How to Map Functional Connectivity Based on Synchronized CMRO$_2$ Fluctuations During the Resting State

Yihong Yang, Ph.D.

Neuroimaging Research Branch
National Institute on Drug Abuse
National Institutes of Health
Resting-state functional connectivity

• Spontaneous fluctuations in resting-state fMRI are significantly correlated between brain regions in specific networks.

• These correlations are thought to reflect synchronized neuronal activity, and are called “functional connectivity” of brain regions.

Modified from Zhang & Raichle, Nat. Rev. Neurol, 2010
Neuronal activity and fMRI detection

Modified from Bonvento, Sibson & Pellerin, Trends in Neurosciences, 2002
Localization of neuronal activity

Jin and Kim, NeuroImage, 2008
ph-fMRI using CBF and BOLD: Visual stim. during cocaine injection

Visual Stim. during cocaine injection

Baseline CBF

CBF change during visual stimulation

Visual stimulation

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Basal CBF</th>
<th>CBF change during visual stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>62.6±22.3*</td>
<td>49.4±18.8%</td>
</tr>
<tr>
<td>3</td>
<td>56.9±19.1*</td>
<td>52.6±16.5%</td>
</tr>
<tr>
<td>6</td>
<td>62.0±17.6</td>
<td>47.4±19.7%</td>
</tr>
<tr>
<td>9</td>
<td></td>
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*p<0.02

NS
BOLD, or not BOLD…

• BOLD has relatively high sensitivity in detecting oxygenation-related contrast, but limited specificity in localizing neuronal activity.

• CBF or CBV based fMRI techniques localize neuronal activity more accurately than BOLD, but have low sensitivity. Be cautious of baseline CBF/CBV changes in pharmacological fMRI.

• CMRO$_2$ based fMRI techniques should have the best localization of neuronal activity, independent of hemodynamic changes. But its sensitivity might be the lowest.
Beyond-BOLD techniques to detect resting-state functional connectivity

- CBF-based rs-fMRI
  - Arterial spin-labeling (ASL) imaging

- CBV-based rs-fMRI
  - Vascular space occupancy (VASO) imaging

- CMRO$_2$-based rs-fMRI
  - Calibrated fMRI
Arterial Spin Labeling

Label by magnetic inversion

Inflow and $T_1$ Decay

Acquire image of tissue + labeled blood

Control

Acquire image of tissue + relaxed blood

Control

Label

$\Delta M$
PET study showed that a set of brain regions (PCC, MPFC, insula, and thalamus) exhibit higher CBF than the whole brain average at rest (default mode), and CBF in these regions decreases from its baseline level during goal-directed tasks.

Raichle et al., PNAS, 2001
Dynamic characteristics of brain activity in the resting state

- Dynamic interactions between brain regions have been revealed using resting-state BOLD.

Fox et al., PNAS, 2005.
Static and dynamic characteristics of brain activity in the resting state

- CBF-based rs-fMRI have the potential to measure the static and dynamic characteristics of resting-state signals under a single modality within the same subjects.
Methodology for CBF-based resting-state fMRI

• Data acquisition
  ➢ Pulsed arterial spin labeling (PASL) imaging.

• Data processing and analysis
  ➢ Removal of BOLD contribution in the ASL signal (Chuang et al., 2008).
  ➢ Removal of physiological noise using ICA.
  ➢ Seed-based cross correlation analysis (seed in PCC).
Static perfusion in the resting state

Zou et al., NeuroImage, 2009
Dynamic perfusion in the resting state - Functional connectivity

Zou et al., NeuroImage, 2009
Functional connectivity strength vs. CBF

Liang et al., PNAS, 2013
Functional connectivity strength vs. CBF in four brain networks

Liang et al., PNAS, 2013
N-back working memory task state

- FCS-rCBF relationship was strengthened at higher task load

Liang et al., PNAS, 2013
Summary of CBF-based rs-fMRI

- ASL can simultaneously assess the static and dynamic brain activity using the same imaging modality within the same subject.

- Static CBF was significantly higher in PCC, MPFC, insula, and thalamus than the global brain average, consistent with previous PET observations. Dynamic analyses showed that these brain regions are highly correlated with PCC.

- Functional connectivity strength is closely coupled with regional CBF at rest and is modulated by cognitive load, suggesting a physiological basis of functional hubs in the brain.
VASO – Vascular space occupancy

CBV change ~ 20-30%

Lu et al., MRM, 2003
Simultaneous VASO, ASL and BOLD

Yang et al., MRM, 2004
Simultaneous VASO, ASL and BOLD: 2 and 8 Hz Visual Stimulation

<table>
<thead>
<tr>
<th></th>
<th>VASO (%)</th>
<th>ASL (%)</th>
<th>BOLD</th>
<th>CMRO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Hz</td>
<td>-1.42±0.50</td>
<td>42.8±12.2</td>
<td>1.28±0.28</td>
<td>15.9±9.80</td>
</tr>
<tr>
<td>8 Hz</td>
<td>-2.48±0.40</td>
<td>68.2±13.0</td>
<td>1.94±0.56</td>
<td>21.4±12.2</td>
</tr>
</tbody>
</table>
CBV-based fMRI for detecting resting-state brain activity

• Developed a 3D-VASO sequence covering the whole brain in a single shot.

• Evaluated the feasibility of the sequence in detecting resting-state brain activity.
VASO and BOLD in a visual-task fMRI

Miao et al., NeuroImage, 2014
VASO and BOLD in resting-state fMRI

- Sensorimotor Network
- Auditory Network
- Primary Visual Network
- Higher Visual Network
- Default-mode Network
- Salience Network
- Left ECN
- Right ECN

Images a) VASO (ICA), b) BOLD (ICA), c) VASO (Seed-based)
Susceptibility artifacts in VASO and BOLD

Miao et al., NeuroImage, 2014
Susceptibility artifacts in VASO and BOLD

Miao et al., NeuroImage, 2014
Frequency specificity of VASO and BOLD
Summary of CBF-based rs-fMRI

- 3D-VASO imaging can measure resting-state brain activity in the whole brain.

- Intrinsic brain networks detected by the 3D-VASO imaging are very consistent with those by BOLD in the human brain. Improved localization of neuronal activity is expected with high resolution (≤ 1 mm).

- 3D-VASO imaging is less sensitive to susceptibility-induced artifacts, and therefore will be useful in brain regions (such as OFC) that suffer from signal loss in BOLD.
Motivations for metabolism-based resting-state fMRI

- The underlying mechanism of rs-fMRI has not been fully understood yet.

- Physiological noise (cardiac and respiratory) and non-neuronal hemodynamic oscillations are potential confounds in rs-fMRI signal.

- Metabolism fluctuations (e.g. CMRO$_2$) are closely related to neuronal activities, but independent to physiological and hemodynamic changes.
Metabolism-based resting-state fMRI

• Simultaneous acquisition of BOLD and ASL signals (dual-echo acquisition).

• Determination of CMRO$_2$ from the BOLD and perfusion signals, based on a biophysical model.

\[
S_{CMRO_2} = (1 - \frac{S_{BOLD\%}}{M})^{1/\beta} (S_{CBF})^{1-\alpha/\beta}
\]

M, $\alpha$ and $\beta$ are constants, which can be determined from experiments or literature.

• Data analysis
  ➢ Seed-based cross correlation analysis (Seeds in PCC, visual, and hippocampus).
Time courses of BOLD, perfusion, and CMRO$_2$ – Visual stimulation

(a) Visual Task

Visual Cortex

BOLD

Perfusion

CMRO$_2$

Default Mode

Hippocampus

Wu et al., NeuroImage, 2009
Time courses of BOLD, perfusion, and CMRO$_2$ – Resting state

(b) Resting State

Visual Cortex

BOLD

Perfusion

CMRO$_2$

Default Mode

Hippocampus

Wu et al., NeuroImage, 2009
Connectivity maps of BOLD, perfusion, and CMRO$_2$ – Visual stimulation

a) Visual Task:

- **BOLD**
  - Z=+5
  - Visual Cortex
  - Z=+14
  - Default Mode
  - Y=+24
  - Hippocampus

- **Perfusion**

- **CMRO$_2$**
  - (M=22%)

Wu et al., NeuroImage, 2009
Connectivity maps of BOLD, perfusion, and CMRO$_2$ – Resting state

b) Resting State:

- **Visual Cortex**
  - BOLD
  - Perfusion
  - CMRO$_2$ (M=22%)
  - $Z=+5$

- **Default Mode**
  - $Z=+14$

- **Hippocampus**
  - $Y=+24$

Wu et al., NeuroImage, 2009
Sensitivity to the parameters in the biophysical model

Wu et al., NeuroImage, 2009
Functional connectivity strength vs. metabolism across Brodmann areas

Liang et al., PNAS, 2013
Summary of Metabolism-Based rs-fMRI

- Functional connectivity of the brain can be detected not only from BOLD and perfusion, but also CMRO$_2$.

- This observation provides direct evidence supporting the hypothesis that spontaneous fMRI signal fluctuations have a metabolic origin.

- Since regional metabolism is closely coupled with local neuronal activity, the fMRI fluctuations are likely associated with ongoing neuronal activity.
## Summary – CMRO$_2$, CBF/CBV, and BOLD

<table>
<thead>
<tr>
<th></th>
<th>CMRO$_2$</th>
<th>CBF &amp; CBV</th>
<th>BOLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantifying brain activity</td>
<td>good</td>
<td>good-fair</td>
<td>limited</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>Low</td>
<td>fair</td>
<td>high</td>
</tr>
<tr>
<td>Spatial specificity</td>
<td>good</td>
<td>good-fair</td>
<td>fair-poor</td>
</tr>
<tr>
<td>Temporal resolution</td>
<td>poor</td>
<td>poor-fair</td>
<td>good</td>
</tr>
<tr>
<td>Spatial coverage</td>
<td>poor</td>
<td>good-fair</td>
<td>good</td>
</tr>
<tr>
<td>Data interpretation</td>
<td>good</td>
<td>good-fair</td>
<td>limited</td>
</tr>
<tr>
<td>Implementation</td>
<td>hard</td>
<td>hard-fair</td>
<td>easy</td>
</tr>
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