Diffusion Tensor Imaging (DTI)
A discussion on understanding and analyzing white matter tracts

Meghan Martz, PhD
Motivations for Today’s Talk

• NeuroMod Study
  – Developmental and sex differences in frontostriatal effective connectivity during real-time fMRI neurofeedback
  – Collecting DTI data
  – Discussions with fMRI analyst Ryan Lash

• Michigan Longitudinal Study
  – Longitudinal study enriched with families with substance use disorder
  – Discussions with Dr. Mary Heitzeg, Mary Soules, Ryan Lash

• ABCD Study

ABCD NEUROIMAGING PROTOCOL

PRESCAN (25-45 minutes)
  - Rescreen for Contraindication for MRI
  - Simulation and motion compliance training
  - Practice fMRI tasks
  - PreScan Questionnaire

SINGLE SCAN SESSION (90-120 minutes)
  - Localizer
  - T1-weighted rs-fMRI
  - DTI, T2, rs-fMRI
  - Task-based fMRI (MID, SST, EN-Back)

TWO SCAN SESSIONS (100-120 minute)
  - SCAN SESSION 1
    - Localizer, T1, rs-fMRI, DTI, T2, rs-fMRI
    - PostScan Questionnaire
    - BREAK
    - PreScan Questionnaire
  - SCAN SESSION 2
    - Localizer, Task-based fMRI (MID, SST, EN-Back)

POSTSCAN (15-20 minutes)
  - PostScan Questionnaire
  - Recognition Memory
  - Post-MID survey
Basics of DTI
Diffusion Tensor Imaging (DTI): Structural imaging technique that measures the orientation and direction of white matter fiber tracts (i.e., myelinated axons) by mapping the diffusion of water molecules.

- Uses existing MRI technology, no contrast agents or chemical tracers.
- Modeled interpretation of fiber connectivity; **not** actually measuring axons, but rather water diffusion that we believe is being impeded by tissue boundaries, membranes, etc.

Soares et al., 2013
Structural vs. Functional Connectivity

MRI

Structural Connectivity
- DTI
- Diffusion Spectrum Imaging (DSI)

Functional Connectivity
- Resting State
- Task-Based
Gray Matter vs. White Matter Recap

- **Gray matter**
  - 40% of brain matter
  - Neuronal cell bodies
  - Processes information

- **White matter**
  - 60% of brain matter
  - Communication between, to, and from gray matter areas
  - Myelin aids in signal communication, greater speed and efficiency
  - Highly ordered
  - Higher water diffusivity parallel to rather than perpendicular to nerve fibers

Tamnes et al., 2018
White Matter Tracts
What is diffusion?

- Random motion of molecules, on a microscopic scale, from higher to lower concentration
- Passive process
Barriers impede free diffusion

Cerebral spinal fluid (CSF)

White matter
### Key Feature of DTI: Anisotropic Diffusion

#### Isotropic
- Absence of barriers
- Diffusion is equal in all directions
- Ex: CSF, a glass of pure water

#### Anisotropic
- Presence of barriers
- Directionally dependent
- Movement typically along fiber tracts
- Ex: cellular membranes, myelinated fibers

#### Diffusion tensor model: 3-dimensional Gaussian model
- 3x3 symmetrical matrix with 3 orthogonal eigenvectors, aka local fiber coordinate system
- 3 eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) give diffusivity in the direction of each eigenvalue
Origins of Diffusion MRI

• Your eyes do not deceive you…

• Pre-DTI
  – Orientation of axon in tissue had to be known
  – Only fixed samples (e.g., axon of giant squid) could be scanned
• Areas of research
  – Autism
  – Schizophrenia
  – Alzheimer’s disease
  – Diagnosis of traumatic brain injury
  – Substance use
  – Developmental change, aging
  – Even used in dolphins! Used post-mortem samples to map sensory and motor system
Considerations in DTI

• Only 1 fiber direction per voxel can be modeled at a time
• Highly sensitive to motion; important when conducting developmental studies
• Susceptible to eddy currents caused by rapid switching of diffusion gradients
• Interpreting tractography; certain regions of the brain contain two or even more differently oriented fiber bundles within the same voxel (crossing, diverging, or kissing fibers)

Tamnes et al., 2018
DTI Data Acquisition
ABCD Study DTI Workflow

Fig. 1. Processing pipeline diagrams. A. Modality-specific processing steps for bias field, distortion, and/or motion correction. B. Processing pipeline input and outputs.

Hagler et al., 2019
Data quality is crucial

- High signal-to-noise ratio: necessary for robust measurement parameters and image accuracy
- Higher field strength: greater precision for diffusion weighting
- Stronger gradients improve signal
• Parallel imaging through RF coils with multiple receiver channels reduces acquisition times and image distortions

• Scan will cause vibrations of the scanner bed
• Average scan time: ~ 5-8 min.

Tamnes et al., 2018
DTI Quality Control and Preprocessing
Quality Control of DTI Data: The Problems

- Mechanically demanding: Fast gradient switching in echo-planar imaging
- Common artifacts
  - Eddy-currents
  - Motion artifacts
  - Slice- and gradient-wise inconsistencies
Quality Control of DTI Data: The Solutions

DTIPrep Workflow

START → Dicom to NRRD Conversion → Image Information Checking → Diffusion Information Checking → Denoising DWI Image (LMMSE Filter)

Gradients-wise Checking → Eddy-current, Head Motion Correction → Baseline Averaging → Interlace-wise Venetian Blind Checking → Slice-wise Intensity Checking

DTI Estimation → Dominant Direction/Vibration Checking → Simulation-based Bias Analysis → Visual Checking → END

Oguz et al., 2014
Quality Control of DTI Data: The Solutions

• **TORTOISE**: [https://tortoise.nibib.nih.gov](https://tortoise.nibib.nih.gov)

**What is TORTOISE?**

The TORTOISE software package is used for processing diffusion MRI data. It contains four main modules:

- **DIFF PREP** is used for image resampling, motion, eddy current distortion, and EPI distortion correction using a structural image as target, and for rigid body re-orientation of single subject data to a common space.

- **DR BUDDi** is used for EPI distortion correction using pairs of diffusion data sets acquired with opposite phase encoding (flip-up flip-down acquisitions).

- **DIFF CALC** software is used for tensor fitting, error analysis, directionally encoded color map visualization and ROI analysis.

- **DR TAMAS** (Diffeomorphic Registration for Tensor Accurate alignMent of Anatomical Structures) is a novel framework for inter-subject registration and template creation from Diffusion Tensor Imaging (DTI) data sets.
DTI Data Processing and Visualization
• Tensor estimation at each voxel
  – Minimum # of diffusion weighted images required for tensor calculation = 6

  – Three main methods: 1) Ordinary Least Squares (most common), 2) Weighted Linear Least Squares, and 3) Non-Linear Least Squares

Soares et al., 2013
Option 1: Scalar - tensor information via a single number representing diffusion magnitude or anisotropy

- **Mean diffusion (MD)**: average of tensor’s eigenvalues; total amount of diffusion in a voxel
- **Fractional anisotropy (FA)**: fraction of anisotropic diffusion; difference between tensor ellipsoid’s shape vs. perfect sphere
  0-1 range: 1=fully anisotropic, 0=isotropic

O’Donnell & Westin, 2011; Surova, 2014; Tamnes et al., 2018
• Option 1: Scalar - tensor information via a single number representing diffusion magnitude or anisotropy
  – **Apparent diffusion coefficient (ADC)**: magnitude of diffusion within tissue
  – **Axial diffusivity**: diffusion rate along main axis of diffusion
  – **Radial diffusivity**: diffusion rate in transverse direction

O'Donnell & Westin, 2011; Surova, 2014
Important note

- Quantified diffusion properties vary across:
  - Individuals
  - Brain region
  - Software
  - Acquisition parameters
  - Processing
  - Analysis methods

- Implications:
  - Cross-study comparisons
  - Multi-site studies
  - Transparency in reporting methods

Harmonizing DTI measurements across scanners to examine the development of white matter microstructure in 803 adolescents of the NCANDA study


Tamnes et al., 2018
• Option 2: Put tensor information into 4 numbers to provide color and brightness value
  – **Blue**: Superior-inferior
  – **Red**: Left-right
  – **Green**: Anterior-posterior
  – Brightness value: indicates tensor anisotropy

Ercan et al., 2015; O’Donnell & Westin, 2011
Option 3: Glyphs – small, 3D representations of major eigenvector or whole tensor
Option 4: Tractography – estimated course of white matter tracts
- Uses principle diffusion direction
- Colors assigned automatically according to atlas-based tractography segmentation

O’Donnell & Westin, 2011
Quantitative Analysis
• Extract summary measures from either specific anatomical regions or whole brain

• **ROI analysis**
  – Manual delineation of *a priori* specific regions or on automated parcellations
  – Applied to quantify diffusion parameters (mainly MD and FA) within those areas

• **Histogram analysis**
  – Whole brain analysis in an automated way, without any *a priori* specified ROIs
  – Histogram of each diffusion parameter (MD, FA, etc.) used to compare groups through statistical tests

Soares et al., 2013
Example ROI Analysis: White matter coherence, substance use, and risk-taking

- Examined bilateral white matter regions containing fiber tracts associated with higher order cognitive functioning and reciprocal frontal-subcortical and cortico-limbic projections in four, a priori selected ROIs.
- Binary parcellation map to obtain average FA coefficients for each ROI.
Key findings

- Lower FA at baseline in the fornix and superior corona radiata predicted follow-up substance use 1.5 years later

- Above and beyond variability accounted for by baseline risk taking, emotional functioning (i.e., depressive symptoms), and family history of an alcohol-use disorder

Addiction Center

Jacobus et al., 2013
• **Voxel Based Analysis (VBA)**
  
  – Voxel-wise method to compare local anisotropy values at whole-brain level between participants
  
  – Need to correct for multiple comparisons; reduce number of comparisons by using an atlas segmentation method to focus on particular areas of interest
  
  – Normalization is crucial; DTI is highly directional and topographical in nature

Diffusion-imaging.com; Soares et al., 2013
• **Multimodal Studies**
  – Changes in diffusion measures can point to alterations in functional patterns and behavior
  – Use conventional MRI or T1 weighted derived masks, segmentations, or parcellations (ROIs) in DTI data to extract combined structural and diffusion data
  – ROIs should be in the same reference space as the DTI data

Mayer et al., 2019; Soares et al., 2013
Review of Example DTI Study
Example Study: Simmonds et al. (2014)

Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study

- Longitudinal study, characterized the timing of white matter development
- Investigated how sex and behavior are associated with different developmental trajectories of white matter
• **White Matter:** Linear increases, increasing less in females than in males

• **Gray Matter:**
  Preadolescent increase and then post-adolescent decrease, sex differences reflect earlier pubertal timing in females

Giedd et al., 1999
Example Study: Simmonds et al. (2014)

- **Sample**: 128 typically developing 8-29 year olds (61 males) scanned 1-5 times
- **DTI acquisition**: Diffusion gradients applied in 6 non-collinear directions averaged over 14 repetitions to increase signal-to-noise ratio
- **DTI preprocessing**: DTIPrep used to automatically identify and correct motion and scanner-induced artifacts; data then visually inspected slice by slice
Example Study: Simmonds et al. (2014)

• **DTI analysis processing (FSL)**
  1. Raw DICOM images converted to NIFTI format
  2. Mask created using brain extraction
  3. Images corrected for head motion and eddy current distortion
  4. Tensor model fit to images – Each voxel assigned 3 eigenvectors and eigenvalues to describe within-voxel water diffusion

• **Additional group analyses**
  1. FA, AD, RD adjusted for registration artifacts and normalized to a template
  2. FA skeleton generated (mean FA map across subjects and thresholded at FA >0.2)

Simmonds et al., 2014
• DTI analysis processing (FSL) – ROI analyses
  – Core white matter tracts
  – White matter regions adjacent to gray matter
• Examined developmental effects and interactions with sex, behavior (visually-guided saccade, antisaccade task as indicators of cognitive control), and hemispheric differences using mixed-effects regressions

Example Study: Simmonds et al. (2014)
• Key findings
  
  – Fractional anisotropy (FA)
    • Showed **increases** with age
    • After adolescence and into adulthood there was continued growth in major frontal and limbic tracts
  
  – Radial diffusivity (RD)
    • Showed **decreases** with age
  
  – Axial diffusivity (AD)
    • Typically decreases with development
    • Timing of developmental change is mainly orthogonal to FA

*Example Study: Simmonds et al. (2014)*
• Key findings
  – **Sex differences**
    • Greater change of FA and RD in males, no significant differences in AD

Example Study: Simmonds et al. (2014)
• **Key findings**
  
  **Behavioral development**
  
  • Earlier maturation of white matter associated with more efficient network integration
  
  • Delayed maturation associated with weaker cognitive control
  
  • Protracted maturation of cingulum contributes to improvements in cognitive control

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Cingulum: White matter fibers projecting from the cingulate gyrus to the entorhinal cortex; facilitates communication between components of the limbic system; supports the ability of the ACC to integrate with other regions of the brain involved in inhibition

Simmonds et al., 2014
Example Study: Simmonds et al. (2014)

- White matter maturation occurs in a hierarchical manner
  - Pathways that support executive control mature through adolescence
  - Pathways involved in socioemotional processing continuing through the twenties
- Males show later maturation than females, which may underlie differential development of sex-related vulnerabilities to psychiatric disorders
- Cognitive outcomes are influenced by the timing of specific neurodevelopmental processes
Discussion and Questions
Questions for Methods Hour Group

• For anyone who has conducted DTI analyses, what issues have you come across? How have you dealt with them?

• Which DTI tools to use?

Table 1 | Software tools for DTI processing used in published studies.

<table>
<thead>
<tr>
<th>DTI software/tools</th>
<th>URL</th>
<th>Main purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D Slicer (Proper et al., 2006)</td>
<td><a href="http://www.slicer.org/">http://www.slicer.org/</a></td>
<td>Tensor estimation, ROI analysis, and tractography</td>
</tr>
<tr>
<td>AFNI (Cox, 2012)</td>
<td><a href="http://afni.nimh.nih.gov/afni">http://afni.nimh.nih.gov/afni</a></td>
<td>Preprocessing and tensor estimation</td>
</tr>
<tr>
<td>BrainImage Suite (Papademetris et al., 2003)</td>
<td><a href="http://www.biomedicalimage.org/">http://www.biomedicalimage.org/</a></td>
<td>Tensor estimation, ROI analysis, and tractography</td>
</tr>
<tr>
<td>BrainVoyager QX (Bouzlel, 2012)</td>
<td><a href="http://www.brainvoyager.com/">http://www.brainvoyager.com/</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>Camino (Cook et al., 2008)</td>
<td><a href="http://web4.cs.ucl.ac.uk/research/medical/camino/pmwiki/pmwiki.php">http://web4.cs.ucl.ac.uk/research/medical/camino/pmwiki/pmwiki.php</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>Dipy (Garyfallidis et al., 2011)</td>
<td><a href="http://dipy.org">http://dipy.org</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>DTeDTIphik (Park et al., 2004)</td>
<td><a href="http://neuroimage.yonsei.ac.kr/dtedti/">http://neuroimage.yonsei.ac.kr/dtedti/</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>DTeDTIphik (Park et al., 2004)</td>
<td><a href="http://graphics.stanford.edu/projects/dtephik/software/">http://graphics.stanford.edu/projects/dtephik/software/</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>DTI-TK (Zhang et al., 2009)</td>
<td><a href="http://dti-tk.sourceforge.net/pmwiki/index.php">http://dti-tk.sourceforge.net/pmwiki/index.php</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>DTIStudio (Liang et al., 2000)</td>
<td><a href="http://www.mristudio.org/wiki/DTIStudioV2">http://www.mristudio.org/wiki/DTIStudioV2</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>ExploreDTI (Ewens et al., 2008)</td>
<td><a href="http://www.exploredti.com/">http://www.exploredti.com/</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>Freesurfer (Fischl, 2012)</td>
<td><a href="http://surfer.nmr.mgh.harvard.edu">http://surfer.nmr.mgh.harvard.edu</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>FSL/FDTI (Smith et al., 2010)</td>
<td><a href="http://www.fmrib.ox.ac.uk/fsl/fdt/index.html">http://www.fmrib.ox.ac.uk/fsl/fdt/index.html</a></td>
<td>Tensor estimation and tractography</td>
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<td>FSL/TFSS (Smith et al., 2006)</td>
<td><a href="http://www.fmrib.ox.ac.uk/fsl/tfss/index.html">http://www.fmrib.ox.ac.uk/fsl/tfss/index.html</a></td>
<td>Tensor estimation and tractography</td>
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<tr>
<td>JMR (Gusis et al., 2000)</td>
<td><a href="http://www.nitrc.org/projects/jmr">http://www.nitrc.org/projects/jmr</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>MedINRIA (Hussaini et al., 2007)</td>
<td><a href="http://www.rocq.inria.fr/medinria/">http://www.rocq.inria.fr/medinria/</a></td>
<td>Tensor estimation and tractography</td>
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<tr>
<td>MRCommons</td>
<td><a href="http://www.stanford.edu/~mrfft">http://www.stanford.edu/~mrfft</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>MRTrix (Tournox et al., 2012)</td>
<td><a href="http://www.brain.org/software/mrtrix">http://www.brain.org/software/mrtrix</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>SATURN (Cardenas et al., 2010)</td>
<td><a href="http://www.fil.ion.ucl.ac.uk/spm/text/">http://www.fil.ion.ucl.ac.uk/spm/text/</a></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>SPM and toolboxes</td>
<td></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>e.g., Diffusion R, OT3 Toolboxes</td>
<td></td>
<td>Tensor estimation and tractography</td>
</tr>
<tr>
<td>TrackVis (Mang et al., 2007)</td>
<td><a href="http://trackvis.org/">http://trackvis.org/</a></td>
<td>Tensor estimation, tractography, and ROI analysis</td>
</tr>
<tr>
<td>TORTOISE (Pierpaoli et al., 2000)</td>
<td><a href="http://science.nichd.nih.gov/neuroconfer/trackvis/display/hpdb/TORTOISE">http://science.nichd.nih.gov/neuroconfer/trackvis/display/hpdb/TORTOISE</a></td>
<td>Tensor estimation, tractography, and ROI analysis</td>
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</tbody>
</table>

• How accurate is it to say “white matter integrity”?
Additional Resources

Andysbrainblog.com

diffusion-imaging.com

DTI Talk by Robert Welsh (2016)

FSL DTI Slides