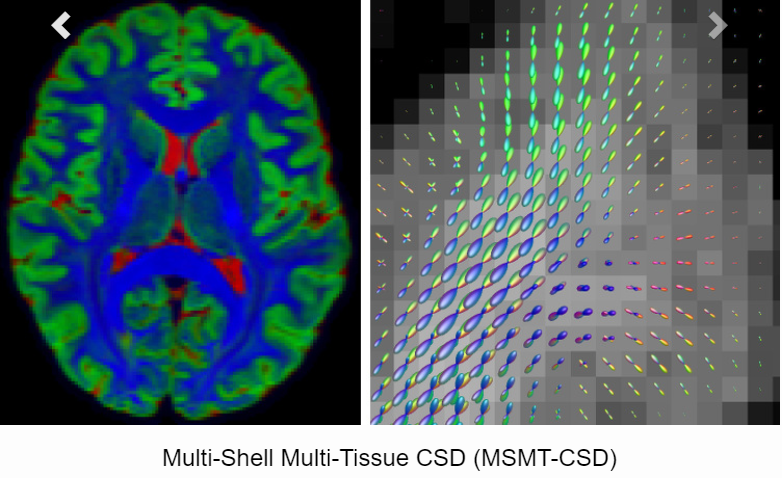
DPRC Diffusion CSD Pipeline

This pipeline takes the data from the preprocessing pipeline. Now, we will do some further analyses, which includes generating *fibre orientation distribution (FOD),* using *constrained spherical deconvolution (CSD)*.

Like the preprocessing steps, most of these postprocessing steps will run through MRtrix3, with some fsl functions. Many of these steps can be found in detail on the mrtrix documentation page.

\*Like what was done with the previous preprocessing script, run this script separately per each group you are interested in analysing in. Each group is separate/unique by the global normalisation step which was applied to them from the preprocessing script.



Resource on CSD and FBA manual: <https://mrtrix.readthedocs.io/en/0.3.16/workflows/fixel_based_analysis.html>

More updated manual (on multi-tisssue CSD: preprocessing, CSD, and FBA): <https://mrtrix.readthedocs.io/en/latest/fixel_based_analysis/mt_fibre_density_cross-section.html>

Steps:

1. Generate response function estimates using multi-tissue CSD
   1. Co-registration t1w and dwi image
   2. 5tt image
   3. Generate response function (odf.txt file)
2. Compute a group average response function of each tissue
3. Create FOD images (wm, gm, csf)
   1. Upsample dwi image
   2. Upsample brain mask images
   3. FOD estimation (multi-tissue SD)
4. Joint bias field correction and intensity normalistion
5. Generate FOD population template
6. Register all subjects to FOD template
   1. Register to FOD template
   2. Warp mask to template
   3. Compute intersection of masks in template space
7. **Generate response function estimation with multi-tissue constrained spherical deconvolution (CSD) (per participant)**

We want to estimate the multi-tissue orientation distribution function (ODF) between the participant groups. Since we have multiple shells, we are separating compartments for each tissue type, which includes a maps of the WM, GM, and CSF signal contributions to dwi data. Three main steps (a, b, c) are carried out in order to do this.

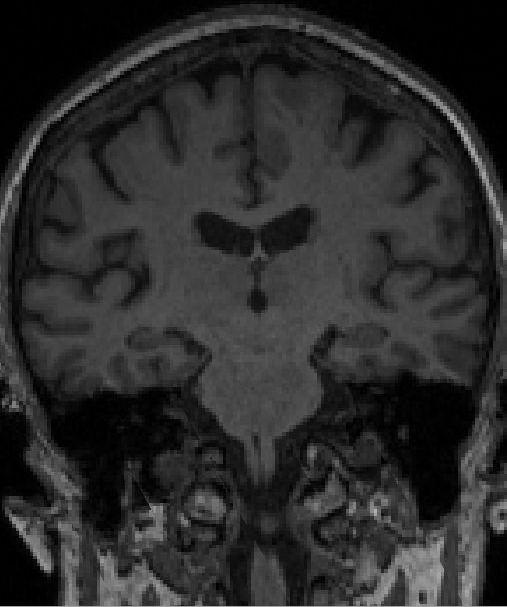
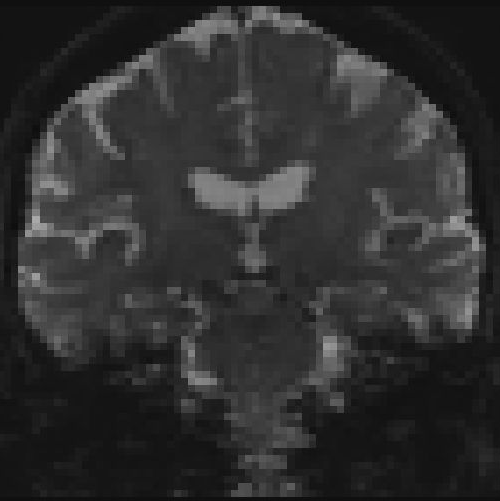
There is an option in that choosing only 1 single subject per each group for the estimate response should be OK. This is because the shape of the estimated white matter response function varies little across subjects. But we can also take the **group average response function (which is what my script does)**, after taking the response function for every participant. So, perform all of these steps on every participant per each group, then take the average response per group.

1. **Co-registration of t1w and dwi image**

Linear registration with 12 df are used.

Command: -flirt (fsl)

Elapsed time: 35 sec

 **+** 

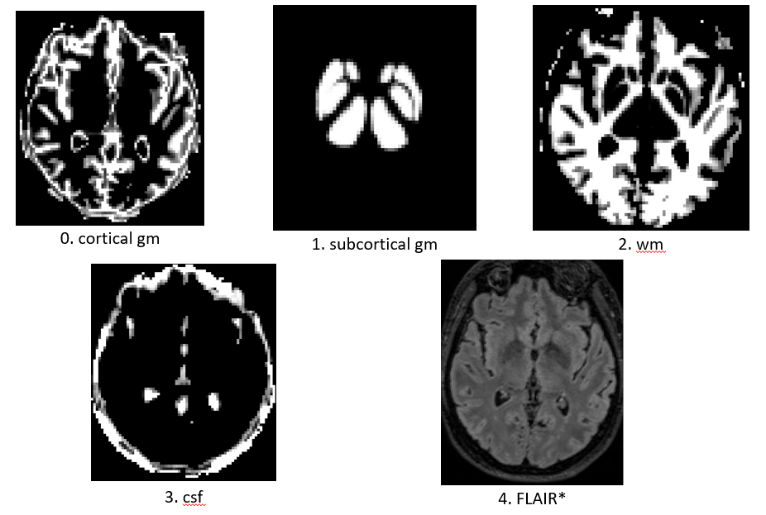
T1w dwi (b0)



Co-registered (anat\_flirt)

1. **Generate a ‘Five-Tissue-Type’ (5tt) image**

The 5 tissues include: cortical gm, subcortical gm, wm, csf, pathological tissue(\*). The 5ttgen script using the fsl algorithm interfaces with FSL to generate the necessary image data from the raw T1 image, using BET, FAST and FIRST.



1. Cortical grey matter
2. Sub-cortical grey matter
3. White matter
4. CSF
5. Pathological tissue\*

Command: 5ttgen -fsl

Elapsed time: 4 min 45 sec

\*How to deal with WMHs, use FLAIR image (haven’t done yet):

<https://community.mrtrix.org/t/5ttgen-recommended-approach-to-dealing-with-white-matter-hyperintensities-wmhs-for-act/3753/3>

Maybe better to use 5ttgen -hsvs algorithm instead – combination of fsl and FreeSurfer tools. Hsvs = hybrid surface and volume segmentation.

1. **Generate response function estimation**

This will be a text file for each of the 3 tissue types.

Command: dwi2response msmt\_5tt

Elapsed time: 46 sec

1. **Compute a group average response function of each tissue**

Take the group average response function per each of the 3 tissues (wm, gm, csf).

%Sample input: responseFunctionCSF

responseFunctionGM 🡪 folders holding all participant response files

responseFunctionWM

Command: responsemean

%Sample output: group\_average\_responseCSF.txt

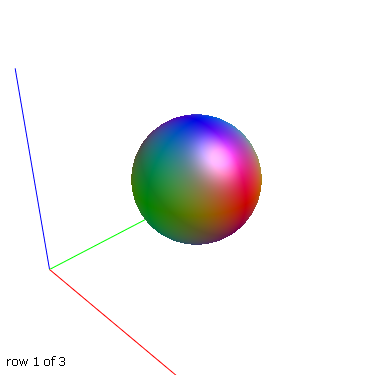
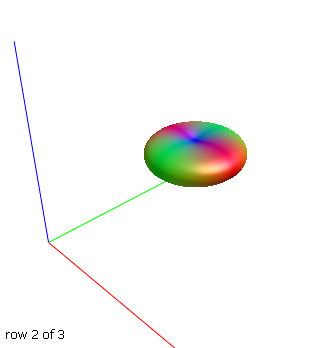
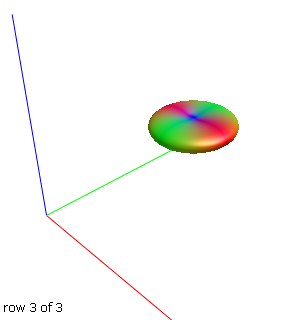
group\_average\_responseGM.txt

group\_average\_responseWM.txt

For a sanity check: you can inspect the basis functions for each tissue (wm, gm, csf) generated at each shell.

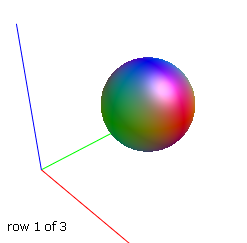
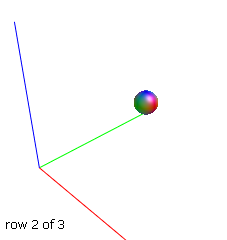
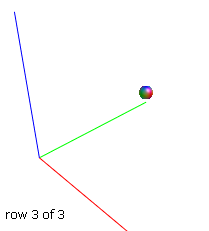
Command: shview

WM (more anisotropic):

B0 B1000 B2000

GM, CSF – should look fairly similar (more isoptropic):

B0 B1000 B2000

1. **Create FOD images (wm, gm, csf)**

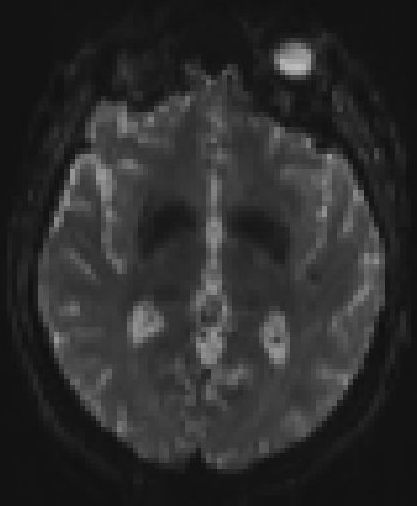
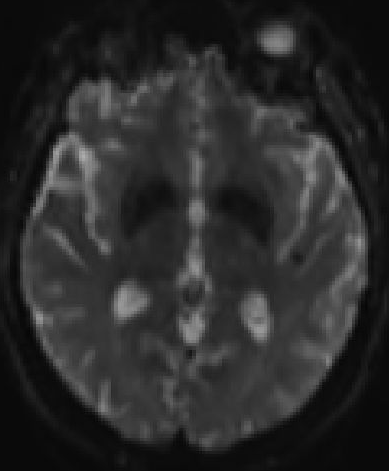
Using the response estimate functions, we will create the FOD images of each tissue.

1. **Upsample DW images**

Upsampling DWI data *before* computing FODs increases anatomical contrast and improves downstream template building, registration, tractography and statistics.

With this step, you have the option to modify the grid of an image without interpolation (cropping or padding) or by regridding (this is what my script does) to an image grid with modified orientation, location and or resolution. The image content remains in place in real world coordinates.

Command: mrgrid -regrid

Pre-upsample dwi data Gaussian smoothing (-regrid)

The -regrid option performs changes of the voxel grid that require interpolation of the image such as changing the resolution or location and orientation of the voxel grid. If the image is down-sampled, the appropriate smoothing is automatically applied using Gaussian smoothing unless nearest neighbour interpolation is selected or oversample is changed explicitly. The resolution can only be changed for spatial dimensions. It is recommended to upsample to an isotropic voxel size of 1.25 mm for human brains (if your original resolution is already higher, you can skip this step).

1. **Upsample brain mask images**

Compute a whole brain mask from the upsampled DW images

Command: dwi2mask

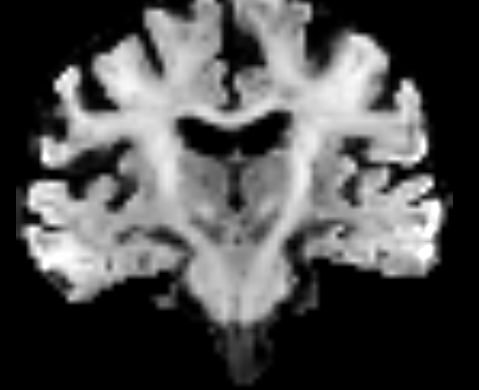
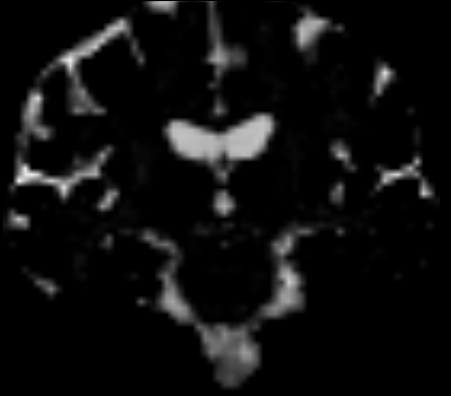
brain mask (no manual corrections) upsampled mask

\*note that upsampled images take a lot of space – 2.6 GB for main dwi data

1. **FOD estimation (multi-tissue SD)**

Use the group average response function estimates calculated from the previous step for this.

Command: dwi2fod msmt\_csd

wmfod.mif gmfod.mif csffod.mif

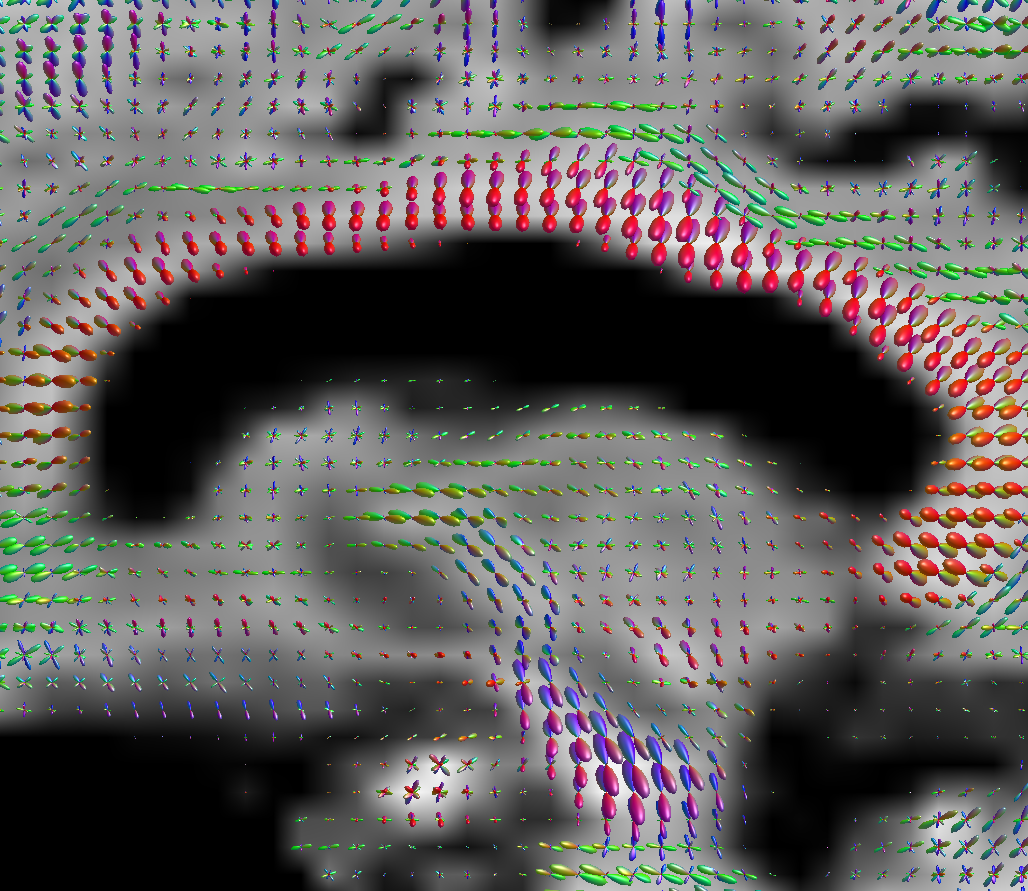
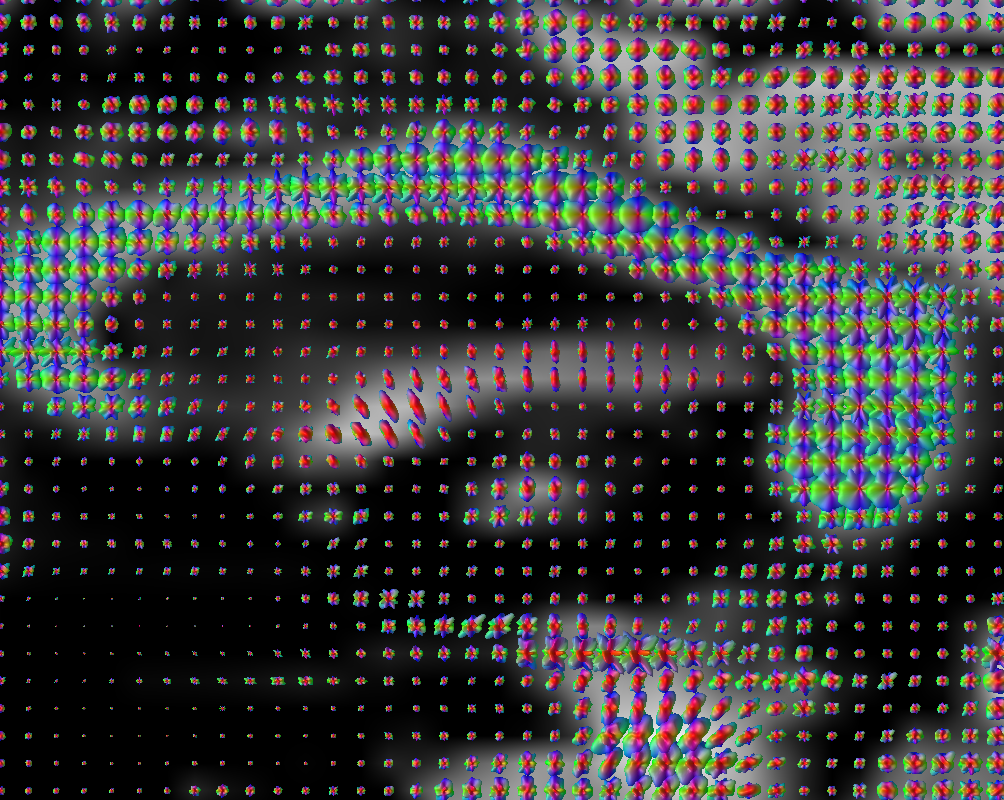


Image of the FOD loaded onto the wmfod template of a participant.

Elapsed time: 1 min 38 sec

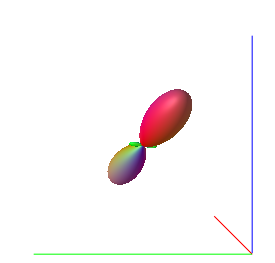
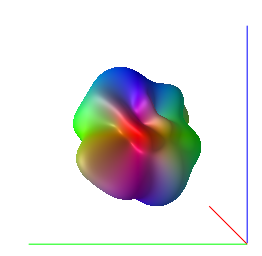
You can also compare this with to the diffusion data before spherical deconvolution was applied to it.

Command: amp2sh



Preprocessed dwi with no spherical deconvolution applied.

You can view a stark difference within a same, single ODF as well.

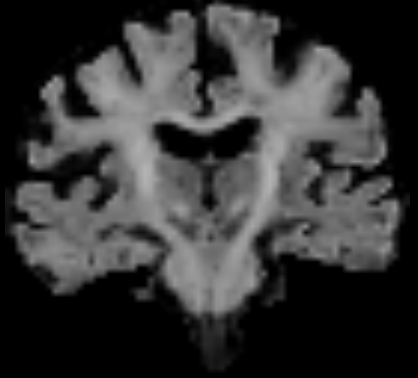
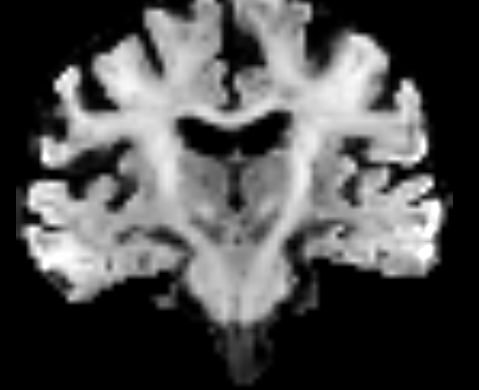
 

Spherical deconvolution no spherical deconvolution

1. **Joint bias field correction and intensity normalisation**

Perform joint bias field correction and global intensity normalisation of the multi-tissue compartment parameters. This command takes as input any number of tissue components (e.g. from multi-tissue CSD) and outputs corresponding normalised tissue components corrected for the effects of (residual) intensity inhomogeneities. Intensity normalisation is performed by optimising the voxel-wise sum of all tissue compartments towards a constant value, under constraints of spatial smoothness (polynomial basis of a given order). Different to the Raffelt et al. 2017 abstract, this algorithm performs this task in the log-domain instead, with added gradual outlier rejection, different handling of the balancing factors between tissue compartments and a different iteration structure. This step is crucial for the FBA pipeline. Use the upsampled masks in this command. This was also done with a similar cohort (HC, MCI, and AD) in Mito et al. (2018) *Fibre-specific white matter reductions in Alzheimer’s disease and mild cognitive impairment*.

Command: mtnormalise

viewed in *mrview*

wmfod.mif normalised (wmfod\_norm.mif)

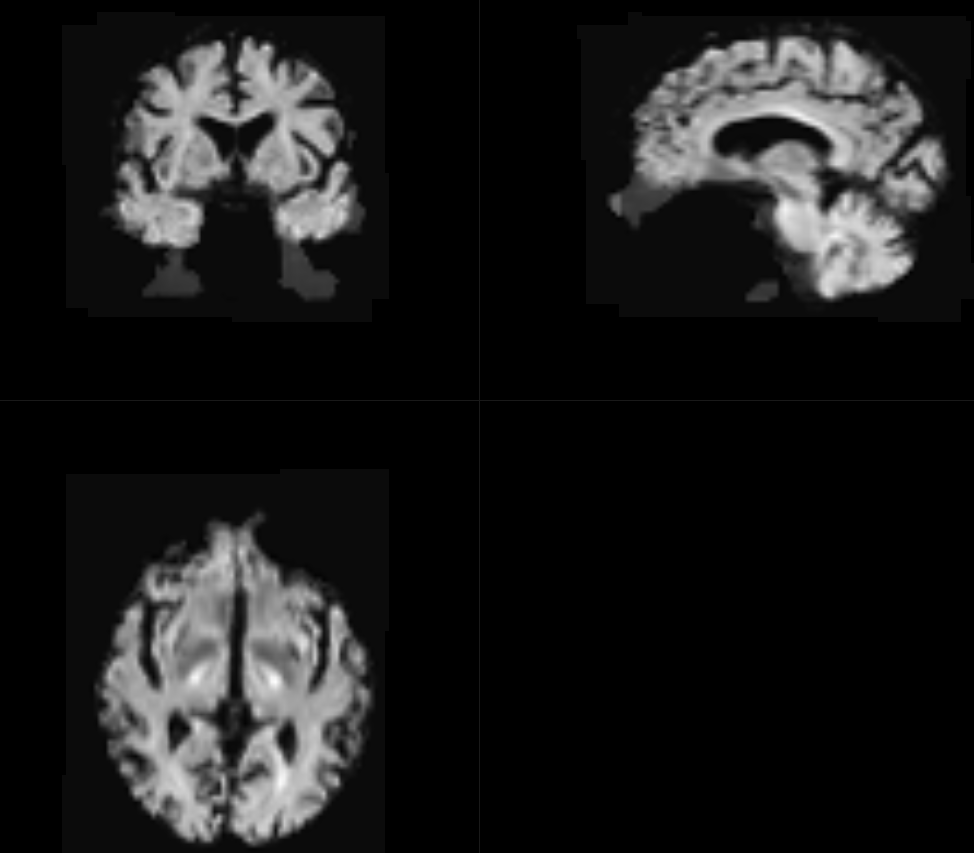
  viewed in *fsleyes*

wmfod.mif normalised (wmfod\_norm.mif)

1. **Generate FOD population template**

Generate a study-specific unbiased FOD template. Generating a population template is one of the most time consuming steps in a fixel-based analysis. If you have a very large number of subjects in your study, you can opt to create the template from a limited subset of 30-40 individuals. Typically, subjects are chosen so the generated template is representative of your population (e.g. similar number of patients and controls, though avoid patients with excessive abnormalities compared to the rest of the population). To build a template, you will use all FOD images, which are segregated into separate folder (e.g. wmFODimages) and put a set of corresponding mask images (with the same prefix as the FOD images) in another folder (using masks speeds up registration significantly).

Run 10 participants from each of the 4 groups (HC, SCD, MCI, AD) to create the template to represent them all. ~40 participants total.



wmfod\_template.mif (only 2 participants atm, so doesn’t look great)

1. **Register all subjects to FOD template**
2. **Register all subjects to FOD template**

Command: mrregister

1. **Warp mask to template**

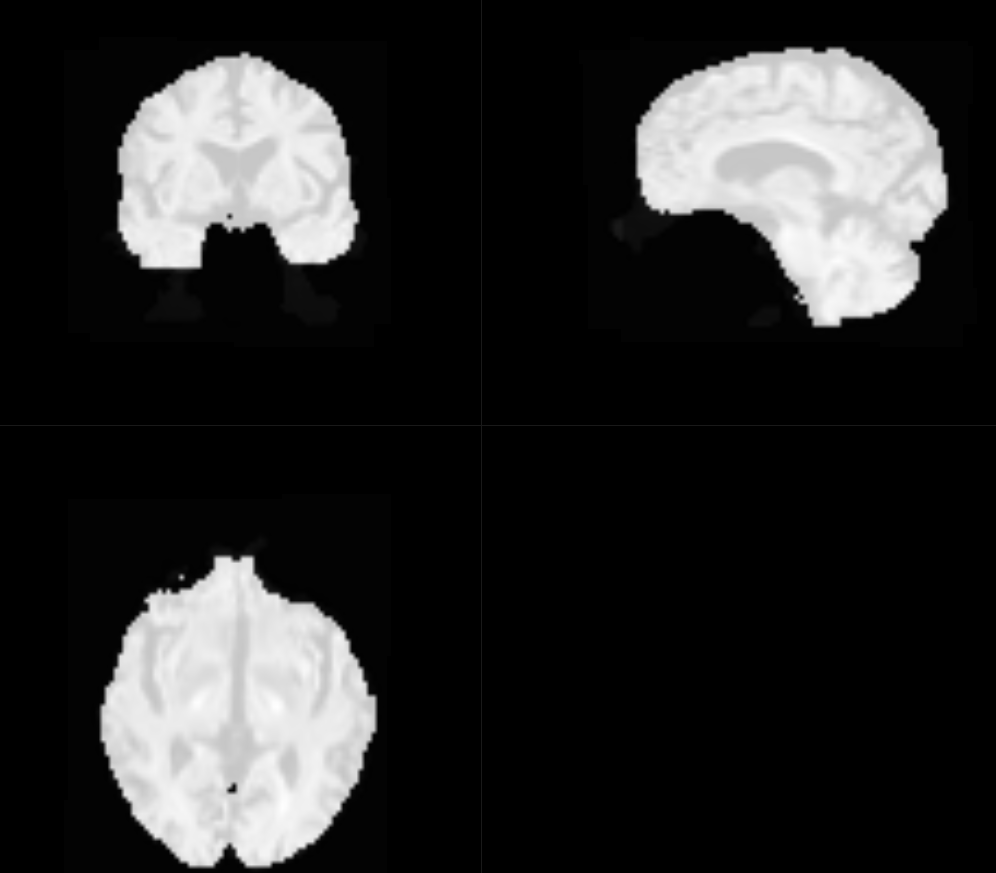
Different subjects have different brain coverage. To ensure subsequent analysis is performed in voxels that contain data from all subjects, we warp all subject masks into template space and compute the template mask as the intersection of all subject masks in template space.

Command: mrtransform

1. **Compute intersection of masks in template space**

Compute the template mask as the intersection of all warped masks.

Command: mrmath



template\_mask\_intersection.mif

References

Mito, R., Raffelt, D., Dhollander, T., Vaughan, D. N., Tournier, J. D., Salvado, O., … Connelly, A. (2018). Fibre-specific white matter reductions in Alzheimer’s disease and mild cognitive impairment. *Brain*, *141*(3), 888–902. https://doi.org/10.1093/brain/awx355