Resting-State fMRI: Current Research, Methodological Issues and Its Applications

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Outline

• Principles & Computational Algorithms
• Methodological Issues & Computational Platform
• Applications to Brain Disorders

Resting-State fMRI: Principles

All of the human high mental functions such as thinking, emotion and consciousness rely on brain, an extremely complex system (Singer, 1999)

Resting-State fMRI: Principles

Task evoked increases
Resting-state energy consumption

There are very important activities in the brain during resting-state (Fox and Raichle, 2007; Zhang and Raichle, 2010)

Raichle et al., 2010. Trends Cogn Sci

Resting-State fMRI: Principles

Task

Baseline

• Traditional fMRI analysis

Activities in the baseline state (usually resting-state)

Raichle et al., 2010. Trends Cogn Sci

Fox and Raichle, 2007. Nat Rev Neurosci
Resting-State fMRI: Principles

- Temporal synchrony of spontaneous fluctuations

Biswal et al., 1995. Magn Reson Med

Task: left and right

Biswal et al., 1995. Magn Reson Med

Resting-State fMRI: Principles

- Functional networks identified by functional connectivity with resting-state fMRI (RS-fMRI)

Sensorimotor network (Cordes et al., 2000. AJNR)

Visual network (Lowe et al., 1998. Neuroimage)

Auditory network (Cordes et al., 2000. AJNR)

Attentional network (Fox et al., 2006. PNAS)

DMN (Greicius et al., 2003. PNAS)

Zhang and Raichle, 2010. Nat Rev Neurol

Biswal et al., 2010. PNAS

Computational Methodology

- Integration approach
- Regional approach
- Graphical approach

Outline

- Resting-State fMRI: Principles
- Data Analysis: Computational Algorithms
- Data Analysis: Methodological Issues
- Data Analysis: Computational Platform
- Applications to Brain Disorders
Integration approach

• Functional Connectivity
• Effective Connectivity: (Friston et al., 2002)
• Hierarchical Clustering: (Cordes et al., 2000; Salvador et al., 2005)
• Self Organization Map: (Peltier et al., 2003)
• ...

The “Resting” Brain

How do we detect organized patterns of intrinsic activity?

Correlate

Resting State Functional Connectivity

• Correlation: Temporal synchrony of spontaneous fluctuations

Correlate

How do we detect organized patterns of intrinsic activity?

Resting State Functional Connectivity

• Correlation

Zhang and Raichle, 2010, Nat Rev Neurol

• Independent Component Analysis

Birn
2015
Computational Methodology

- Voxel-mirrored homotopic connectivity (VMHC)

Gee et al., 2011
Zuo et al., 2010

Directionality

- Statistical techniques
  - Structural Equation Modeling (McIntosh and Gonzalez-Lima, 1994)
  - Dynamic Causal Modeling (Friston et al., 2003)
  - Granger Causality Analysis (GCA) (Granger, 1969; Goebel et al., 2003)
- ... 
- Lesion studies
- Brain stimulation

Craddock, Yan et al., 2013. Nat Methods

Yan et al., 2011. PLoS ONE

Yan et al., 2011. PLoS ONE
Regional approach

“Integrative” is really good, but:

Decreased functional connectivity

Question: Is A, B, C, or ……abnormal?

Regional Homogeneity (ReHo)

Similarity or coherence of the time courses within a functional cluster

ReHo: motor task state vs. pure resting state

Rest > Motor
Motor > Rest

a) Higher ReHo in bilateral primary motor cortices during motor task
b) Higher ReHo in default mode network (PCC, MPFC, IPL) during rest

(Zang et al., 2004)

Amplitude of low frequency fluctuations

(z = 3)

(ALFF)

PET

(Raichle et al., 2001)

ALFF

(Zang et al., 2007)

Improvement: fractional ALFF

(Zou et al., 2008, J Neurosci Methods)
Computational Methodology

**Improvement: fractional ALFF**

Zou et al., 2008. J Neurosci Methods

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**Graph theoretical analysis**

- **Degree connectivity, functional connectivity density, degree centrality:** (Buckner et al., 2009; Tomasi et al., 2010; Cole et al., 2010; Zuo et al., 2012)
- ...

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**Random:**
- low $C_p$
- low $L_p$


**Small-world:**
- high $C_p$
- low $L_p$

Small-world networks contain many local links and a few long-distance links (so-called “shortcuts”).

$C_p$: average clustering of a network
$L_p$: average shortest path length of a network

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**Degree centrality**

Yan et al., 2011. PLoS ONE

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**Module**

Buckner et al., 2009. J Neurosci

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Cole et al., 2010. Neuroimage

Zuo et al., 2011. Cereb Cortex
**Computational Methodology**

Dynamic perspective

- **A Growing Range of R-fMRI Indices for Intrinsic Brain Function**
  - Voxel strength: ALFF/fALFF
  - Regional synchronization: ReHo
  - Homotopic connectivity: VMHC
  - Global connectivity: Degree Centrality
  - Global Signal Correlation

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Methodological Issues

• Head motion

Yan et al., 2013a. Neuroimage
Yan et al., 2013. Front Hum Neurosci

• Standardization

Yan et al., 2013b. Neuroimage

• Multiple-comparison correction


• And many many more…

Methodological Issues: Head Motion

Head motion is a critical factor in R-fMRI data processing.

Need an effective motion correction strategy!

Proposed an effective head motion correction strategy

- Individual-level correction with the Friston-24 model
- Group-level correction with head motion covariate

- Cited: 573 times
- ESI Top 1% highly cited paper

Methodological Issues: Standardization

Proposed an effective standardization strategy

Mean regression + SD division

- Cited: 176 times
- ESI Top 1% highly cited paper

Methodological Issues

Standardization

Collaborate with Dr. Xi-Nian Zuo @ IPCAS
Dr. Jia-Hong Gao @ PKU

National Natural Science Foundation of China (81671774) (PI: Yan)
Beijing Municipal Science & Technology Commission (Z161100000216152) (PI: Gao)
National Basic Research (973) Program (2015CB351702) (Co-I: Zuo)
The last 15 years of fMRI research might be totally useless.

Due to the recent discovery of an fMRI bug, about 40,000 papers on brain research may now be invalid.

**Reproducibility and Multiple Comparison Correction**

**Multiple Comparisons**

- Gaussian Random Field Theory Correction
- Monte Carlo simulations (AlphaSim)

**Permutation Test**

**Threshold-Free Cluster Enhancement (TFCE)**
Chen, Lu, Yan*, 2018. Human Brain Mapping

20 vs. 20 Permutation 1000 times

Family wise Error Rate

Chen, Lu, Yan*, 2018. Human Brain Mapping

20 vs. 20 Permutation 1000 times

Test-retest Reliability

Sex differences in test and retest

Chen, Lu, Yan*, 2018. Human Brain Mapping

Test-retest reliability

V1: significant voxels in test
V2: significant voxels in retest
V1∩V2: voxels significant in both test and retest

Chen, Lu, Yan*, 2018. Human Brain Mapping

Chen, Lu, Yan*, 2018. Human Brain Mapping

Moderate test-retest reliability

ALFF, rALFF, ReHo are better than DC and VMHC

Chen, Lu, Yan*, 2018. Human Brain Mapping

Permutation test TFCE, a strict multiple comparison correction strategy, reached the best balance between family-wise error rate (under 5%) and test-retest reliability / replicability

Chen, Lu, Yan*, 2018. Human Brain Mapping

212 M vs. 208 F × 2 times

Chen, Lu, Yan*, 2018. Human Brain Mapping

PT with TFCE outperforms
Sample Size Matters

Randomly draw \( k \) subjects from the “SWU 4” site in the CORR dataset, which has two sessions of 116 males and 105 females.

Chen, Lu, Yan*, 2018. Human Brain Mapping

Reproducibility of R-fMRI Metrics on the Impact of Different Strategies for Multiple Comparison Correction and Sample Sizes

- Permutation test with TFCE reached the best balance between FWER and reproducibility
- Although R-fMRI indices attained moderate reliabilities, they replicated poorly in distinct datasets (replicability < 0.3 for between-subject sex differences, < 0.5 for within-subject EOEC differences)
- For studies examining effect sizes similar to or even less than those of sex differences, results from a sample size <80 (40 per group) should be considered preliminary, given their low reliability (< 0.23), sensitivity (< 0.02) and PPV (< 0.26).

Permutation Test with TFCE

Integrated from PALM (Winkler et al. 2016. Neuroimage)

Yan* et al., 2016. Neuroinformatics

ESI Top 1% highly cited (>60 times)

The R-fMRI Maps Project

Part of the Human Brain Data Sharing Initiative (HBDSI), IPCAS

The R-fMRI Maps Project

Shared data of 4770 subjects:
1. Amplitude of low frequency fluctuations (ALFF)
2. Fractional ALFF (fALFF)
3. Regional Homogeneity (ReHo)
4. Voxel-mirrored homotopic connectivity (VMHC)
5. Degree Centrality (DC)
6. Functional Connectivity Matrices
   a. Automated Anatomical Labeling (AAL) atlas
   b. Harvard-Oxford atlas
   c. Craddock’s clustering 200 ROIs
   d. Zalesky’s random parcellations
   e. Dosenbach’s 160 functional ROIs
In addition, gray matter, white matter and CSF density and volume files were shared

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DPARSF: a MATLAB toolbox for "pipeliner" data analysis of resting-state fMRI


共同通讯作者：持续更新至今
Cited: 1500 times

传统fMRI处理软件：参数多，设置繁，易出错

时间层矫正
头动矫正
生理噪声
回归
配准
平滑
滤波
结果

DPARSF: 流水线式fMRI数据处理软件

12种不同的软件...使用得最多的软件是SPM（56%），然后是DPARSF（29%）和FSL（25%）...

Haris I. Sair
约翰·霍普金斯大学教授

 Twelve different software packages were used in the 100 studies. Many articles utilized the use of multiple software for analysis. The most commonly used software was SPM (56%) followed by DPARSF (29%) and FSL (25%). Other less commonly used software included AFNI and various MATLAB toolboxes, such as the GIFT toolbox and the Concor toolbox.

Data Organization

ProcessingDemoData.zip
FunRaw
Sub_001
Sub_002
Sub_003

Functional DICOM data

Structural DICOM data

Resting State fMRI Data Processing

Yan et al., 2016. Neuroinformatics
Cited: 181 times. ESI top 1% high cited

DPABI

Yan et al., 2016. Neuroinformatics

ESI Top 1% Highly Cited Paper
Future Directions

- R-fMRI methodology
- Mechanism of R-fMRI: electrophysiology/fMRI recording
- Modulation and intervention: medication and brain stimulation
- Application to brain disorders

Further Help

http://rfmri.org/Course

http://rfmri.org/wiki

The R-fMRI Journal Club

Official Account: RFMRILab

第五届DPABI/DPARSF特训营暨DPABISurf加强营

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Very Important: Daily completion of 20

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