Resting-state fMRI and DTI

David C. Zhu, Ph.D.
Associate Professor of Radiology and Psychology
Cognitive Imaging Research Center
Michigan State University, East Lansing, Michigan, USA
Facts

- The brain is only about 2% of total body mass.
- But it consumes about 20% of the body’s total energy at “rest”.
- Engaging in active tasks increases neuronal metabolism less than 5%.

What is this energy at “rest” consumed by?

The on-going spontaneous neuronal activity
Oxygenated and deoxygenated hemoglobin (Hb)
Two Main Paths of BOLD (Blood Oxygen Level-Dependent) fMRI

First 1-2 seconds

**Stimulation**

Neuronal Activity

\[ \text{CMR}_{\text{glucose}} \]

\[ \text{CMR}_{\text{O}_2} \]

Blood Oxygen Level

Deoxygenated hemoglobin: paramagnetic

**Blood Magnetic Susceptibility Effects**

\[ T_2^* \text{ decay} \]

fMRI Image Signal Intensity

Later seconds

Cerebral Blood Flow (CBF)

Blood Oxygen Level

Oxygenated hemoglobin: diamagnetic

**Blood Magnetic Susceptibility Effects**

\[ T_2^* \text{ decay} \]

fMRI Image Signal Intensity
Resting-state fMRI based functional connectivity analyses

Assumptions

Strong BOLD fMRI temporal correlation

Strong neuronal synchronous activity

Strong functional connectivity

Same/intact network
Two popular methods of processing for resting-state fMRI

1. Correlation analysis
2. Independent component analysis (ICA)
Seed-based correlation analysis

\[ S_{measure} = S_{intrinsic} + S_{random} \]
Time courses of correlated and uncorrelated regions
Resting-state fMRI pre-processing steps

1. Slice-timing and motion correction.
2. Remove baseline, linear and quadratic system trends.
3. Spatial blurring.
4. Remove “Nuisance” signals of
   (a) Global mean
   (b) CSF
   (c) White matter
5. Band-pass filtering: 0.009 Hz – 0.08 Hz
Seed Region #1: pC/rsp (posterior cingulate/retrosplenial cortex)

**Group Integration**
(17 subjects):
Whole-brain corrected $P < 0.0325$.
Mean structural normalized connectivity distribution $> 10^{-4}$.

Seed Region #2 : Right SPL (superior parietal lobule)

Group Integration (17 subjects):
Whole-brain corrected $P < 0.0325$.
Mean structural normalized connectivity distribution $> 10^{-4}$. 
Seed Region #3: Left Cuneus

**Group Integration**
(17 subjects):
Whole-brain corrected $P < 0.0325$.
Mean structural normalized connectivity distribution $> 10^{-4}$.

Left cuneus  ↔  Right cuneus
Independent Component Analysis

http://www.fmrib.ox.ac.uk/fsl/melodic/index.html
ICA example results with MELODIC in FSL

IC 1: Default Mode Network
IC 25: Visual Network
Default-Mode Network

Medial temporal lobe (MeTL)
(hippocampus, parahippocampal gyrus, entorhinal gyrus)
(memory processing)

Medial prefrontal cortex (MePFC)
(Medial frontal cortex, anterior cingulate cortex, superior frontal cortex)
(facilitation)

Structural connectivity
(diffusion MRI fiber tracking)

Posterior cingulate cortex/retrospenial cortex (PCC/RSC)
(Integration)

temporoparietal junction cortices (TPJC):
(angular gyrus, superior/middle temporal gyrus, parietal lobule, supramarginal gyrus)

Alzheimer’s disease and amnestic mild cognitive impairment weaken connections within the default-mode network

7 minute resting-state fMRI EPI scan (relax and eyes open in dim-light condition):

38 contiguous 3-mm axial slices,
22 cm × 22 cm FOV,
64 × 64 matrix size,
27.7 ms TE, 2500 ms TR,
80° flip angle,
164 time points.
Functional connectivity with seed region at the right isthmus of cingulate cortex (Normal > AD)

PET

(a) R TPJC
(b) PCC/RSC
(c) L TPJC
(d) PET: NC > AD
Structural connectivity with the seed region in the associated white matter of the right isthmus of cingulate cortex

NC > AD

NC > aMCI
A potential biomarker in sports-related concussion: brain functional connectivity alteration of the default-mode network measured with longitudinal resting-state fMRI over 30 days.

The DMN Network
Mean default-mode network connectivity
(7 concussed, 11 control)

Overall DMN Connectivity ($R$)

Day 1 | Day 7 | Day 30

- Concussed
- Control

$R$: 0.35, 0.4, 0.35
DMN after concussion (n = 7)

(Node # 1 = left PCC, 2 = left ACC/MeFC, 3 = left SFG, 4 = left IPL/AG, 5 = left hippocampus, 6 = right PCC, 7 = right ACC/MeFC, 8 = right SFG, 9 = right IPL/AG, 10 = right hippocampus)

Node 1 2 3 4 5 6 7 8 9 10 R value
1 2 3 4 5 6 7 8 9 10

Mean correlation R on Day 1

Mean correlation R on Day 7

Mean correlation R on Day 30

Node 1 2 3 4 5 6 7 8 9 10 p value
1 2 3 4 5 6 7 8 9 10

t test of Day 1 vs. Day 7

t test of Day 7 vs. Day 30

t test of Day 1 vs. Day 30
DMN of control subjects (n=11)
(Node # 1 = left PCC, 2 = left ACC/MeFC, 3 = left SFG, 4 = left IPL/AG, 5 = left hippocampus, 6 = right PCC, 7 = right ACC/MeFC, 8 = right SFG, 9 = right IPL/AG, 10 = right hippocampus)

Mean correlation $R$ on Day 1

Mean correlation $R$ on Day 7

Mean correlation $R$ on Day 30

$t$ test of Day 1 vs. Day 7

$t$ test of Day 7 vs. Day 30

$t$ test of Day 1 vs. Day 30
The mean functional connectivity to left isthmus of cingulate cortex (ICC) of the concussed group (correlation $R > 0.25$, $n = 7$)

Day 1

Day 7

Day 30

(b) ANOVA: Day 1 vs. Day 7 ($n = 8$)

(c) ANOVA: Day 1 vs. Day 30 ($n = 7$)
Case study
The functional and structural connectivity to left isthmus of cingulate cortex of a concussed subject over one month (correlation $R > 0.4$ and connectivity distribution $> 1000$).

<table>
<thead>
<tr>
<th>Seed regions</th>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green: functional seed</td>
<td>Orange: structural seed</td>
<td>Red: overlap regions.</td>
<td>Orange: structural seed</td>
</tr>
</tbody>
</table>

The above functional connectivity reduction from Day 1 to Day 7 was seen in 8 of our 9 concussed cases.
Resting-state fMRI based functional connectivity analyses

Assumptions

- Strong BOLD fMRI temporal correlation
- Strong neuronal synchronous activity
- Strong functional connectivity
- Same/intact network

Vascular confound

Why?

The underlying cellular and molecular bases
Introduction to Diffusion Tensor Imaging (DTI)
Fick’s Law describes particle movement

Net flux (mole mm²/s): \[ J = -D \frac{\Delta C}{\Delta x} \]

Diffusion coefficient D is in mm²/sec

\[ \frac{\Delta C}{\Delta x} = \text{concentration gradient in mole/mm}^4 \]

High concentration \[ J \rightarrow \] Low concentration
Figure 5.20 Diffusion

- Start location
- End location

Time

*Functional Magnetic Resonance Imaging 2e, Figure 5.20*
Stejskal-Tanner Diffusion-weighted Sequence
Isotropic Diffusion

Signal attenuation due to diffusion coefficient $D$

$$A = \frac{S}{S_0} = e^{-bD}$$

Where $b =$ commonly called “$b$ factor”, which characterizes the gradient pulses (timing, amplitude, shape) = clinical practice, $1000 \text{ s/mm}^2$
Stejskal-Tanner Diffusion-weighted Sequence

\[ b = \gamma^2 G^2 \delta^2 \left( \Delta - \frac{\delta}{3} \right) \]
Anisotropic Case (for example, axons)

\[ b = \begin{bmatrix} b_{xx} & b_{xy} & b_{xz} \\ b_{yx} & b_{yy} & b_{yz} \\ b_{zx} & b_{zy} & b_{zz} \end{bmatrix} \]

\[ D = \text{diffusion tensor} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \]

\[ A = e^{-bD} \]

\[ A = e^{-\left( b_{xx}D_{xx} + b_{yy}D_{yy} + b_{zz}D_{zz} + 2b_{xy}D_{xy} + 2b_{xz}D_{xz} + 2b_{yz}D_{yz} \right)} \]
Diagonalization

$$DE = E\Lambda$$

$E = \text{eigen vector (unit vector)}$

$$\Lambda = \text{eigen value} = \begin{bmatrix}
\lambda_1 & 0 & 0 \\
0 & \lambda_2 & 0 \\
0 & 0 & \lambda_3
\end{bmatrix}$$

Laboratory frame  Diffusion ellipsoid
Mean diffusivity = $\lambda_{\text{mean}} = (\lambda_1 + \lambda_2 + \lambda_3)/3$

The level of tissue constraint

Fractional Anisotropy = $FA = \frac{\sqrt{3[(\lambda_1 - \lambda_{\text{mean}})^2 + (\lambda_2 - \lambda_{\text{mean}})^2 + (\lambda_3 - \lambda_{\text{mean}})^2]}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$

the directionality of diffusion

Axon fiber integrity

Mean diffusivity map

FA map
<table>
<thead>
<tr>
<th></th>
<th>Mean diffusivity</th>
<th>Anisotropy (1-volume ratio)</th>
</tr>
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<tbody>
<tr>
<td>Cerebrospinal fluid (CSF)</td>
<td>3.19 ± 0.10</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>Gray matter (frontal cortex)</td>
<td>0.83 ± 0.05</td>
<td>0.08 ± 0.05</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>0.67 ± 0.02</td>
<td>0.08 ± 0.03</td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyramidal tract</td>
<td>0.71 ± 0.04</td>
<td>0.93 ± 0.04</td>
</tr>
<tr>
<td>Corpus callosum (splenium)</td>
<td>0.69 ± 0.05</td>
<td>0.86 ± 0.05</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>0.64 ± 0.03</td>
<td>0.70 ± 0.08</td>
</tr>
<tr>
<td>Centrum semiovale</td>
<td>0.65 ± 0.02</td>
<td>0.27 ± 0.03</td>
</tr>
</tbody>
</table>

*Measurements were obtained in normal volunteers using diffusion tensor MRI (from ref. 31).
Deterministic approach:
Answer Yes/no.

Software: (1) DTI Studio
(2) MedINRIA

Probabilistic approach:
How probable two voxels/regions connected together
Software: FSL
Probabilistic tracking at Right Fornix
Data Acquisition

GE 3T Signa® HDx MR scanner with an 8-channel head coil.

12 minute and 6 second DTI scan (full-brain coverage):
  Dual spin echo EPI sequence,
  48 2.4-mm axial slices,
  22 cm × 22 cm FOV, 128 × 128, 2 NEX,
  75 ms TE, 13.7 s TR,
  parallel imaging acceleration factor = 2,
  $b = 1000$ s/mm$^2$, 25 directions
DTI Analysis with the Diffusion Toolbox (FDT v2.0) in FSL software package

Eddy-current distortion and motion correction.

Applied Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques with the crossing fibers (n = 2) modeled (BEDPOSTX).

Applied probabilistic tractography (PROBTRACKX) to each seed region to calculate the corresponding connectivity distributions.

The connectivity distributions were then normalized by the total number of generated tracts from the seed region.

Integration

• Resting-state fMRI allows the examination of brain function connectivity (1).

• Diffusion tensor imaging (DTI) fiber tracking allows the evaluation of structural connection between cortical regions (2).

1. Fox MD, Raichle ME. Nat Rev Neurosci. 2007; 8:700-711.
Test both functional and structural connectivity.
Case study
The functional and structural connectivity to left isthmus of cingulate cortex of a concussed subject over one month (correlation $R > 0.4$ and connectivity distribution $> 1000$).

Seed regions
Green: functional seed
Orange: structural seed

Day 1
structural

Day 7

Day 30

Red: overlap regions.

The above functional connectivity reduction from Day 1 to Day 7 was seen in 8 of our 9 concussed cases.
Volumetric Analysis and Segmentation with FreeSurfer
<table>
<thead>
<tr>
<th></th>
<th>Left-Putamen</th>
<th>Left-Pallidum</th>
<th>Time point 0</th>
<th>Time point 1</th>
<th>% change</th>
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<tbody>
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<td>Region</td>
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