dx\right]^2}.$$

2. Repeat steps (i) to (iii) for all 10 subjects.

Figure 4 shows boxplots of the RISE for the 10 subjects across values of n. As n increases, both RISE and RISE variance tends to decrease, indicating that lNso warping estimation converges towards the true intensity warping function defining the scanner effect as the number of scans increases. We think this will be useful in the planning of future multisite studies, although we caution against over-interpreting these results to choose a priori the number of traveling subjects necessary to account for scanner effects.

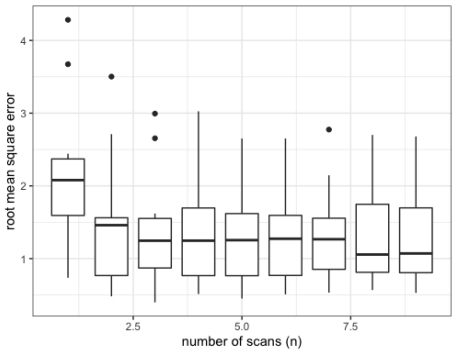

Figure 4: Boxplots of root integrated square error when different numbers of scans are used to calculate the warping function.