



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

严超赣

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Outline

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

2

Resting-State fMRI: Principles

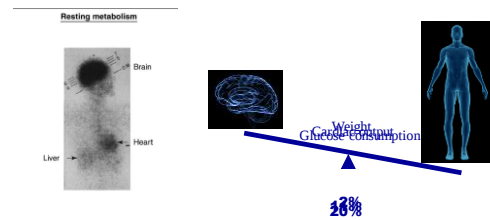


All of the human high mental functions such as thinking, emotion and consciousness rely on brain, an extremely complex system (Singer, 1999)

<http://psychcentral.com/news/2010/11/03/new-insights-on-brains-internal-wiring/20500.html>

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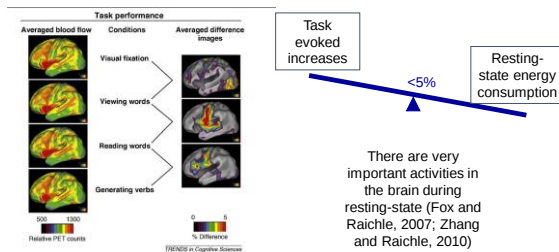
Resting-State fMRI: Principles



Raichle et al., 2010. Trends Cogn Sci

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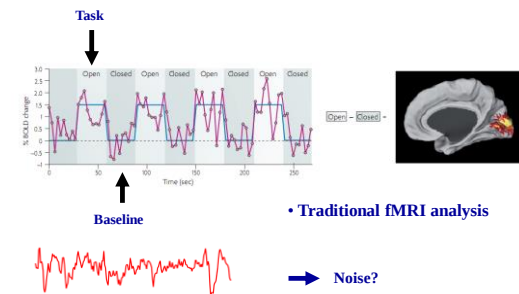
Resting-State fMRI: Principles



Raichle et al., 2010. Trends Cogn Sci

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Resting-State fMRI: Principles



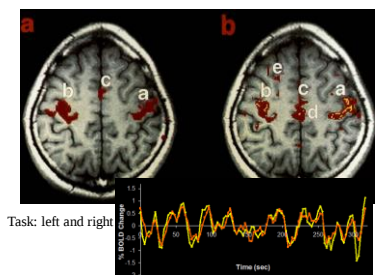
Activities in the baseline state (usually resting-state)

Fox and Raichle, 2007. Nat Rev Neurosci

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Resting-State fMRI: Principles

- Temporal synchrony of spontaneous fluctuations

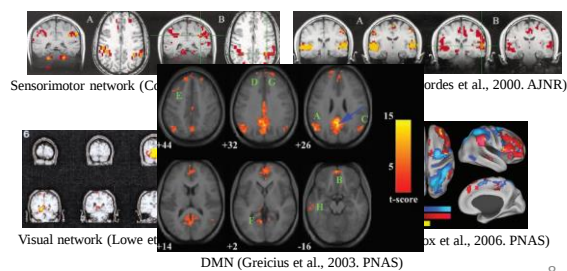


Biswal et al., 1995. Magn Reson Med

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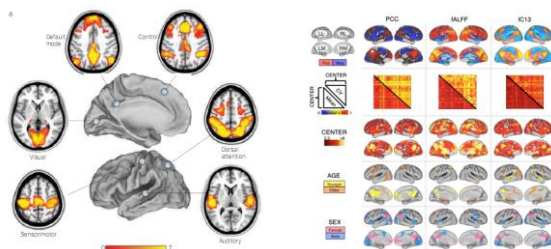
Resting-State fMRI: Principles

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



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Resting-State fMRI: Principles



Zhang and Raichle, 2010. Nat Rev Neurol

Biswal et al., 2010. PNAS

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Resting-State fMRI: Principles

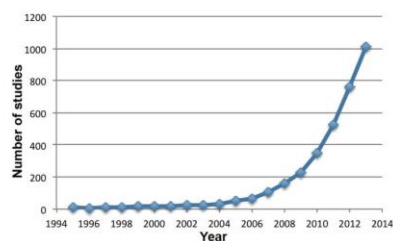


Figure 1. Number of R-fMRI related studies in PubMed (key words: "resting+state+fMRI").

Yan et al., 2015. F1000Res

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Outline

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

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Computational Methodology

- Integration approach
- Regional approach
- Graphical approach

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Computational Methodology

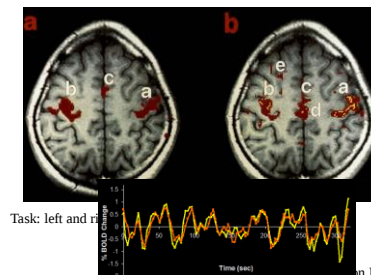
Integration approach

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

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Computational Methodology

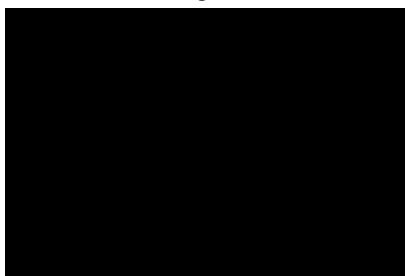
- Correlation: Temporal synchrony of spontaneous fluctuations



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Computational Methodology

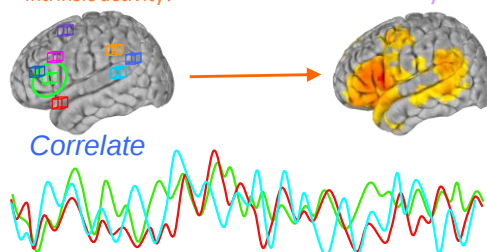
The “Resting” Brain



Courtesy of Dr. Daniel Margulies

Computational Methodology

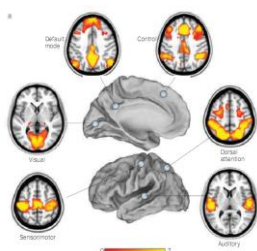
- How do we detect organized patterns of intrinsic activity?
- Resting State Functional Connectivity



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Computational Methodology

- Correlation

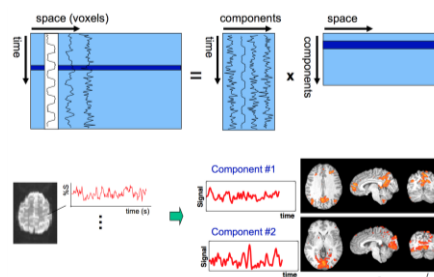


Zhang and Raichle, 2010. Nat Rev Neurol

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Computational Methodology

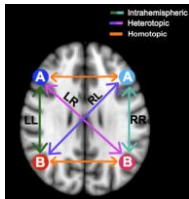
- Independent Component Analysis

Birn
2015

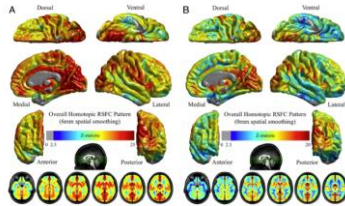
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Computational Methodology

• Voxel-mirrored homotopic connectivity (VMHC)



Gee et al., 2011

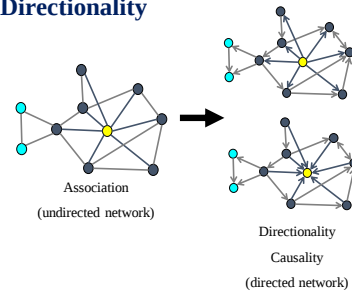


Zuo et al., 2010

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Computational Methodology

Directionality



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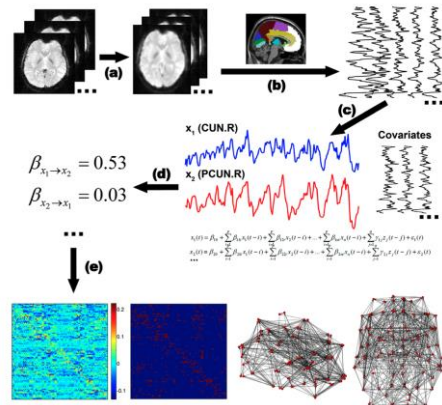
Computational Methodology

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

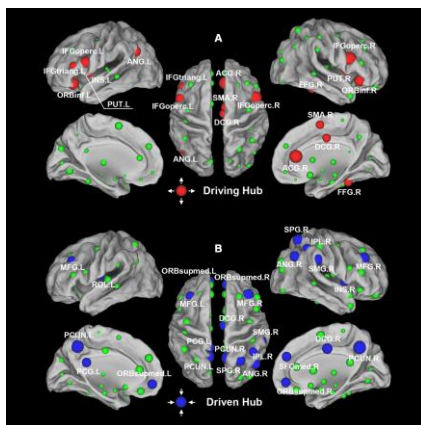
Craddock, Yan et al., 2013. Nat Methods

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Yan et al., 2011. PLoS ONE

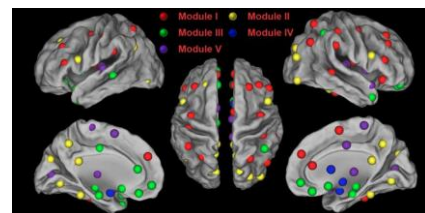
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Yan et al., 2011. PLoS ONE

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Computational Methodology



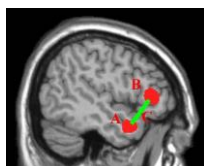
Yan et al., 2011. PLoS ONE

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Computational Methodology

Regional approach

“Integrative” is really good, but:



Decreased
functional connectivity

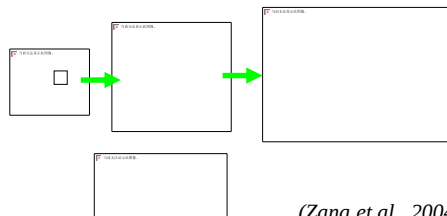
Question: Is A, B, C, or.....abnormal?

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Computational Methodology

Regional Homogeneity (ReHo)

Similarity or coherence of the time courses within a functional cluster

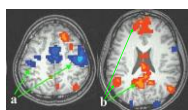


(Zang et al., 2004)

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Computational Methodology

ReHo: motor task state vs. pure resting state



Rest > Motor

Motor > Rest

a) Higher ReHo in bilateral primary motor cortices during motor task

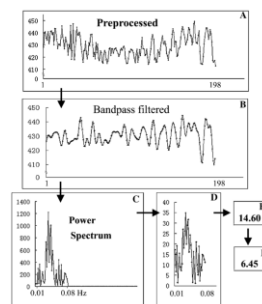
b) Higher ReHo in default mode network (PCC, MPFC, IPL) during rest (Raichle et al., 2001; Greicius et al., 2003)

(Zang et al., 2004)

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Computational Methodology

Amplitude of low frequency fluctuations

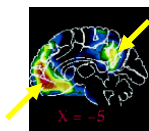


Zang et al., 2007

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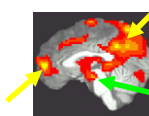
Computational Methodology

ALFF



PET

(Raichle et al., 2001)



ALFF

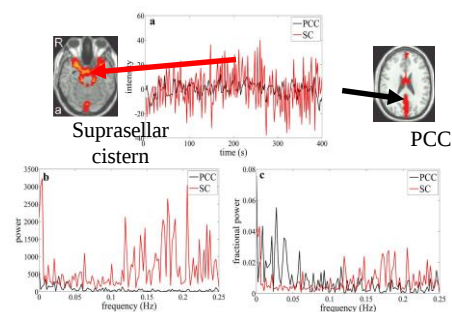
(Zang et al., 2007)

noise

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Computational Methodology

Improvement: fractional ALFF

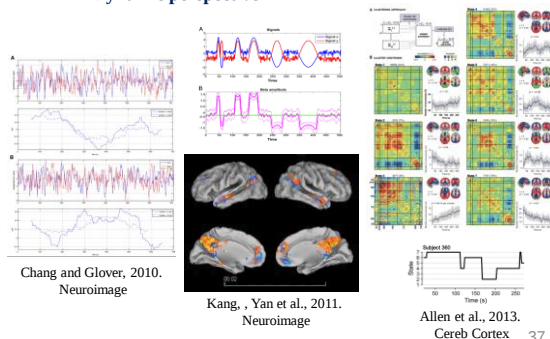


Zou et al., 2008. J Neurosci Methods

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Computational Methodology

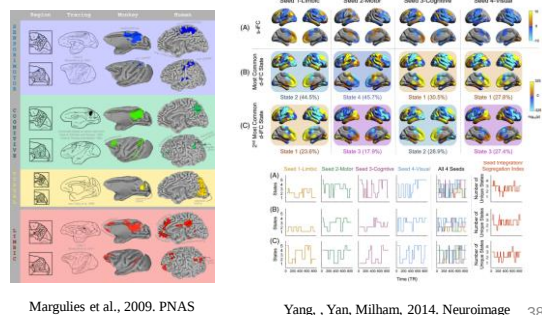
Dynamic perspective



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Computational Methodology

Dynamic perspective



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Computational Methodology

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

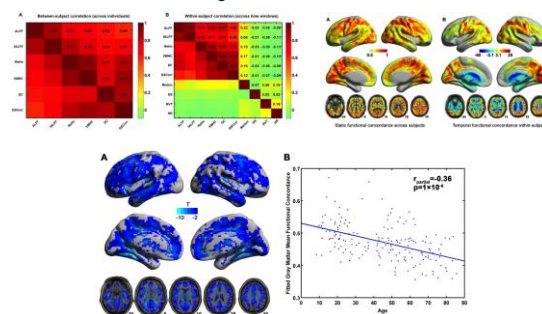


Global Signal Correlation

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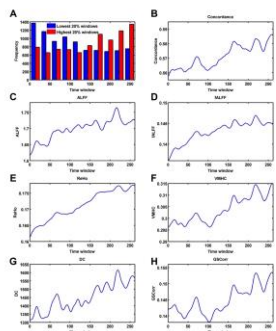
Computational Methodology

Concordance Among Indices of Intrinsic Brain Function



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Computational Methodology



Yan et al., 2017. Science Bulletin

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Methodological Issues

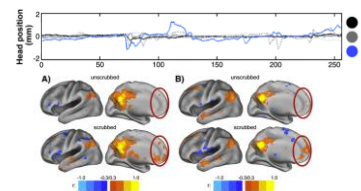
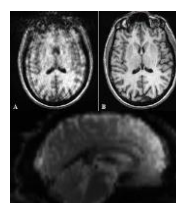
- Head motion
- Standardization
- Multiple-comparison correction
- And many many more...

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

Yan et al., 2013b. Neuroimage

Chen, Lu, Yan*, 2017. Human Brain Mapping

Methodological Issues: Head Motion



Power et al, 2012. Neuroimage
Van Dijk et al, 2012. Neuroimage

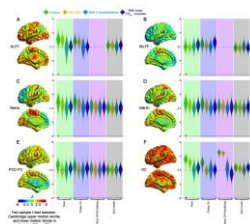
Head motion is a critical factor in R-fMRI data processing.

Need an effective motion correction strategy!

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Methodological Issues: Head Motion



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

Yan et al., 2013a. Neuroimage

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Methodological Issues: Standardization

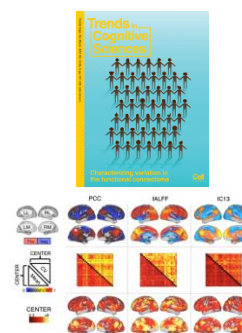


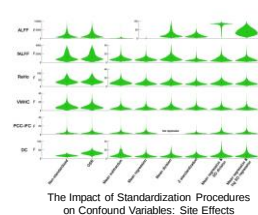
Table 1. Factors can introduce unwanted variations in fMRI measurement.

Category	Factor
1. Acquisition-related variations	Scanner make and model (Friedman and Glover, 2006b), sequence type (single vs. echo planar, single-echo vs. multi-echo) (Birnbaumer et al., 2002), parallel vs. conventional acquisition (Fennberg et al., 2010; Liu et al., 2005), coil type (surface vs. volume, number of channels, orientation), repetition time, number of repetitions, flip angle, echo time, and acquisition volume (field of view, voxel size, slice thickness), slice prescription (Friedman and Glover, 2006a)
2. Experimental-related variations	Participant instructions (Pfeiffer et al., 2011), eyes-open/eyes-closed (Yan et al., 2009; Yang et al., 2007), visual displays, experiment duration (Yang et al., 2007; Van Dijk et al., 2010)
3. Environment-related variations	Sound attenuation measures (Cho et al., 1998; Elger et al., 1999), attempts to improve participant comfort during scans (e.g., music, videos) (Cullen et al., 2006), head-motion resistant techniques (e.g., vacuum pad, foam pad, bite bar, plaster cast head fixation) (Edward et al., 2000; Menon et al., 1997), room temperature and moisture (Gauthier et al., 2005)
4. Participant-related variations	Circadian cycle (Shannon et al., 2011), premenstrual phase (et al., 2006), caffeine (Buck-Dorn et al., 2008), and mood states (Tanaka et al., 2011), sleepiness / arousal (Horowitz et al., 2006), sleep deprivation (Gamm et al., 2010), scanner anxiety (de Leeuw et al., 2010), and menstrual cycle status (for women) (Pfeiffer et al., 2005)

Yan et al., 2013b. Neuroimage

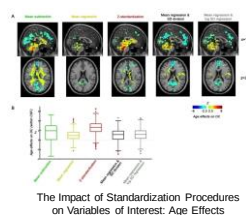
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Methodological Issues: Standardization



Proposed an effective standardization strategy

Mean regression + SD division



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

Yan et al., 2013b. Neuroimage

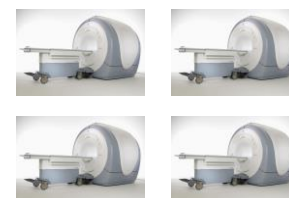
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Methodological Issues

Standardization

Collaborate with Dr. Xi-Nian Zuo @ IPCAS

Dr. Jia-Hong Gao @ PKU

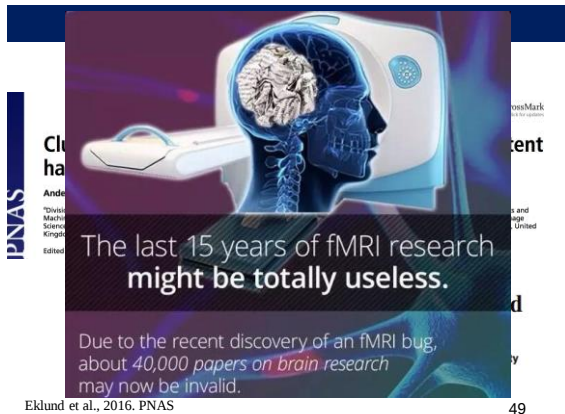


National Natural Science Foundation of China (81671774) (PI: Yan)

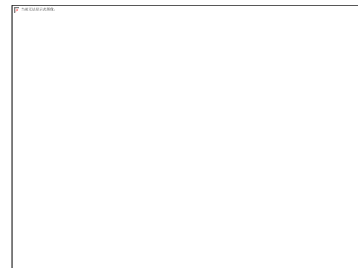
Beijing Municipal Science & Technology Commission (Z161100000216152) (PI: Gao)

National Basic Research (973) Program (2015CB351702) (Co-I: Zuo)

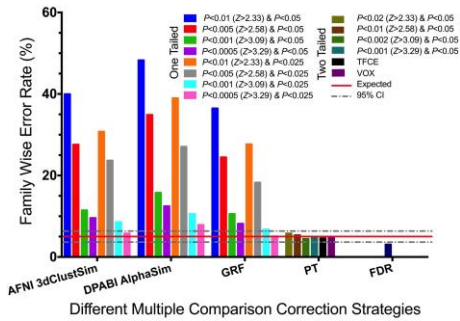
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Eklund et al., 2016. PNAS



Family wise Error Rate

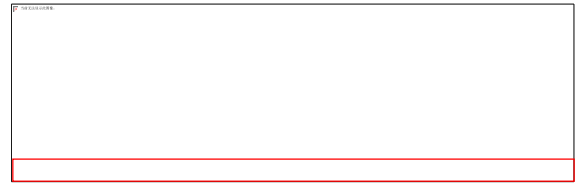


20 vs. 20 Permutation 1000 times

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

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Family wise Error Rate



20 vs. 20 Permutation 1000 times

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

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Family wise Error Rate

TABLE II. FWER under correction of three kinds of cluster-based correction with the strictest threshold, 6 versions of PT-based correction as well as FDR correction

	Voxel threshold	Cluster threshold	FWER									
			ALFF	lALFF	ReHo	DC	VMHC	ALFF with GSR	lALFF with GSR	ReHo with GSR	DC with GSR	VMHC with GSR
Smoothness (mm, $xy \times yz$)			7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96	7.84 × 7.34 × 7.96
AFNI 3dClustSim (one-tailed)	$P < 0.0005$ ($Z > 3.29$)	$P < 0.025$	6.86	7.20	6.86	7.20	6.86	7.20	6.86	7.20	6.86	7.20
DPABI AlphaSim (one-tailed)			7.96	8.36	7.96	8.36	7.96	8.36	7.96	8.36	7.96	8.36
GRF (one-tailed)			7.96	8.36	7.96	8.36	7.96	8.36	7.96	8.36	7.96	8.36
PT cluster extent correction (one-tailed)	$P < 0.02$ ($Z > 2.33$)	$P < 0.05$	5.11	5.35	4.98	5.22	5.25	4.85	5.09	5.30	5.11	4.85
	$P < 0.01$ ($Z > 2.58$)	$P < 0.05$	5.88	6.05	5.88	6.05	5.88	6.05	5.88	6.05	5.88	6.05
	$P < 0.002$ ($Z > 3.09$)	$P < 0.05$	4.55	4.71	4.55	4.71	4.55	4.71	4.55	4.71	4.55	4.71
	$P < 0.001$ ($Z > 3.29$)	$P < 0.05$	4.48	4.64	4.48	4.64	4.48	4.64	4.48	4.64	4.48	4.64
PT TFCE			4.48	4.64	4.48	4.64	4.48	4.64	4.48	4.64	4.48	4.64
PT VOL			4.48	4.64	4.48	4.64	4.48	4.64	4.48	4.64	4.48	4.64
FDR correction			5.11	5.35	4.98	5.22	5.25	4.85	5.09	5.30	5.11	4.85

The smoothness in the second row is the estimated effective smoothness of the final metric maps used to statistical analysis, and was different from the applied smoothness (4 mm FWHM) in pre-processing. The effective smoothness was used to calculate the significance of cluster-based correction (i.e., GRF theory correction, AFNI 3dClustSim and DPABI AlphaSim).

20 vs. 20 Permutation 1000 times

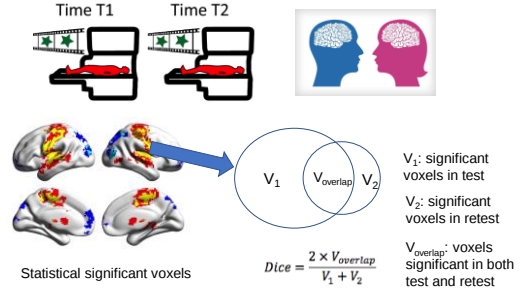
Chen, Lu, Yan*, 2018. Human Brain Mapping

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Test-retest Reliability

Test-retest reliability

Sex differences in test and retest



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

Test-retest Reliability

TABLE III. Test-retest reliability of sex differences for all R-fMRI metrics with and without GSR under correction of three kinds of cluster-based correction with the strictest threshold, six kinds of PT-based correction and FDR correction, calculated between the first and second sessions in the CORR dataset

	Voxel threshold	Cluster threshold	Test-retest reliability (dice coefficient)									
			ALFF	lALFF	ReHo	DC	VMHC	ALFF with GSR	lALFF with GSR	ReHo with GSR	DC with GSR	VMHC with GSR
AFNI 3dClustSim (one-tailed)	$P < 0.0005$ ($Z > 3.29$)	$P < 0.025$	0.65	0.51	0.50	0.34	0.39	0.64	0.48	0.44	0.28	0.24
DPABI AlphaSim (one-tailed)			0.65	0.51	0.49	0.34	0.39	0.64	0.48	0.45	0.27	0.27
GRF (one-tailed)			0.64	0.51	0.50	0.35	0.39	0.65	0.48	0.43	0.28	0.24
PT cluster extent correction (one-tailed)	$P < 0.02$ ($Z > 2.33$)	$P < 0.05$	0.65	0.70	0.56	0.45	0.40	0.62	0.48	0.45	0.30	0.40
	$P < 0.01$ ($Z > 2.58$)	$P < 0.05$	0.67	0.66	0.52	0.32	0.33	0.60	0.63	0.46	0.27	0.32
	$P < 0.002$ ($Z > 3.09$)	$P < 0.05$	0.63	0.55	0.51	0.36	0.38	0.63	0.52	0.47	0.23	0.32
	$P < 0.001$ ($Z > 3.29$)	$P < 0.05$	0.64	0.51	0.48	0.37	0.38	0.64	0.48	0.44	0.28	0.26
PT TFCE			0.68	0.75	0.54	0.48	0.44	0.66	0.74	0.44	0.31	0.42
PT VOL			0.66	0.74	0.48	0.37	0.32	0.65	0.31	0.38	0.31	0.44
FDR correction			0.64	0.67	0.54	0.39	0.37	0.63	0.64	0.47	0.23	0.29

For test-retest reliability for all the 31 kinds of multiple comparison correction strategies, please see Supporting Information Table S13

➤ Moderate test-retest reliability

➤ ALFF, lALFF, ReHo are better than DC and VMHC

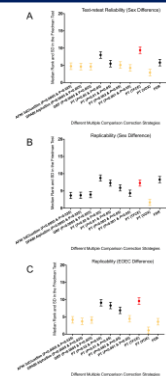
Chen, Lu, Yan*, 2018. Human Brain Mapping

212 M vs. 208 F × 2 times

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PT with TFCE outperforms

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

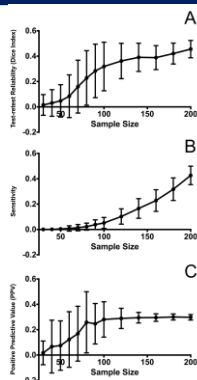


Chen, Lu, Yan*, 2018. Human Brain Mapping

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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

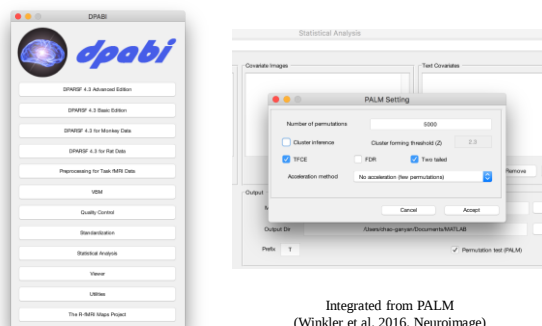
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Reproducibility of R-fMRI Metrics on the Impact of Different Strategies for Multiple Comparison Correction and Sample Sizes

- 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 (reproducibility < 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).

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Permutation Test with TFCE

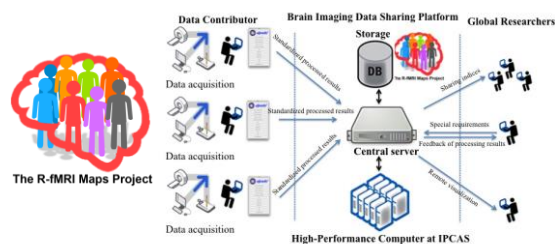


Yan* et al., 2016. Neuroinformatics

ESI Top 1% highly cited (>60 times)

63

The R-fMRI Maps Project



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

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The R-fMRI Maps Project

Shared data of 4770 subjects:

- Amplitude of low frequency fluctuations (ALFF)
- Fractional ALFF (fALFF)
- Regional Homogeneity (ReHo)
- Voxel-mirrored homotopic connectivity (VMHC)
- Degree Centrality (DC)
- Functional Connectivity Matrices
 - Automated Anatomical Labeling (AAL) atlas
 - Harvard-Oxford atlas
 - Craddock's clustering 200 ROIs
 - Zalesky's random parcellations
 - Dosenbach's 160 functional ROIs

In addition, gray matter, white matter and CSF density and volume files were shared

[illegible]Downloaded by
593 researchers

65

Outline

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

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静息态功能磁共振数据处理平台

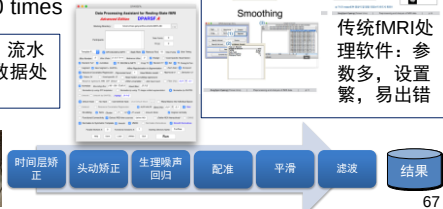
Frontiers in
SYSTEMS NEUROSCIENCE
DPARSF: a MATLAB toolbox for "pipeline" data analysis of
resting-state fMRI
Yu-Chen Ge¹ and Yong-Pu Peng²
Frontiers in Systems Neuroscience | www.frontiersin.org | July 2016

Yan and Zang, 2010. Front
Syst Neurosci.

共同通讯作者; 持续更新至今

Cited: 1500 times

DPARSF: 流水
线式fMRI数据处
理软件



67

同行评价及影响

Brain Connectivity
Volume 8, Number 8, 2018
© 2018 SAGE Publications
DOI: 10.1177/1063426918782488

COMMUNICATION

Reporting of Resting-State Functional Magnetic
Resonance Imaging Preprocessing Methodologies

Syed Hameed Wahneke¹, Saadeh Mirbagheri², Shrut Agarwal³, Anshu Karmali⁴,
Nourah Farwan Faisal Alotaibi⁵, Anwar Chaudhry⁶, Michael D'Armentano⁷,
Santanu K. Guha⁸, Jay J. Ptasch⁹, and Harris I. Sair¹⁰



Harris 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 Conn toolbox.

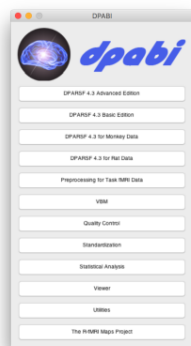
12种不同的软件...使用得最多的软件是SPM (56%), 然后是**DPARSF (29%)** 和FSL (25%) ...

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数据处理与共享平台

- 整合方法学改进
- 处理流程规范化
- 统计分析
- 大数据共享平台

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



69

DPARSF

Data Organization

ProcessingDemoData.zip

FunRaw

Sub_001
Sub_002
Sub_003

Functional DICOM data

T1Raw

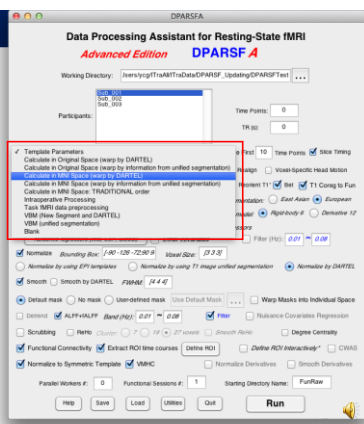
Sub_001
Sub_002
Sub_003

Structural DICOM data

70

Resting State fMRI Data Processing

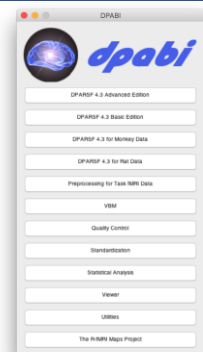
Template Parameters



DPABI

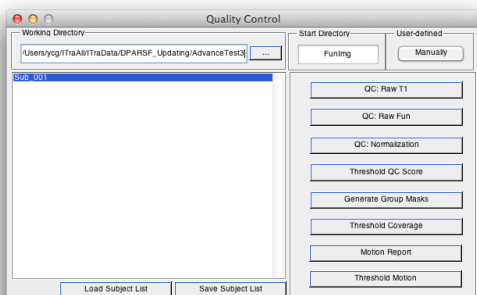
Yan et al., 2016. Neuroinformatics

ESI Top 1% Highly Cited Paper



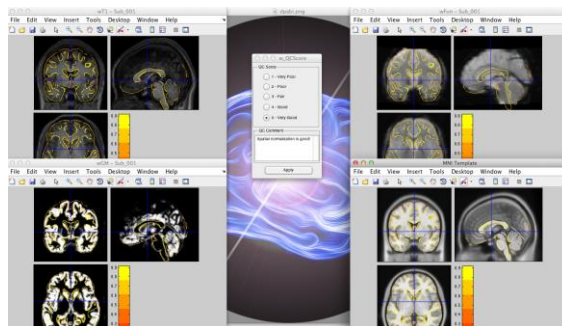
72

Quality Control



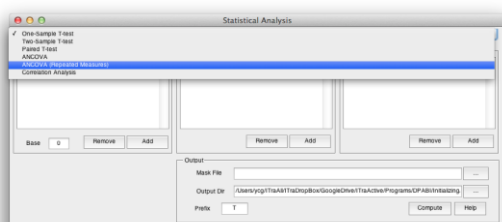
73

Quality Control



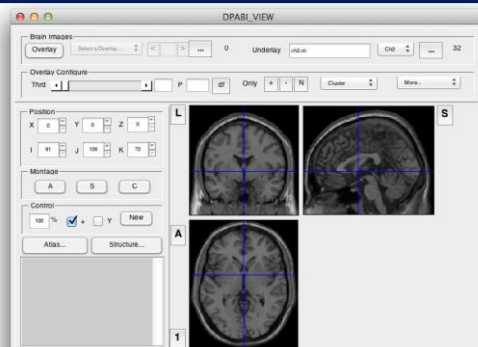
74

Statistical Analysis



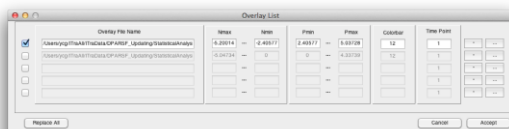
75

DPABI Viewer



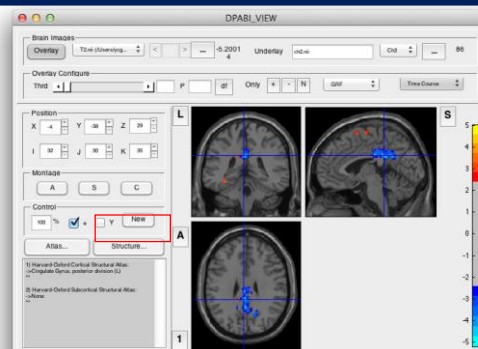
76

DPABI Viewer



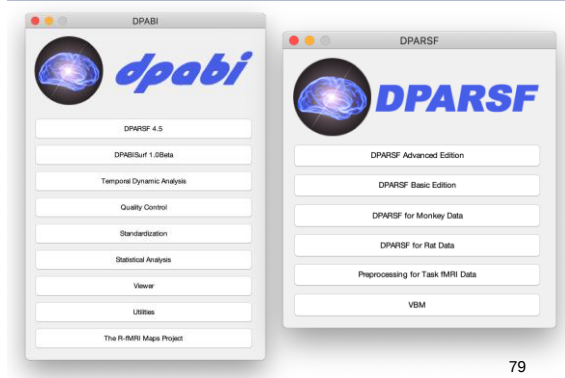
77

DPABI Viewer



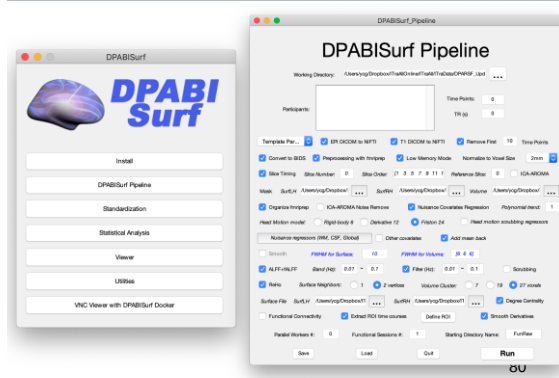
78

DPABISurf

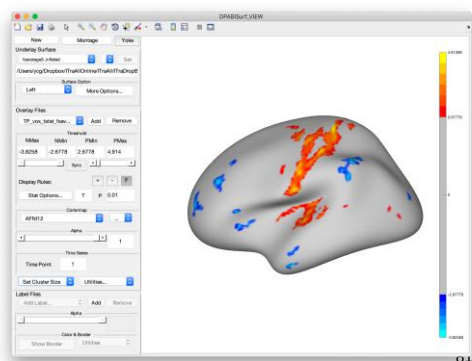


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DPABISurf



DPABISurf



Future Directions

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

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Further Help



<http://rfmri.org/Course>



<http://rfmri.org/wiki>



The R-fMRI Journal Club



Official Account: RFMRILab

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DPABI特训营与DPABISurf加强营



第五届DPABI/DPARSF特训营
暨DPABISurf加强营通知
中国·北京 2019.7.20~7.22

定期举办, 请关注<http://rfmri.org>

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深度特训与数据分析



静息态功能磁共振成像数据处理深度特训

从您见到这条消息开始，您便将有机会与中国科学院 The f-MRI Lab 的静息态功能磁共振专家团队共同探索大脑的奥秘！深度思维特训期间，您将会亲身体验

- 数据处理 专家指导下高效学习静态功能磁共振成像数据处理
- 思路设计 与国际知名专家讨论形成研究思路
- 论文撰写 系统的 SCI 论文写作训练



静息态功能磁共振成像深度数据分析

功能磁共振成像越来越成为一种主流的科研手段,然而功能磁共振的数据分析却是一项具有高度挑战性的工作。海量的原始数据,繁多的分析步骤,复杂的分析方法都让研究者无所适从,恰当的分析方法可以从普通的数据中挖掘出富有创新性的结果,而不恰当的分析则可能让精心收集的数据黯然失色。深度大脑科学联合中国科学院 The R-MRML Lab 的专业功能磁共振成像团队推出了一款功能磁共振数据分析解决方案,助力临床对早期功能磁共振数据需求的一站式解决。

<http://deepbrain.com>

DPABISurf工作站

DPABI工作站

序号	名称	技术参数	市场参考价格
1	DPAH服务器工作站 (Windows)	14.6寸宽屏液晶显示器、笔记本电脑式	
2	DPAH服务器工作站 (Windows)	14.6寸宽屏液晶显示器、4230U, 16G内存, 256G固态硬盘+1TB机械硬盘, PCIe, 独立显卡, 标准配置	¥ 8999
3	DPAH计算工作站	便携式显示器	
4	Linux (Ubuntu)	2080显卡带显示器支架(14.2寸) CPU: i7-8750U, 20GB RAM, 740GB, 8TB SSD, *13.3寸 EDCI 80000, 64GB SSD, 256000T/H, *4K 75 Hz, 2000-3000, 10000, 7000毫安, 重量: 4400-1300, DVD-RW 8X, 三年质保	¥ 9999
5	DPAH Computational Core		
6	DPAH移动工作站 (Windows)	15.6英寸窄边框显示器工作站 六代i7处理器+二核8070+16G内存+256G固态硬盘+1TB机械硬盘, P1000 4K高清显卡	¥ 24999
7	DPAH Mobile Core Windows		

4.	DPAF部署工作站 (Mac)	Mac Pro 4核8线程Intel Xeon W 处理器, 2.5GHz Turbo Boost 最高可达 4.5GHz, 64GB 内存 256GB SSD CXCX E, 17.3 英寸显示屏, Radeon Pro Vega 56 图形处理器 8C+16M 显存	¥24999
5.	DPAF部署工作站 (Mac)	13 英寸 MacBook Pro 八核处理器 二核 Intel Core i7 处理器, Turbo Boost 最高可达 4.5GHz, 16GB 内存 240GB SSD CXCX E, 13.3 英寸显示屏, Radeon Pro 5600 图形处理器 8C+8M 显存, 支持 Pro DisplayPort 及 mini 4 针 DisplayPort 接口, 兼容 Pro Display 面板, 约 9 英寸 3 重 D	¥13999
6.	DPAF部署工作站	按需求配置及定制, 能够满足大型业务需求, 提供最佳性价比及定制化服务	定制

<http://deepbrain.com/DPABICore>

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DPABI计算工作站

2.	DPABI计算工作站 (Linux/Windows) DPABI Computational Core	塔式服务器 20核40线程英特尔至强E114 2.2G *2, 9.6GT/s *2 UPI, 14M Turbo, HT(BSW), 4*16GB RDIMM, 64C内存, 2666MT/s, 4*4TB 7.2K RPM SAS, 16TB硬盘, 冗余电 源, RAID卡: H330, DVD-RW 双电 三年服务	¥59999
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<http://deepbrain.com/DPABICore>

DPABISurf 并行计算:

每天完成 **20** 个被试的皮层计算!!!

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The R-fMRI Lab



WeChat Official Account: RFMRILab

Acknowledgments



Chinese Academy of
Sciences
Xi-Nian Zuo
Hangzhou Normal
University
Yu-Feng Zang
NYU Child Study
Center
F. Xavier Castellanos
Child Mind Institute
Michael P. Milham

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- National Natural Science Foundation of China
 - National Key R&D Program of China
 - Chinese Academy of Sciences

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