fMRI Methods Journal Club: DTI
Outline for today’s discussion

- **Theoretical overview of DTI**
  - What is DTI?
  - Advantages/Disadvantages to this technique
  - Some applications of DTI in the literature

- **Implementing DTI in your lab**
  - Introduction of available software packages w/ examples
  - DTI analysis
  - BIAC pipeline: Connectome Mapper Tool Kit

- **A complementary tool for investigating white matter**
  - Lesion Segmentation Tool

- **Useful papers/links**
What is DTI?

“Diffusion tensor magnetic resonance imaging (DTI) is a non-invasive method to determine the underlying composition and integrity of nerves, neural fibers, etc.”

Beaulieu, NMR Biomed, 2002
Provides a way to look at the other “tissue”, white matter
A quick comparison of MRI and DTI images...

Mori et al, Neuron, 2006
What is DTI?

- Diffusion tensor magnetic resonance imaging (DTI) is a non-invasive method to determine the underlying composition and integrity of nerves, neural fibers, etc.

- Primarily dependent on the way water diffuses within different brain structures

- What factors influencing how water diffuses?
  - Underlying tissue micro-structure (neurons, glia, etc.)
  - Changes in Temperature (heat)
  - Viscosity as indexed by the number of molecular-molecular interactions

- The “difficulty” in the mobility of water molecules to travel may reveal the underlying structure of the tissue
Two different forms of diffusion...

The mobility of molecules is referred to a physical constant, the \textit{diffusion coefficient}, and when measured by DTI, yields a measure called \textit{apparent diffusion coefficient}.

In isotropic diffusion, diffusion of the molecules is equal in all directions whereas anisotropic diffusion refers to diffusion that is greater in one direction than the rest.
Potential sources of this anisotropy?

“Barriers” to optimal mobility to water diffusion perpendicular to the axon could be as shown in this schematic, the axonal membrane, neuro-filament, and microtubule structures.

Beaulieu, NMR Biomed, 2002
Diffusion Tensor aids in measuring diffusion along different directions

Mukherjee et al., AJ NR, 2008
From a diffusion measurement along multiple axes a “diffusion ellipsoid” is created.

One can get an FA map with darker regions more isotropic than lighter more anisotropic regions.

From this “diffusion ellipsoid” one can get the local fiber orientation by identifying the longest axis.

Color-coded orientation map can then be created; R (left-right), B (sup-inf), G (ant-post).
Indices one can get from DTI...

- Axial Diffusivity (AD)
  - Reflects diffusivity along the longitudinal/main axis ($\lambda_1$)

- Radial Diffusivity (RD)
  - Reflects average of the two minor axes ($\frac{\lambda_2 + \lambda_3}{2}$)

- Mean Diffusivity (MD)
  - Reflects average of all three eigenvectors ($\frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$)

- Fractional Anisotropy (FA)
  - Measure that ranges from 0 (isotropic) to 1 (very anisotropic)

\[ \sqrt{\frac{1}{2} \left( (\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2 \right) / \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \]
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\[
\sqrt{\frac{1}{2} \sqrt{\frac{1}{\sqrt{\frac{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}}}
\]

Mori et al, Neuron, 2006
Examples of studies using DTI...

Davis and colleagues employed DTI using manual/deterministic tractography and TBSS to look at age-related deficits on long-white matter tracts

- Looked at DTI measures of RD and AD for each of the tracts in younger and older adults

- Study also included neuropsych measures
Examples of studies using DTI...

Metzler-Baddeley et al., traced tracts (fornix, PHG cingulum, uncinate fasciculus) involving regions that were functionally known to be involved in episodic memory and looked at the underlying structural integrity of the three tracts.
Fuentemilla et al., were interested in looking at how differences in the accuracy of memory could be driven by anatomical differences as gauged by white matter integrity in “memory-relevant” tracts.
Some Advantages & Disadvantages to DTI...

**Advantages**
- Non-invasive and Requires the use of no contrast agents or tracers
- Works within the existing fMRI framework – no major additional setup required
- Allows for a more refined understanding of the underlying structural fidelity
- How does structural connectivity inform functional connectivity and vice versa → DTI via FA indices could help w/ structural connectivity

**Disadvantages**
- DTI is sensitive to noise and motion impacting SNR & tractography
- Problems with tensor fitting and diffusion-weighting gradients
FSL’s TBSS: Tract-Based Spatial Statistics

- [http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS](http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS)

FMRIB58_FA-skeleton_1mm.nii.gz

FMRIB58_FA_1mm.nii.gz  MNI152_T1_1mm_brain.nii.gz
Skeleton-based stats with FSL’s *randomise*

http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise
http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS

design_ttest2 design 4 4

test_groups.mat  test_groups.con
/NumWaves 2  /NumWaves 2
/NumPoints 8  /NumContrasts 2
/PPheights 1 1 /PPheights 1 1
/Matrix
1 0
1 0
1 0
0 1

Example of code to run “randomise”
randomise -i all_FA_skeletonised.nii.gz -o test_groups
-m mean_FA_skeleton_mask.nii.gz -d test_groups.mat
-t test_groups.con -n 1000 -T2 -V

test_groups_tfce_corrp_tstat2.nii.gz
TBSS code

http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS

- 1) tbss_1_preproc *.nii.gz
- 2) tbss_2_reg –T
  - Or, tbss_2_reg –n (for study-specific option, see website)
- 3) tbss_3_postreg –T
  - Or, tbss_3_postreg –S (for study-specific option, see website)
- 4) tbss_4_prestats 0.2 (to threshold meanFA skeleton and create all_FA_skeletonised.nii.gz)

Alternatively, for Steps 2 & 3, you could use the following FSL functions:

- fsl_reg ${subj}_FA ${FSLDIR}/data/standard/FMRIB58_FA_1mm ${subj}_to_FMRIB58 –FA
  - For registration, which is what the tbss_2_reg is doing anyway
- fslmerge –a all_FA *to_FMRIB58.nii.gz
  - creates a 4D file with all subjects’ registered FA images
- fslmaths all_FA –max 0 –Tmin –bin mean_FA_mask –odt char
  - Create mean_FA_mask.nii.gz
- # ## to use the TBSS mean_FA template (FMRIB58) and create skeleton
- fslmaths ${FSLDIR}/data/standard/FMRIB58_FA_1mm -mas mean_FA_mask mean_FA
- fslmaths mean_FA -bin mean_FA_mask
- fslmaths all_FA -mas mean_FA_mask all_FA
- $FSLDIR/bin/imcp $FSLDIR/data/standard/FMRIB58_FA-skeleton_1mm mean_FA_skeleton
Semi-automated ROI definition and deprojection method
ROI deprojection code

**NOTE:** FOR ALL THESE FSL FUNCTIONS, TO LEARN MORE ABOUT THE FUNCTION OR PARAMETER OPTIONS, TYPE THE NAME OF THE FUNCTION IN AN INTERACTIVE NODE

- Register all subjects’ T1 images (e.g., “…_anat_...nii.gz”) to MNI T1 template
  
  for j in `$FSLDIR/bin/imglob *_anat*` ; do
  
  flirt -ref ${FSLDIR}/data/standard/MNI152_T1_1mm_brain -in $j -omat ${OUTPUTDIR}/${j}_to_MNI_aff.mat –out ${OUTPUTDIR}/${j}_flirted
  
  fnirt --in=$j --aff=${OUTPUTDIR}/${j}_to_MNI_aff.mat --
  
  cout=${OUTPUTDIR}/${j}_to_MNI_nonlin_warps --config=T1_2_MNI152_2mm --
  ref=${FSLDIR}/data/standard/MNI152_T1_1mm_brain --
  refmask=${FSLDIR}/data/standard/MNI152_T1_1mm_brain_mask
  
  applywarp --ref=${FSLDIR}/data/standard/MNI152_T1_1mm_brain --in=${j} --
  
  warp=${OUTPUTDIR}/${j}_to_MNI_nonlin_warps --out=${OUTPUTDIR}/${j}_in_MNI
  
  done

- Register (nonlinearly) a subject’s FA image to MNI’s FA template
  
  Fsl_reg subj_FA ${FSLDIR}/data/standard/FMRIB58_FA_1mm subj_to_FMRIB58 --FA

- Get the inverse nonlinear registration transformation parameters
  
  invwarp --ref=subj_FA -- warp=subj_to_FMRIB58_warp --out=FMRIB58_into_subj_warp

- Deproject an ROI using the inverse warp
  
  applywarp –ref=subj_FA –in=ROI.nii.gz –warp=FMRIB58_into_subj_warp –out=ROI_in_subj_FA
Tractography

CMTK Pipeline -> TrackVis
Connectome Mapping Tool Kit (CMTK)

Image processing pipeline that integrates

- Anatomical (T1/T2)
- Resting State fMRI
  - BIAC RS pipeline
- Diffusion Tensor Imaging
  - Via Diffusion Toolkit (DTK)
- BIAC-connectomemapper

connectomics.org
TrackVis

Fiber tracking visualization and analysis

- Provides statistics such as track count, volume, and fiber length
- Numerous filtering options
- ROI placement within tracts

trackvis.org
What you need

- **CMTK**
  - DTI data with BXH headers
  - Anatomical T1 images for registration (.bxh)
  - Cluster access

- **TrackVis**
  - .trk file output from CMTK
  - Newer computer with 1-2GB memory
What you get
TrackVis

- Overlay scalar maps generated in participant space
- Provides statistics such as FA, RD, and MD
Limitations

- All steps must be run (12+ hours)
- Post-hoc WM seeding by default
  - Whole brain tractography using freesurfer GM atlas
- TrackVis forces 2 x 2 x 2 for visualization
- TrackVis is very memory/graphics intensive
Helpful links

- CMTK - connectomics.org
- TrackVis - trackvis.org
- BIAC - wiki.biac.duke.edu
Lesion Segmentation Tool (LST)

fMRI Methods Journal Club
February 4, 2013
Automated Lesion Segmentation

• Lesion: any abnormality in tissue due to injury or disease

• Lesion Segmentation Tool (LST): white matter lesion detection
  ▫ lesion growth algorithm

  ▫ open source toolbox in SPM

  ▫ technical aspects:
    • Java VM for MATLAB: Increase heap space using Java.opts
    • minimum of 10G requested on cluster

Find voxel intensities

Segment voxels into tissue classes

*derived from T1 image*

Find voxels that are hyper-intense outliers of each tissue class

Detection of lesions

*derived from T2 FLAIR image coregistered to T1*
LST Module and Utilities

Lesion maps in T1 space

Volume of lesion load (mL)
LST Input

Batch Editor

Module List

Current Module: PVE label estimation and lesion segmentation

Help on: PVE label estimation and lesion segmentation

T1 volumes

Options for lesion segmentation

- Initial threshold: 1.0
- Lesion belief map: GM
- MRF parameter: 1
- Maximum iterations: 50
- Threshold for binary lesion map: 0

Writing options

- Lesion Map
- Lesion probability map: yes
- Binary lesion map: none
- Normalized lesion map: none
- Other images: yes

Current Item: T1 volumes

Select raw T1 images. You can select images of more than one subject. The FLAIR images must be selected in the same order.

T1

T2 FLAIR
LST Output: Lesion map

Base image: T2 FLAIR
*bias-corrected FLAIR image in the space of the T1 image*

Lesion map
(Threshold, $k = 0.30$)
LST Output: Lesion map continued...

- Location is key!
  - Periventricular region
  - Deep white matter region

- Setting parameters
  - conservative and liberal thresholds
  - altering the algorithm via lesion growth initialization: GM seed vs. GM & WM seed
LST Output: Volume

Potential for:

- Group comparisons
- Comparisons with behavioral data
- Informing threshold choice
Future ventures?

- Relating lesion data to DTI data:
  - Does lesion location correspond to measures of decreased white matter integrity?

- Relating lesion data to behavioral measures:
  - Does the amount or location of lesions predict behavioral performance?

- Group comparisons of lesion load
  - Aging
Useful Links

- LST’s website: [http://www.applied-statistics.de/lst.html](http://www.applied-statistics.de/lst.html)

1) Classify voxels according to intensity range of tissue classes (based on segmentation of the T1 image)

- Individual native T1-image generates a partial volume estimate label (range: 1-3) corresponding to intensity class
  1 = CSF
  2 = GM
  3 = WM

2) Find hyperintense-outliers of intensity distribution for each tissue class, (based on the T2 FLAIR image)

- Standard module’s generation of lesions: Hyper-intense outliers of the GM class are projected to the sum of hyper-intense outliers of CSF, GM, and WM classes