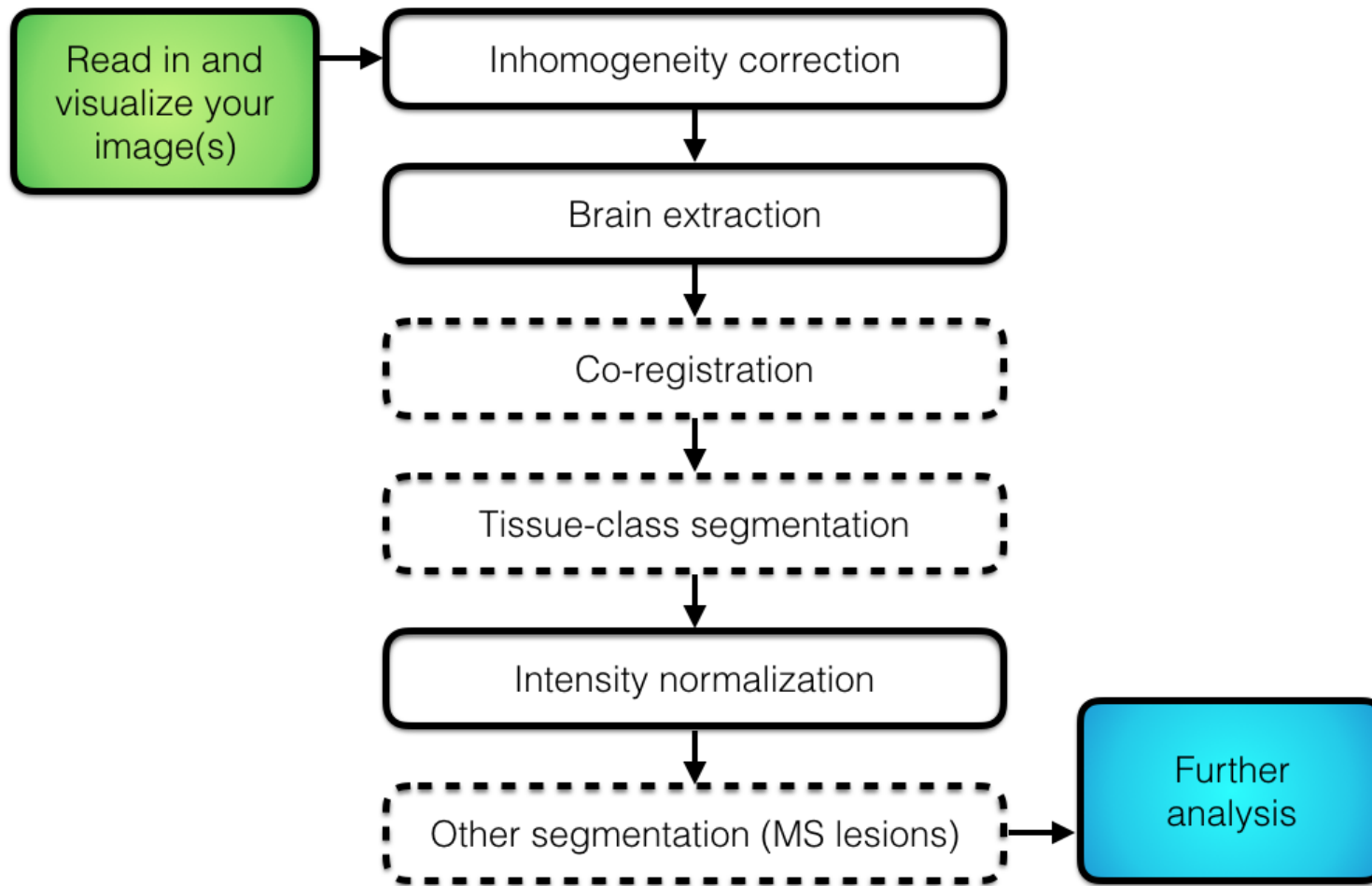


Intensity Normalization

Overall Pipeline



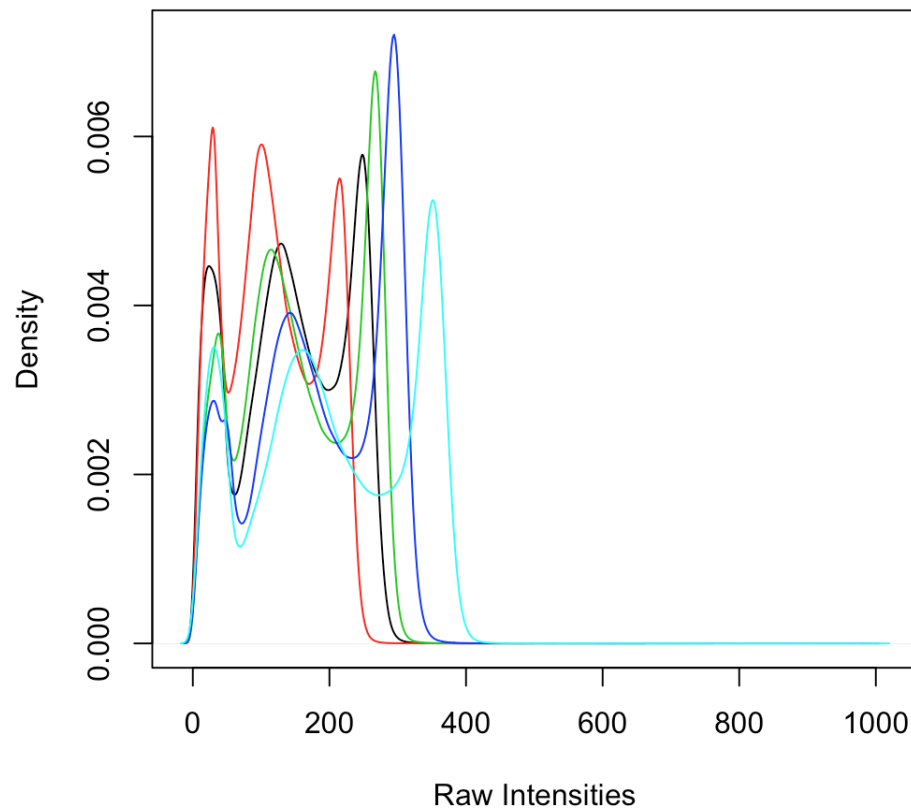
Intensity normalization

- Conventional MRI intensities (T1-w, T2-w, PD, FLAIR) are acquired in arbitrary units
- Images are not comparable across scanners, subjects, and visits, even when the same protocol is used.
 - This affects algorithm performance, prediction, inference.
 - Even simple things like thresholding an image
- Intensity normalization brings the intensities to a common scale across people.
- In this tutorial we will normalize intensities within subject using two methods:
 - Whole-brain normalization
 - White Stripe normalization (Shinohara et al. 2014).

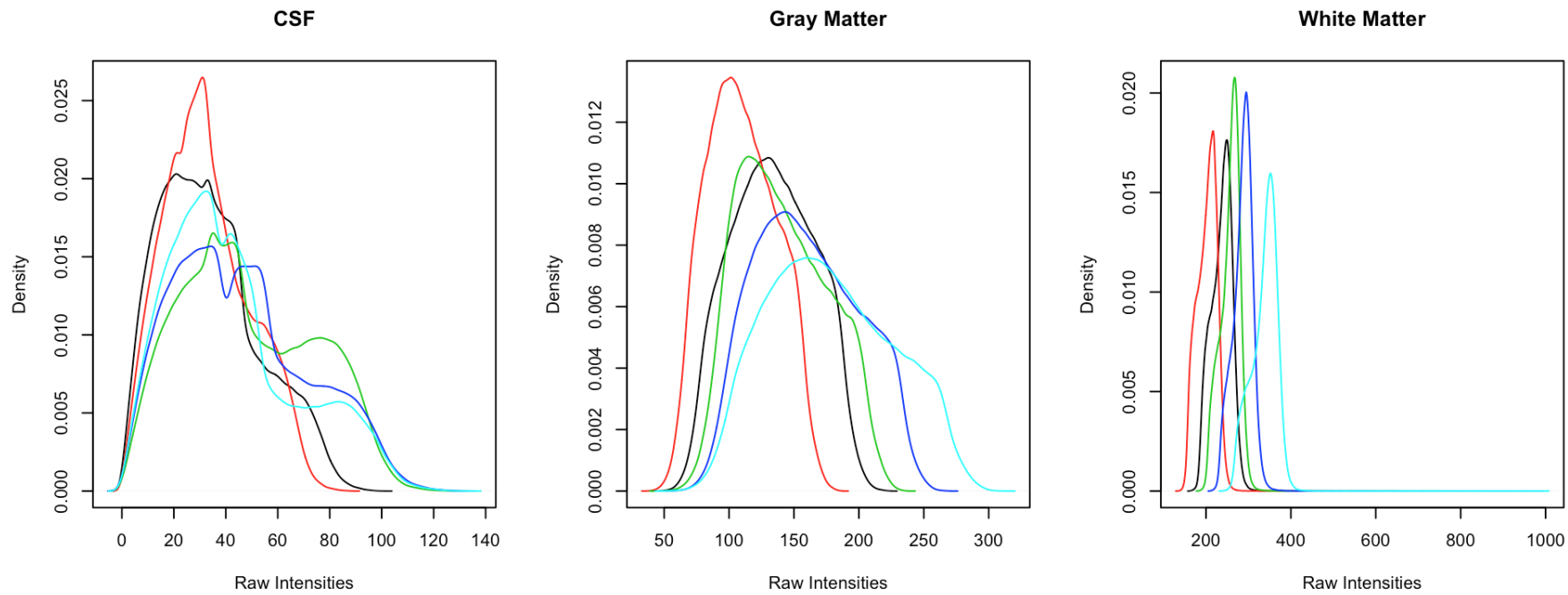
Visualizing whole-brain intensities (each line is a person)

- We will work with the T1-w images from the training data.
- Full brain densities are mixtures of the three tissue class distributions.

Distribution of all Voxels in Brain Mask



Visualizing the intensities by tissue class



And these are all the same scanner/protocol!

Whole-brain normalization

- Let's Z-score each voxel using mean μ_{WB} and standard deviation σ_{WB} computed from all voxels in the brain mask.

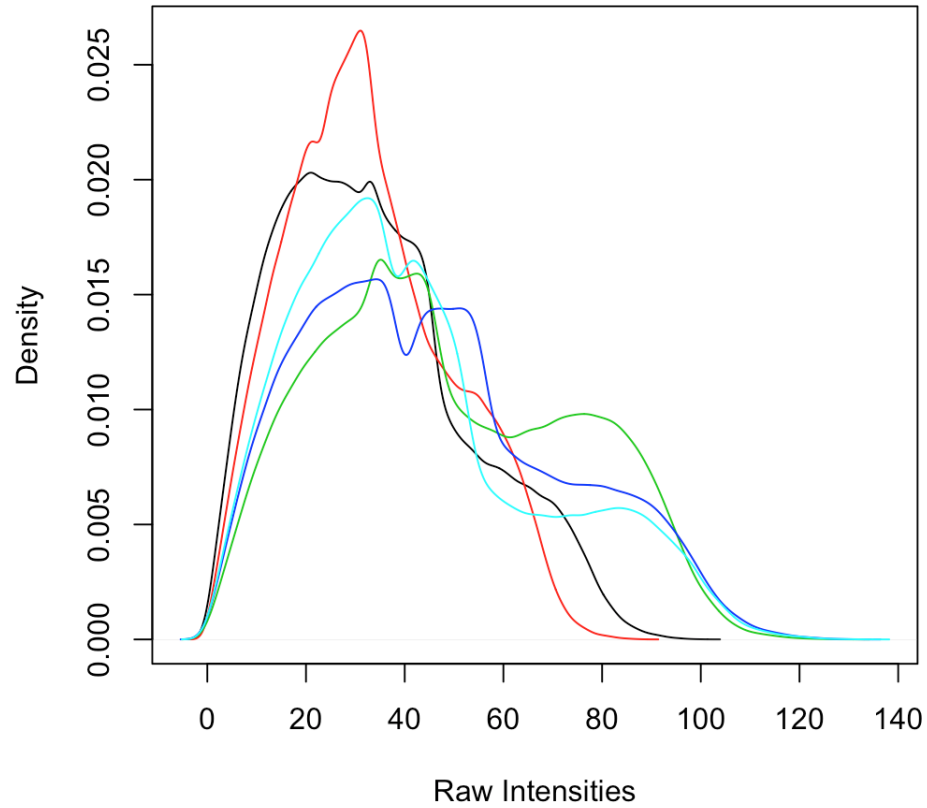
$$T1_{WB} = T1 - \mu_{WB}\sigma_{WB}$$

- `zscore_img` is a function in `neurobase` that does this.
- It takes an image and a binary mask. The default is to use all voxels in the brain mask.

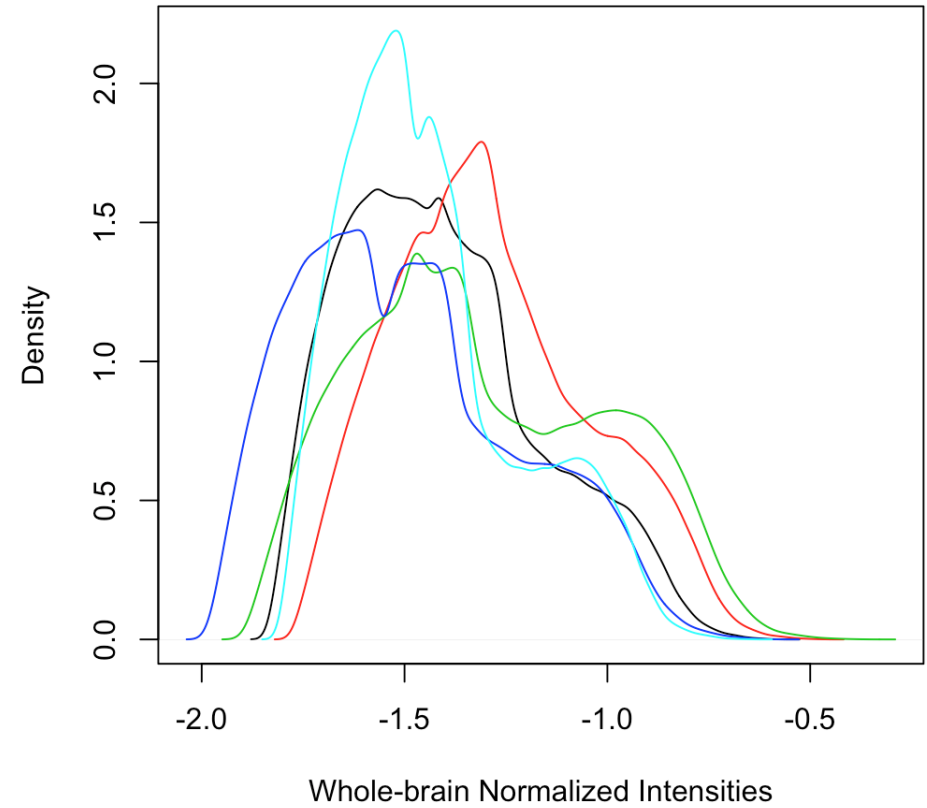
```
zscore_img(img = img, mask = mask)
```

Whole-brain normalized intensities

CSF Before



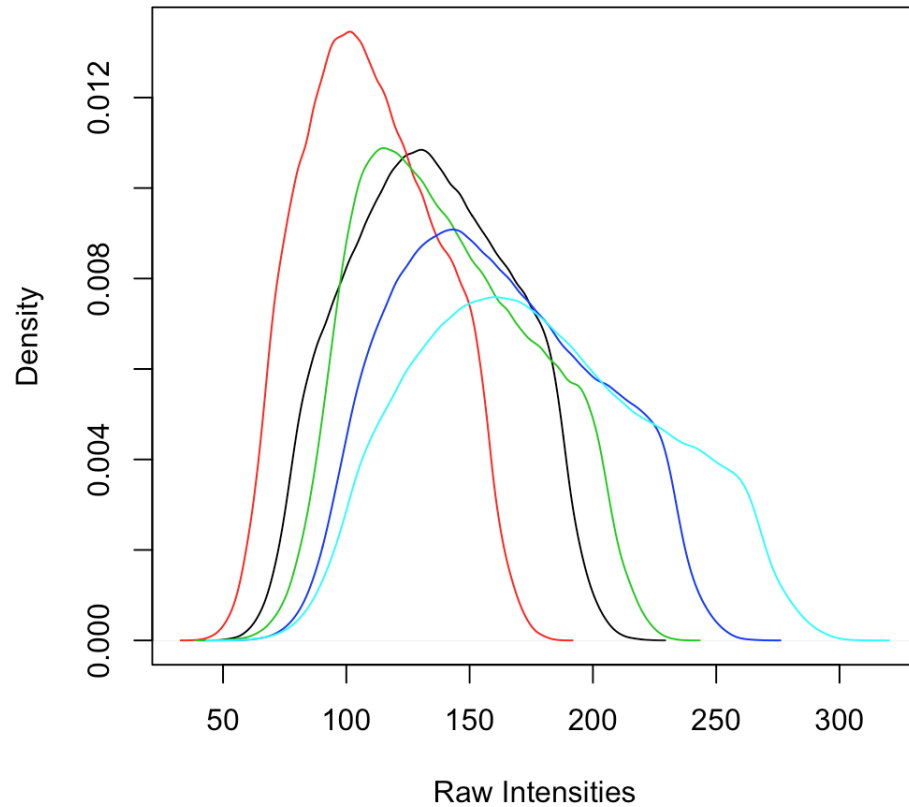
CSF After



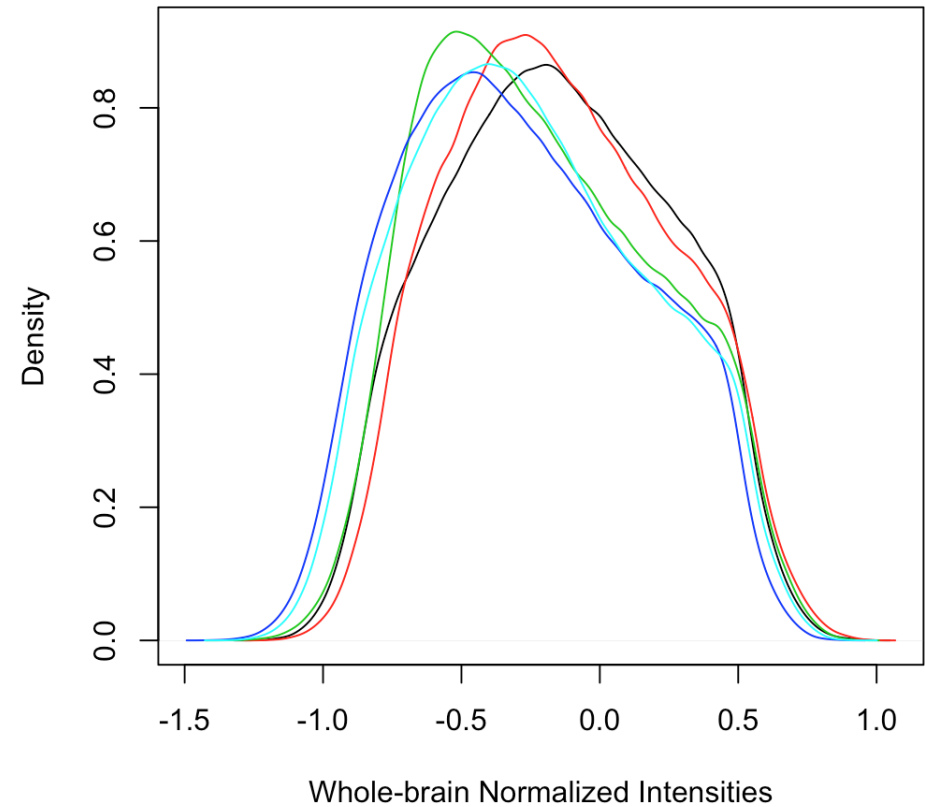
Whole-brain normalized intensities

- Gray matter distributions are more comparable.

Gray Matter Before

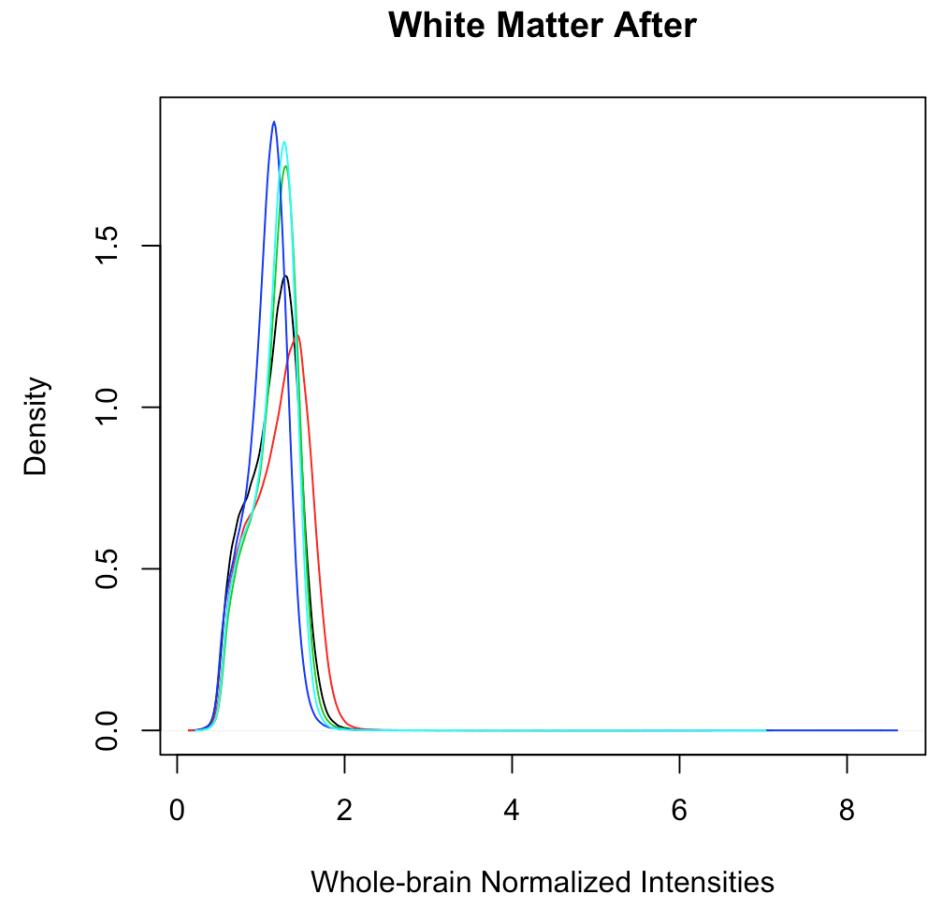
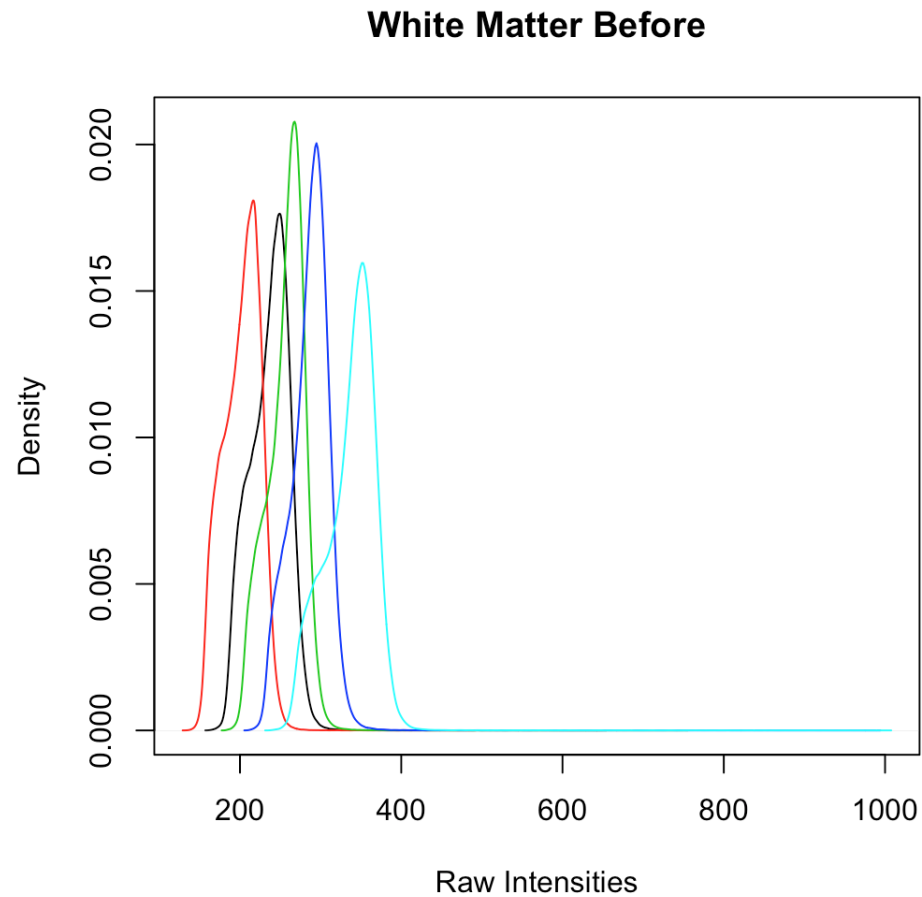


Gray Matter After



Whole-brain normalized intensities

- White matter distributions are more comparable.



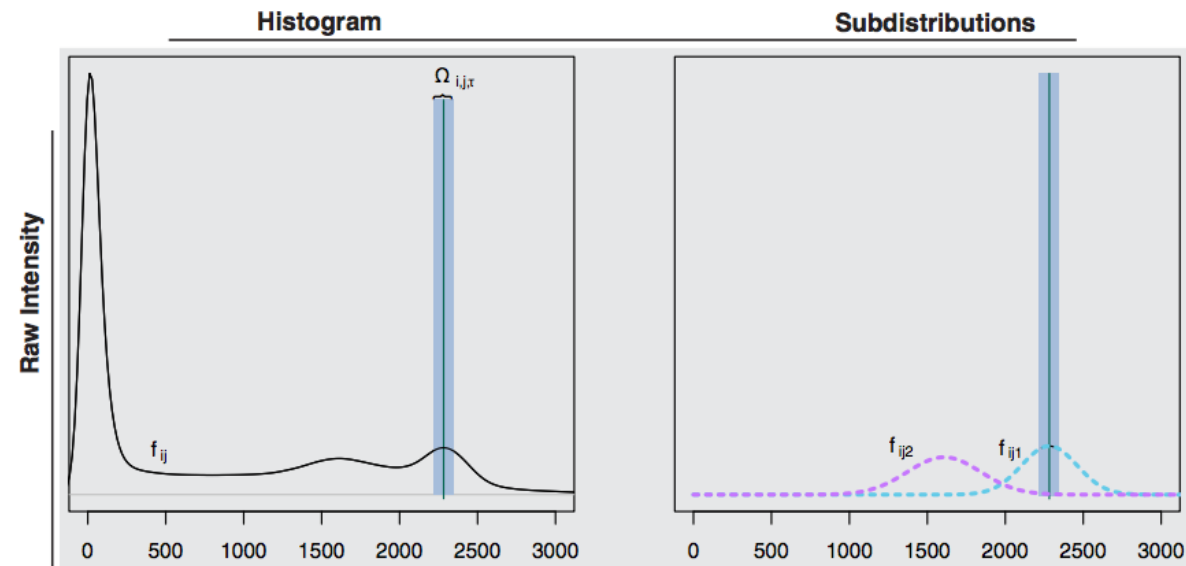
Other Normalizations: White Stripe

- Whole-brain normalization may be sensitive to outliers.
- Lesions in MS can have very high intensities, which lead to bad estimates of mean/variance
 - Other more robust transformations may be used, such as using the median to center, IQR to scale, etc.
- White Stripe (Shinohara et al. 2014) is based on parameters obtained from a sample of normal appearing white matter (NAWM), which is robust to outliers.
 - The idea is to make normal appearing white matter comparable across subjects and visits.

White Stripe normalization

Procedure:

1. Find white matter area on histogram



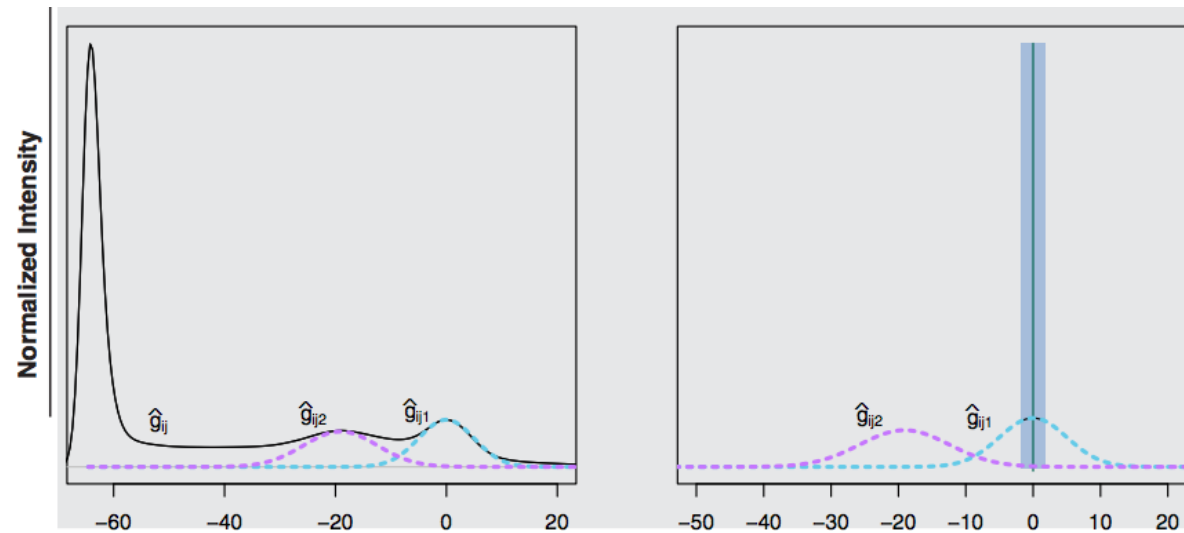
White Stripe normalization

Procedure:

1. Find white matter area on histogram
2. Estimate mean μ_{WS} and variance σ_{WS} of voxel intensities in that area
3. Normalize with those means/variances: $T1_{WS} = T1 - \mu_{WS}\sigma_{WS}$

White Stripe normalization

- After normalization, NAWM will have a standard normal distribution and units will be in standard deviations of NAWM.
- Gray matter and CSF distributions may not be comparable after White Stripe.



White Stripe normalization

Procedure:

1. Find white matter area on histogram
 2. Estimate mean μ_{WS} and variance σ_{WS} of voxel intensities in that area
 3. Normalize with those means/variances: $T1_{WS} = T1 - \mu_{WS}\sigma_{WS}$
- After normalization, NAWM will have a standard normal distribution and units will be in standard deviations of NAWM.
 - Gray matter and CSF distributions may not be comparable after White Stripe.

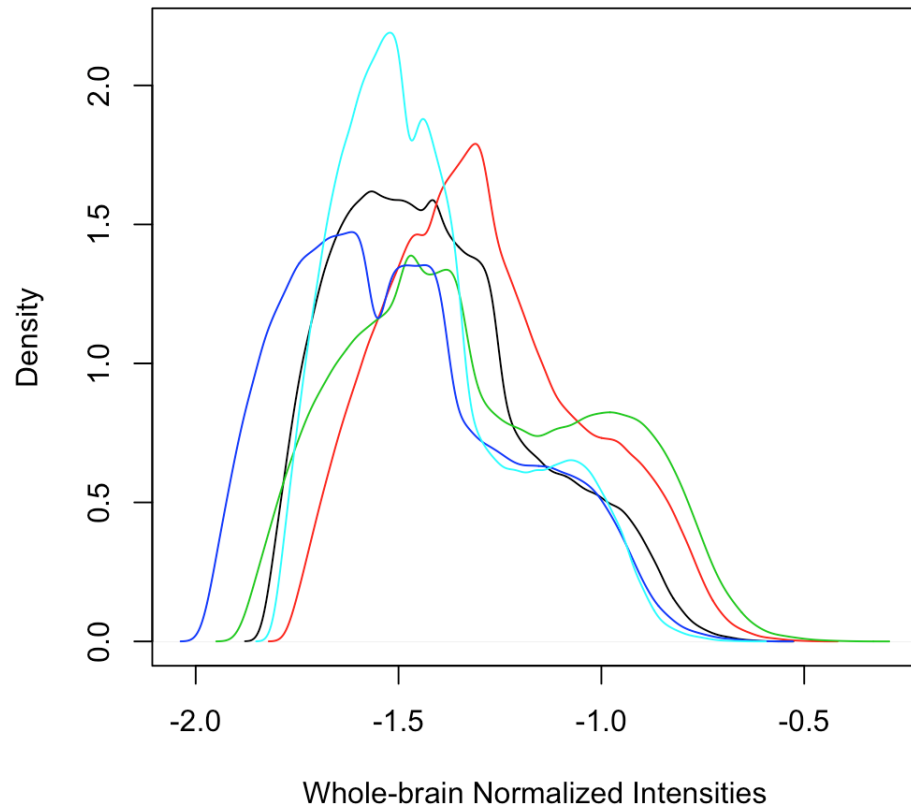
White Stripe normalization code

```
library(WhiteStripe)
ind = whitestripe(img = t1, type = "T1", stripped = TRUE)$whitestripe.ind
ws_t1 = whitestripe_norm(t1, indices = ind)
```

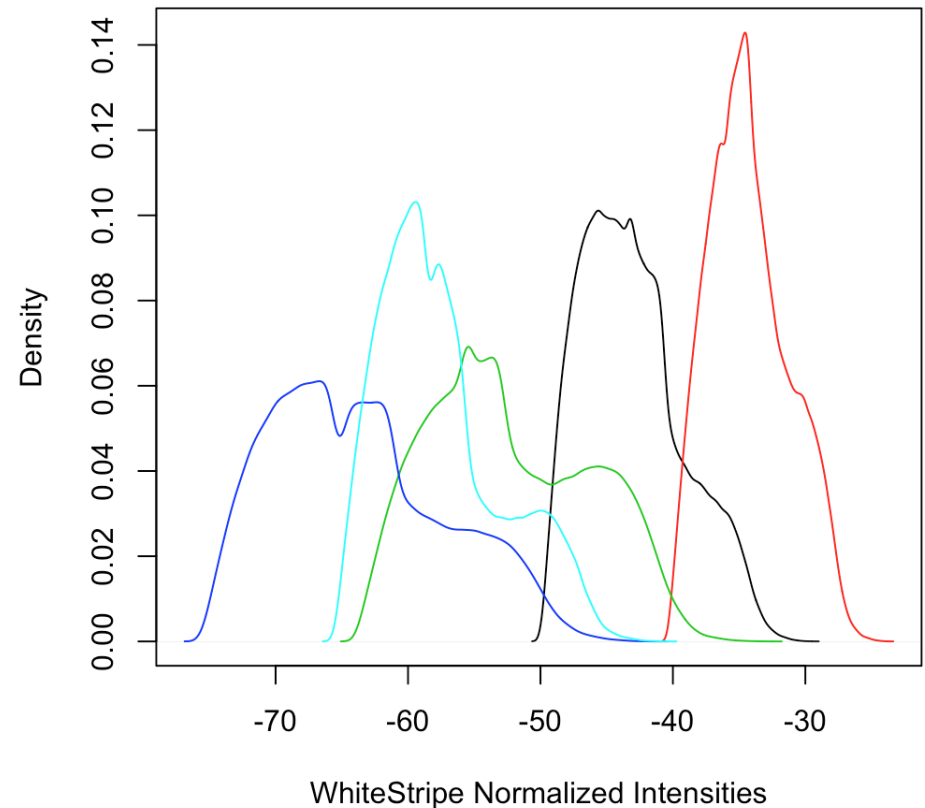
- The `whitestripe` function takes an image, image type (in our case T1), and a logical indicating whether the image has been skull stripped.
- The indices of voxels in the NAWM used for estimating the normalization parameters are located in the list element `$whitestripe.ind`.
- The function `whitestripe_norm` takes an image and the indices from a call to `whitestripe` and returns the White Stripe normalized image as a nifti.

WhiteStripe normalized intensities

Whole-brain: CSF

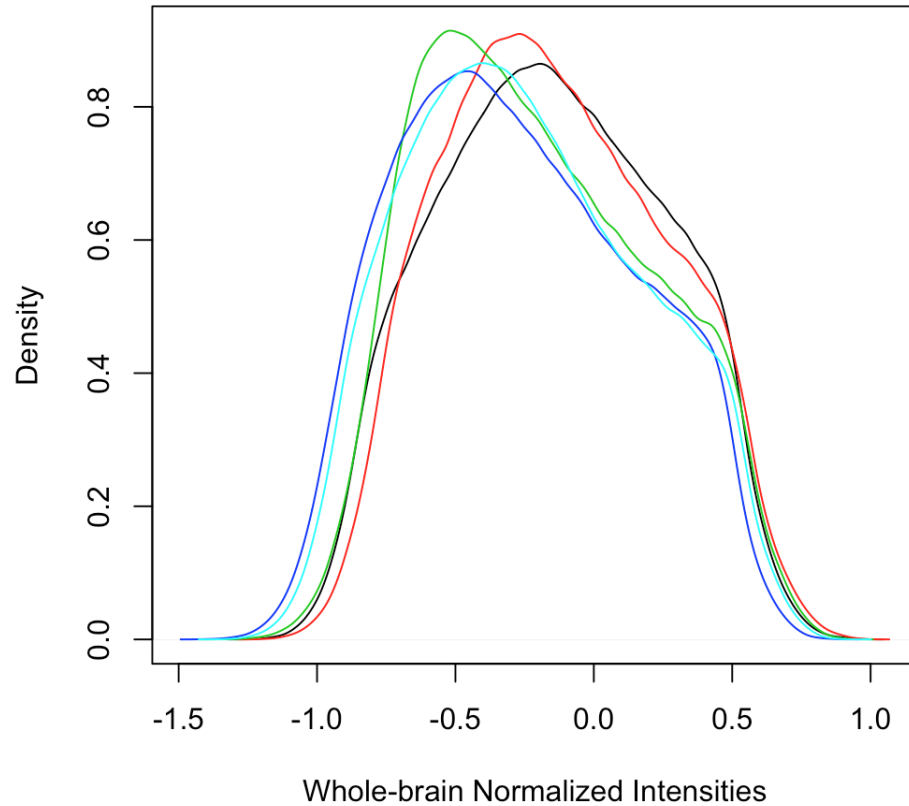


White Stripe: CSF

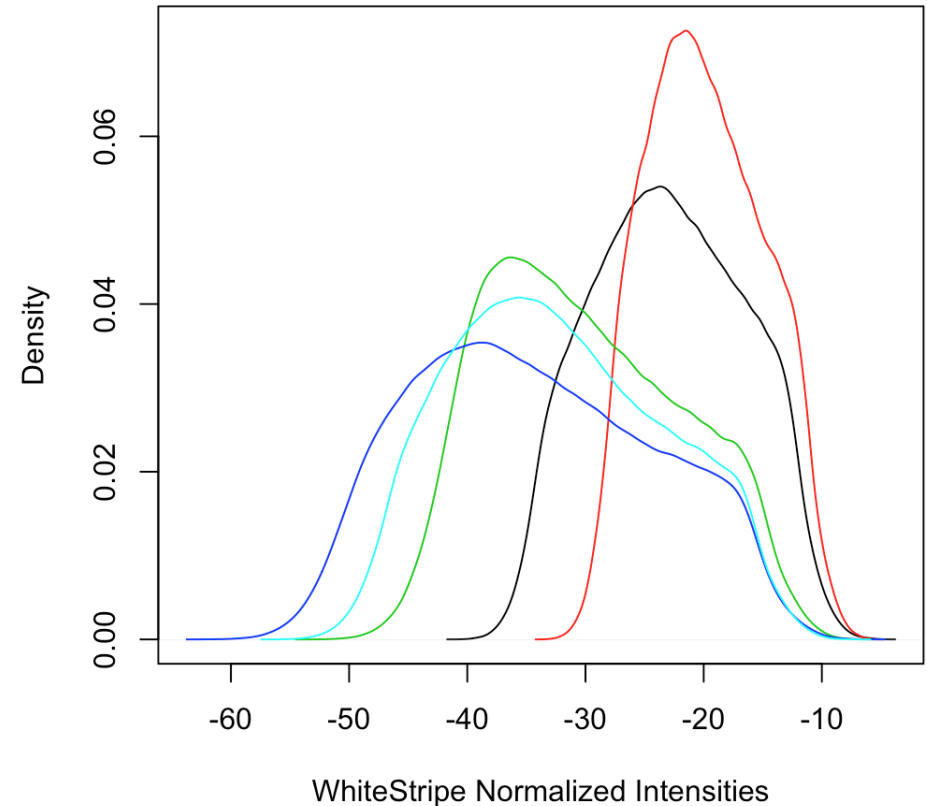


WhiteStripe normalized intensities

Whole-brain: Gray Matter

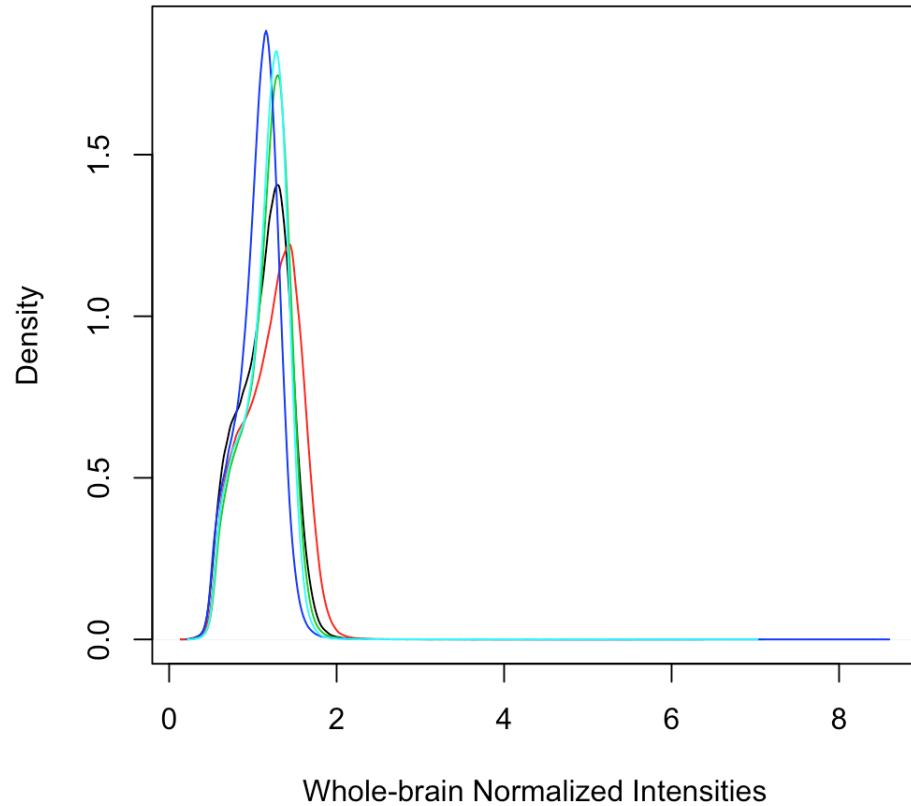


White Stripe: Gray Matter

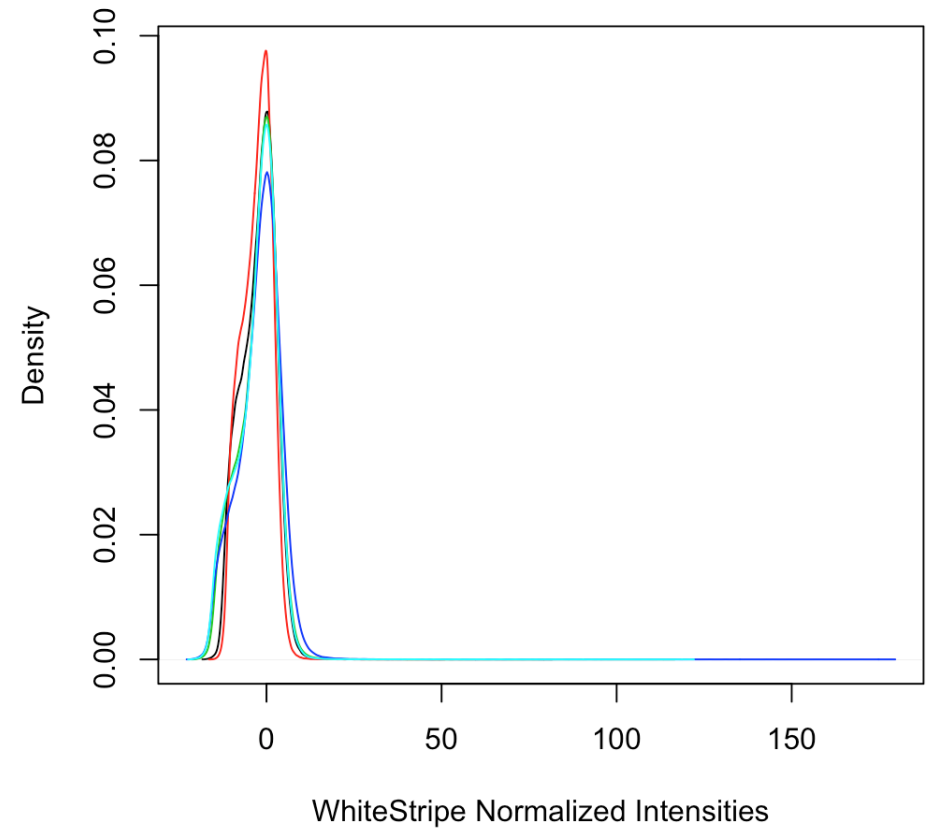


WhiteStripe normalized intensities

Whole-brain: White Matter



White Stripe: White Matter



Conclusions

- Intensity normalization is an important step in any image analysis with more than one subject or time point to ensure comparability across images.
- White Stripe normalization may work better and have better interpretation than whole-brain normalization for subsequent lesion segmentation algorithms and analysis.
- Other intensity normalization methods that make intensities comparable across subjects for all tissues exist.
 - RAVEL, which is an extension of WhiteStripe is one example (Fortin et al. 2016).
 - Located at <https://github.com/Jfortin1/RAVEL>
 - This was shown to have better comparability than histogram matching

Website

http://johnmuschelli.com/imaging_in_r

References

Fortin, Jean-Philippe, Elizabeth M Sweeney, John Muschelli, Ciprian M Crainiceanu, Russell T Shinohara, Alzheimer's Disease Neuroimaging Initiative, and others. 2016. "Removing Inter-Subject Technical Variability in Magnetic Resonance Imaging Studies." 132. Elsevier: 198–212.

Shinohara, Russell T, Elizabeth M Sweeney, Jeff Goldsmith, Navid Shiee, Farrah J Mateen, Peter A Calabresi, Samson Jarso, et al. 2014. "Statistical Normalization Techniques for Magnetic Resonance Imaging." 6. Elsevier: 9–19.