Diffusion Tensor Imaging: Analysis options in pediatric neuroimaging research

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Course objectives

• The participant will:
  1. Identify the principles of Diffusion Tensor Imaging and Fiber Tractography
  2. Recognize the significance of the DTI scalars including fractional anisotropy (FA), mean (MD), axial (AD) and radial (RD) diffusivity and their changes in different conditions
  3. Describe different analytic approaches of DTI data and their advantages and disadvantages.

Outline

1. Basic knowledge about DTI + fiber tractography
2. Artifacts and how to avoid or correct them
3. Qualitative DTI/tractography analysis
4. Quantitative analysis:
   i. Region of interest (ROI) based analysis
   ii. Atlas-based analysis
   iii. Voxel-based analysis
   iv. Tract-based spatial statistics
5. Structural connectome

Diffusion tensor imaging (DTI)

Characterization of 3D shape of diffusion

• Diffusion = in all directions: isotropic
• Diffusion ≠ in all directions: anisotropic

Isotropic ↔ Anisotropic diffusion

Free diffusion ↔ Isotropic diffusion

Restricted diffusion ↔ Anisotropic diffusion
Characterization of diffusion

- Measure diffusion along various directions (> 6)
- Calculate shape of the ellipsoid

3x3 tensor matrix = 9 elements

Fractional anisotropy (FA)

- FA = ratio of the anisotropic component of the diffusion tensor to the whole diffusion
- Rotationally invariant scalar that quantifies the shape of the diffusion tensor
- FA: $0 < 1$

\[
FA = \sqrt{\frac{1}{2} \left( (\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2 \right)} \left/ \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right.
\]
Color-coded fractional anisotropy (FA)

Diffusion encoded color maps (DEC)

Powerful visualization of the fiber orientation = important anatomical information

Color-coding: qualitative information

Fractional anisotropy (FA)

• FA depends on several factors
• Myelin/myelination plays a key role

Fractional anisotropy (FA)

Axial and radial diffusivity

Axial diffusivity (AD)
• Rate of diffusion in the direction that is parallel to the main direction of diffusion
• \( AD = \lambda_1 \)
• Biomarker of axonal injury?

Radial diffusivity (RD)
• Rate of diffusion in the direction that is perpendicular to the main direction of diffusion
• \( RD = (\lambda_2 + \lambda_3)/2 \)
• Biomarker of myelin injury?
Axial ↔ Radial diffusivity

<table>
<thead>
<tr>
<th>White matter characteristics</th>
<th>Axial diffusivity</th>
<th>Radial diffusivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase myelination</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Dense axonal packing</td>
<td>Unaffected</td>
<td>Low</td>
</tr>
<tr>
<td>Large axonal diameter</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Axonal degeneration</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Demyelination</td>
<td>Unaffected</td>
<td>High</td>
</tr>
</tbody>
</table>

Feldman HM et al., J Dev Behav Pediatr, 2010

Fiber tractography (FT)

- Post-processing technique => reconstruction of the course of major fibers in the brain (several algorithms)
- Assumption: each voxel contains a single, coherently oriented bundle of axons

It is all about connecting the dots

because believing
will give you the confidence
to follow your heart
- Steve Jobs
Traffic square

How do I get to the correct place?

1. Get a good guidance (GPS or FA/angle thresholds)
2. Know where you start (airport address or initial seed point)
3. Know your destination (congress address or end seed point)

Fiber tractography (FT)

- Extract the correct/relevant information

Fiber tractography (FT): limitations

1. Crossing, kissing, merging or diverging fibers
2. High dependency on FA and angle thresholds
   - Tracking of pathways that do not exist (false positive) or ineffective tracking of existing pathways (false negative)
   - Interpretation of FT results needs knowledge of brain anatomy

Crossing fiber

1. In regions with crossing, kissing, merging or diverging fibers = more than one population of fibers
2. New techniques needed with a higher number of diffusion directions (HARDI, Q-Ball) => higher acquisition time

References:
- Jbabdi S and Johansen-Berg H, Brain Connect, 2011
Threshold dependency

- FA > 20° + Angle > 30°
- FA > 20° + Angle > 45°
- FA > 20° + Angle > 70°

Causes of artifacts

1. Magnetic susceptibility of CSF-, bone- and air-tissue interface (3T>1.5T)
2. Motion (ghosting)
3. Cardiac pulsation ➔ pulsatile CSF ➔ motion
4. Eddy currents:
   - Caused by changing magnetic field gradients during the image acquisition (changing with each direction)
   - Distortion of images (spatial)

Optimization techniques

**Image acquisition**

1. Dual spin-echo sequence = reduce eddy current
2. Cardiac gating = avoid cardiac pulsation artifacts (one image during R-R interval)
3. Rapid image acquisition = motion artifacts less likely
4. Blip up/down

**Image post-processing**

1. Affine registration = correct for motion artifacts and eddy currents
2. RESTORE = correct for cardiac pulsation and subject motion artifacts

EPI DTI sequence parameters for children

<table>
<thead>
<tr>
<th></th>
<th>1.5 T MR-Scanner</th>
<th>3.0 T MR-Scanner</th>
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<tbody>
<tr>
<td>b-value 1</td>
<td>0 s/mm²</td>
<td>0 s/mm²</td>
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<tr>
<td>b-value 2</td>
<td>1000 s/mm²</td>
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<td>Diffusion gradients</td>
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<tr>
<td>EPI factor</td>
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<td>96</td>
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<tr>
<td>Slice thickness</td>
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<tr>
<td>TR</td>
<td>7100 ms</td>
<td>7100 ms</td>
</tr>
<tr>
<td>TE</td>
<td>84 ms</td>
<td>92 ms</td>
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<tr>
<td>FoV</td>
<td>240 mm</td>
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</tr>
<tr>
<td>Acquisition time</td>
<td>5.21 min</td>
<td>5.21 min</td>
</tr>
</tbody>
</table>

Qualitative analysis

- Morphological information
- Based on color-coded FA maps and FT
- Knowledge of normal DTI images is mandatory
- Application: e.g. brain malformations to better understand the pathogenesis

Joubert syndrome

- Molar tooth sign
- Normal anatomy

Pantoli A et al, AJNR, 2011
Joubert syndrome

- Abnormal axonal guidance:
  - Involving superior cerebellar peduncles and corticospinal tracts (absence of decussation)
  - Shown by DTI and confirmed by neuropathology
  ➔ Joubert syndrome = axonal guidance disorder

Pontine tegmental cap dysplasia (PTCD)

Pontine tegmental cap dysplasia = axonal guidance disorder

DTI in Joubert syndrome

FT in Joubert syndrome

DTI in PTCD

FT in PTCD
**New disorder (?)**

- 6.5-year-old boy with learning difficulty + global developmental delay

**Quantitative analysis**

- Region of interest (ROI) based analysis
- Atlas-based analysis (ABA)
- Voxel-based analysis (VBA)
- Tract-based spatial statistics (TBSS)

**ROI-based analysis**

- Manual = ROIs are manually placed
- Selected anatomical regions = hypothesis driven

**Advantages**

1. Accurate especially for subjects with large anatomical changes
2. Low number of regions = higher statistical power and possibility to depict small differences

**Disadvantages**

1. Reproducibility ➔ multiple measurements + ICC calculation
2. Time consuming?
3. Hard to include the entire (3D) anatomical structure
4. Not applicable without hypothesis
5. Differences are missed in regions not included in the analysis

**ROI-based analysis: DTI of the brainstem in achondroplasia**

- Skeletal dysplasia with narrowing of cranio-cervical junction + foramen magnum
- Goal = To study the microstructural integrity of brainstem white matter tracts in children with achondroplasia compared to age-matched controls
ROI-based analysis: DTI in achondroplasia

- 7 ROIs; FA, MD, AD, RD
- 2 analysis by first reader, 1 analysis by second reader ➔ inter-/intra-rater reliability
- Comparison patients ⇔ controls
- Correlation with:
  - Severity of CCJ narrowing
  - Neurological findings

ROI-based analysis: DTI in achondroplasia

- Lower brainstem: ↓ FA + ↑ MD and RD in patients compared to controls
- ↑ MD+RD+AD in bilateral CST/MCP = white matter injury not limited to lower brainstem
- ↓ FA in lower brainstem ⇔ ↑ CCJ narrowing ➔ anatomical proximity lower brainstem ⇔ CCJ
- No correlation DTI ⇔ clinical findings

ROI-based analysis: vanishing white matter disease

- Leukodystrophy characterized by injury + cystic degeneration of the white matter
- Goal = Longitudinal DTI studies in 1 child with VWM

ROI-based analysis: vanishing white matter disease

- 10 ROIs; FA, MD, AD, RD; 2 DTI studies

Atlas- + voxel-based analysis

- No underlying theory about where we might find group differences ➔ global approach
  1. Atlas-based analysis = automatically segmentation of the brain into 170-180 well defined anatomical areas
  2. Voxel-based analysis = analysis of each voxel within the brain (>100,000)
Normalization process

- Standardization of info about location of brain structures
- Transformation to an age-matched template
- Two steps:
  1. Linear = low degree of freedom transformation, good for aligning images within subject
  2. Non-linear = high degree of freedom transformation


Templates

- Age appropriate template is needed
- Differences in contrast, shape and size subject template = poor accuracy of normalization

Oshin K et al, Int J Devl Neuroscience, 2013

Atlas + voxel-based analysis

- Diffeomorphic transformation (LDDMM)
  - Large Deformation Diffeomorphic Metric Mapping
  - Properties of LDDMM:
    - Highly elastic: important for normalization of brains with atrophy and/or ventriculomegaly
    - Preservation of topology
    - Reciprocal transformation: allows ABA + VBA


Atlas-based analysis

**Advantages**
1. "Limited" number of anatomical information (170-180 regions)
2. Evaluation of native images

**Disadvantages**
1. Information about anatomical localization lower than VBA
2. Less sensitive for very small lesions

ABA in children after hemispherectomy

- Hemispherectomy = surgical therapy for intractable seizures arising from a single cerebral hemisphere
- Goal = to study the changes of DTI metrics in the white matter regions of the remaining hemisphere (model for brain plasticity?)

Meoded A, Poretti A et al, in preparation
ABA in children after hemispherectomy

- n=19
  - Congenital etiology (n=11)
  - Acquired etiology (n=8)
- ABA of the remaining cerebral hemisphere
- Measurement of FA, MD, AD and RD in each anatomical region

Meoded A, Poretti A et al, in preparation

FA + AD ↓ and MD + RD ↑ = secondary Wallerian degeneration
- Wallerian degeneration: commissural + association > projection
- Presurgical DTI changes + postsurgical DTI normalization: acquired > congenital → reorganization, plasticity?

Voxel-based analysis

**Advantages**
1. Unbiased whole brain analysis
2. Sensitive for small lesions
3. Specific locations of significant group differences/correlations is automatically shown

**Disadvantages**
1. High number of information (millions of voxels) → low statistical power, correction for multiple comparison needed
2. Accuracy of voxel-to-voxel alignment across subjects is not high (correspondence problem)
3. Not sensitive for widespread lesions

Tract-Based Spatial Statistics (TBSS)

- Variation of whole-brain analysis
- FA images from multiple subjects are aligned to a common space
- Tract representation including only voxels at the center of tracts common to all
- The resulting skeleton data for all subjects are analyzed

**Advantages**
1. All locations across the brain are tested without a priori hypotheses
2. Powerful statistical module

**Disadvantages**
1. Skeletons are derived for the entire white matter region and no distinction between white matter structures is made
2. Variations in the periphery of white matter tracts may be missed (not included)
3. Possible effect of brain atrophy
TBSS in Niemann Pick disease type C

- Niemann Pick disease type C (NPC) = rare neurometabolic disease
- Goal = study the microstructural changes in patients with NPC compared to age-matched controls

n=8
- Measurement of FA, MD, AD and RD
- Diffuse reduction in FA and increase in MD, AD and RD in patients compared to age-matched controls

Poretti A, Meoded A et al, in preparation

The human connectome

- Human brain = network of nerve cells, regions and systems whose interconnections are largely unmapped
- Human connectome = map of the brain’s structural connections, rendered as a network
- Network = set of nodes + edges
- New ideal tool to study brain structure, performance and plasticity

Nodes
- Network elements
- Represent neuronal populations or brain regions

Edges
- Links between pairs of nodes
- A pair of nodes is mostly linked by:
  - A single undirected edge or
  - Two directed edges in opposite directions

Structural connectivity
- Pattern of physical connections between brain regions
- Based on DTI

Functional connectivity
- Pattern of statistical dependencies between distributed and neural elements
- Based on fMRI

1. Topology analysis:
   - Network metrics ➔ global/regional network organization
   - Information: segregation, integration, small worldness, centrality (Hubs)
2. Network based statistics:
   - Strength of connectivity between brain regions at a pairwise level
   - Subnetworks

**Topology analysis**

- Segregation = ability for processing to occur within densely interconnected groups
- Clustering coefficient = fraction of connections that connect the neighbors of a given node
- Integration = ease for brain regions to communicate based on route of information flow; Shorter path shorter = higher integration
- Small world = well-designed network combining high clustering and short path

**Topology analysis**

- Centrality = measurement of the influence of a node compared to the rest of the network
- Betweenness centrality = fraction of short paths between nodes of the network that pass through a give node
- Hub = region with high degree of connections (high centrality)
- Assortativity = correlation between the degrees of connected node pairs

**Connectome reconstruction**

- DTT in native space
- T2, T2* MPRAGE
- Data registered to MNI space

**Structural connectome in agenesis of the corpus callosum (AgCC)**

- Patients
  - N=10
  - Mean age at MRI = 6.5 y, SD 4.5 y
- Controls
  - N=10
  - Mean age at MRI = 5.9 y, SD 4.7 y

**Topology analysis: AgCC ↔ controls**

- ↑ Cluster coefficient ($p=0.005$)
- ↓ Small worldness ($p=0.005$)
- ↑ Transitivity ($p=0.003$)
- ↓ Assortativity ($p=0.03$)

**Hubs in patients**

Network hubs = nodes with betweenness of 2SD > mean betweenness

Meoded A, Poretti A et al, in preparation
Hubs in controls

Network hubs = nodes with betweenness of 2SD > mean betweenness

Topology analysis of network modules

- Controls: 6 modules
- Patients: 5 modules

Network based statistics

Intrahemispheric left fronto-parietal:
children with AgCC \(\triangleleft\) virtual callosotomy controls, \(p=0.013\)

Interhemispheric fronto-cerebellar:
children with AgCC \(\triangleleft\) virtual callosotomy controls, \(p=0.021\)

Intrahemispheric left temporo-occipital:
children with AgCC \(\triangleleft\) virtual callosotomy controls, \(p=0.048\)

Structural connectome in AgCC

1. AgCC = more segregated + less integrated brain connectome
2. No hub in the cerebellum in patients = global connectivity ↓
3. Highly inter-connected interhemispheric fronto-cerebellar network + two insular hubs = brain plasticity → ↑ interhemispheric flow of information through alternative pathway (anterior commissure?)
Stuctural connectome in AgCC

4. Lower modularity = connectome reorganization to reduce connection cost at the expense of decreasing integrative capacity?

Conclusions

• DTI/FT = ideal neuroimaging to study the pediatric brain
• Application to several pediatric neurology diseases
• Qualitative and quantitative analysis
• Different methods for quantitative analysis
• Method depends on research question

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