Resting-state fMRI:
Applications in Cognitive and Clinical Neuroscience

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Overview

• Numerous intrinsic connectivity networks
• Relation to normal brain function
  – Functional correlates of network strength
  – Effect of fluctuations on evoked behavior/responses
  – Connectivity to study continuous, subject-driven states
• Relevance to neuropsychiatric diseases
  – Neurodegenerative diseases
  – Coma, epilepsy, depression
Functional Connectivity

\[ r = 0.75 \]

\[ r = 0.59 \]

\[ r = 0.80 \]
A Network for Every Function and a Function for Every Network

Beckmann et al., *Philos Trans R Soc Lond*, 2005
ICNs for Salience Detection and Executive Control

Seeley et al., J Neurosci, 2007
Replicated with Independent Component Analysis

Seeley et al., *J Neurosci*, 2007
Correlations with Behavior

Seeley et al., *J Neurosci*, 2007
ECN Correlates with IQ

Song et al., *Neuroimage*, 2008
Left Inferior Frontal to Superior Temporal Connectivity Correlates with Reading Competence

Koyama et al., *J Neurosci*, 2011
Spontaneous Fluctuations and Intertrial Variability

Fox et al., *Neuron*, 2007
Spontaneous Fluctuations and Behavior 1

Fox et al., Neuron, 2007
Spontaneous Fluctuations and Behavior 2

Boly et al., PNAS 2007
Spontaneous Fluctuations and Behavior 3

Hesselmann et al., *PNAS* 2008
Whole-Brain Connectivity
Defining Continuous, Subject-Driven

One-Sample T-Test

Shirer et al., *Cer Cortex*, In press
Classification

Fit = 2.52

Fit = 0.97

Fit = 1.71

Fit = 1.37

Shirer et al., Cer Cortex, In press
Accuracy

LOOCV: 84% (47 of 56)
Independent Sample: 85% (34 of 40)

Structural ROIs (AAL): 65% (26 of 40)
fROIs > AAL for all scan lengths (p < 0.001)

Shirer et al., Cer Cortex, In press
Functional ROIs Available:

The following links may be used to download our atlas of functional ROIs (fROI). Currently 90 ROIs are available, but we are working to expand our fROI atlas. A paper detailing the creation of these 90 fROIs has been accepted for publication in *Cerebral Cortex*:


Dorsolateral Prefrontal Cortex: Dawr-soh-lat-er-uhl pre-ruhn-ti kawr-tek

A brain region implicated in complex cognitive functions like reasoning, set-shifting, and working memory.
Exponential Growth of Resting State fMRI Studies

Disorders Studied
- Autism
- Schizophrenia
- Alzheimer’s Disease
- Parkinson’s Disease
- Multiple Sclerosis
- ADHD
- PTSD
- TBI
- OCD
- Depression/Bipolar
- Anxiety Disorder

…

Slide and scopus search courtesy of Rasmus Birn, Medical College of Wisconsin
Hypometabolism in AD

Resting PET: 34 healthy subjects versus 14 AD patients.
Default-Mode Network in AD

ICA-based detection of default-mode network in healthy aging (A) and AD (B).

Greicius et al., PNAS, 2004
Default-mode in healthy aging versus
85% sensitivity
77% specificity

Greicius et al., *PNAS*, 2004
Reduced DMN Connectivity in MCI

Sorg et al., *PNAS* 2007
Reduced DMN Connectivity in PiB+ Controls

Hedden et al., *J Neurosci*, 2009
Sheline et al., *Biol Psych* 2010
Network-Based Neurodegeneration

"Resting" BOLD amplitude

Seeley et al., Neuron, 2009

Fire Together, Wire Together, Expire Together
Anti-Correlations without Global Scaling
(Group Level)

Chang and Glover, Neuroimage 2010
FTD vs AD = Salience vs DMN

Zhou et al., *Brain*, 2010
FTD vs AD = Salience vs DMN

Zhou et al., *Brain*, 2010
Increased Connectivity in Young ApoE4 Carriers

Filippini et al., *PNAS*, 2009
ApoE and Connectivity in Healthy Aging

38 E4s (29 female), 62 nonE4s
All PIB-
mean age 62

Sheline et al., J Neurosci, 2010
ApoE and Connectivity in Healthy Aging 2

Table. Sample Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CN No APOE e4 (n=56)</th>
<th>CN APOE e4 (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, No (%)</td>
<td>21 (38)</td>
<td>21 (38)</td>
</tr>
<tr>
<td>APOE e4 genotype, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/2</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>2/3</td>
<td>5 (9)</td>
<td>0</td>
</tr>
<tr>
<td>3/3</td>
<td>50 (89)</td>
<td>0</td>
</tr>
<tr>
<td>2/4</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>3/4</td>
<td>0</td>
<td>51 (91)</td>
</tr>
<tr>
<td>4/4</td>
<td>0</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>79 (64-91)</td>
<td>78 (63-90)</td>
</tr>
<tr>
<td>Median education, y (range)</td>
<td>14 (3-20)</td>
<td>13 (8-20)</td>
</tr>
<tr>
<td>Median short test score (range)</td>
<td>36 (30-38)</td>
<td>35 (29-38)</td>
</tr>
<tr>
<td>Median CDR sum of boxes (range)</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Abbreviations: CN, cognitively normal; CDR, Clinical Dementia Rating scale.

a Demographics with the cognitively healthy patients matched 1 to 1.

b P=.008.
Single-Patient Level: Seizure Focus Localization

Increased remote and local connectivity

Stufflebeam et al., *J Neurosurg*, 2011
Prognosis for Coma Recovery

Vanhaudenhuyse et al., Brain, 2010
Single-Patient Level: Disorders of Consciousness

Soddu et al.,
Hum Brain Mapp, 2011
Single-Patient Level: Disorders of Consciousness

Soddu et al.,
*Hum Brain Mapp*, 2011
The Subgenual Cingulate in Depression

Mayberg et al., *Neuron*, 2005
Increased Subgenual Cingulate Connectivity in Depression

Greicius et al., *Biol Psychiatry*, 2007
BA25 Connectivity Correlates with Current Episode Duration

$r = 0.49$
$p < 0.05$

Greicius et al., *Biol Psychiatry*, 2007
Increased Subgenual Connectivity in Depression 2

Sheline et al., *PNAS* 2010
Alzheimer's Disease
Before-After Donepezil
p < 0.05, uncorrected
# Test-Retest Reliability

**Table 7**

Voxelwise analysis: Significant and Reliable Functional Connectivity

<table>
<thead>
<tr>
<th>Seed ROI</th>
<th>BA</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Z Score</th>
<th>Multi-Scan</th>
<th>Inter-Session</th>
<th>Intra-Session</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
<td>Max</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>L. PCC</strong></td>
<td>29/30</td>
<td>6</td>
<td>56</td>
<td>28</td>
<td>12.1</td>
<td>0.65</td>
<td>0.80</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>L. vmPFC</strong></td>
<td>10/11</td>
<td>6</td>
<td>-54</td>
<td>-4</td>
<td>7.7</td>
<td>0.54</td>
<td>0.54</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>L. ITG</strong></td>
<td>21</td>
<td>64</td>
<td>12</td>
<td>-18</td>
<td>7.6</td>
<td>0.69</td>
<td>0.84</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>R. MFG</strong></td>
<td>11</td>
<td>-4</td>
<td>-38</td>
<td>-18</td>
<td>7.6</td>
<td>0.50</td>
<td>0.68</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>L. precuneus</strong></td>
<td>19</td>
<td>38</td>
<td>80</td>
<td>36</td>
<td>7.4</td>
<td>0.54</td>
<td>0.67</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>L. medial PPC</strong></td>
<td>9</td>
<td>8</td>
<td>-48</td>
<td>34</td>
<td>7.3</td>
<td>0.07</td>
<td>0.66</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>R. medial PPC</strong></td>
<td>9/10</td>
<td>-12</td>
<td>-58</td>
<td>12</td>
<td>6.9</td>
<td>0.55</td>
<td>0.59</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>R. ITG</strong></td>
<td>21</td>
<td>-62</td>
<td>6</td>
<td>-22</td>
<td>6.8</td>
<td>0.57</td>
<td>0.65</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>R. MFG</strong></td>
<td>6</td>
<td>-24</td>
<td>-24</td>
<td>44</td>
<td>6.7</td>
<td>0.65</td>
<td>0.79</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>R. MTG</strong></td>
<td>-46</td>
<td>62</td>
<td>26</td>
<td>6.5</td>
<td>0.79</td>
<td>0.37</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>L. Infral gyr</strong></td>
<td>18</td>
<td>10</td>
<td>56</td>
<td>4</td>
<td>6.5</td>
<td>0.43</td>
<td>0.69</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>L. SFG</strong></td>
<td>6</td>
<td>-28</td>
<td>38</td>
<td>6.5</td>
<td>0.64</td>
<td>0.78</td>
<td>0.51</td>
<td>0.77</td>
</tr>
</tbody>
</table>

**PCC Negative Connectivity**

| L. anterior insula | 38 | 2  | -2 | -7.3 | 0.33 | 0.50 | 0.25 | 0.62 | 0.29 | 0.56 |
| R. anterior insula | -40 | -2 | -4 | -7.2 | 0.41 | 0.73 | 0.42 | 0.76 | 0.36 | 0.73 |
| R. precentral gyrus | -58 | -10 | 2  | -7.2 | 0.75 | 0.83 | 0.71 | 0.77 | 0.69 | 0.78 |
| BL SMA/preSMA      | -2  | -6 | 48 | -7.0 | 0.42 | 0.59 | 0.39 | 0.68 | 0.50 | 0.78 |
| L. PPL             | 62  | 30 | 22 | -7.0 | 0.51 | 0.73 | 0.52 | 0.71 | 0.41 | 0.73 |
| R. SFC             | 6   | -20 | 4  | 62  | -7.0  | 0.07 | 0.48 | 0.13 | 0.40 | 0.01 | 0.56 |
| R. AG              | 39  | -62 | 36 | 34  | -6.6  | 0.57 | 0.72 | 0.52 | 0.75 | 0.52 | 0.84 |
| L. MOG             | 19  | 54 | 66 | 10  | -6.6  | 0.64 | 0.72 | 0.42 | 0.58 | 0.98 | 0.66 |
| R. IFG             | 45  | -46 | -42 | 6  | -6.5  | 0.62 | 0.72 | 0.95 | 0.68 | 0.98 | 0.72 |
| R. precentral gyrus | 6  | -48 | 0  | 38  | -6.5  | 0.50 | 0.68 | 0.29 | 0.68 | 0.45 | 0.64 |
| L. precentral gyrus | 6  | 58  | -2 | 8   | -6.4  | 0.49 | 0.72 | 0.36 | 0.59 | 0.59 | 0.73 |
| L. MFG             | 46  | 38 | -40 | 22  | -6.4  | 0.49 | 0.65 | 0.40 | 0.64 | 0.53 | 0.75 |

Shehzad et al., Cereb Cortex, 2009
Conclusions

• Intrinsic connectivity network strength reflects cognitive and emotional attributes
• Evoked behavior and responses abide by the tyranny of spontaneous fluctuations
• Connectivity allows exploration of continuous, subject-driven states
• Numerous potential clinical applications for diagnostics and gauging response to treatment
  – Pharmaceutical companies adding resting state as a biomarker
  – ADNI 2 has resting-state data (already online)
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