

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)

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

Resting-State fMRI: Principles

Resting metabolism

Caloric consumption

20%

Raichle et al., 2010. Trends Cogn Sci

Resting-State fMRI: Principles

Task performance

Averaged blood flow Conditions Averaged difference images

Visual fixation Viewing words Reading words Generating verbs

<5% Resting-state energy consumption

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

TRENDS in Cognitive Sciences

Raichle et al., 2010. Trends Cogn Sci

Resting-State fMRI: Principles

Task

Baseline

Traditional fMRI analysis

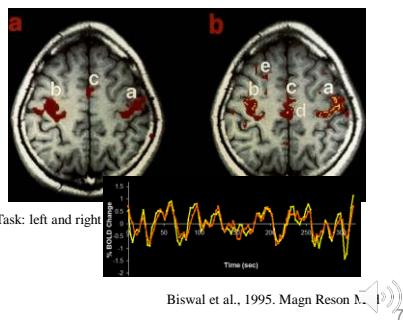
Noise?

Activities in the baseline state (usually resting-state)

Fox and Raichle, 2007. Nat Rev Neurosci

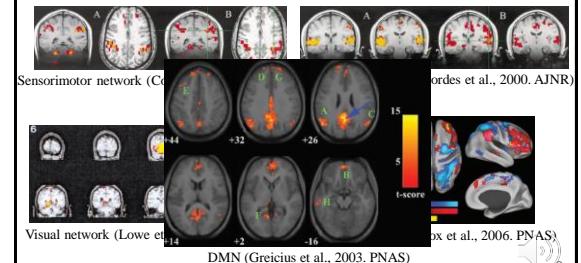
Resting-State fMRI: Principles

- Temporal synchrony of spontaneous fluctuations

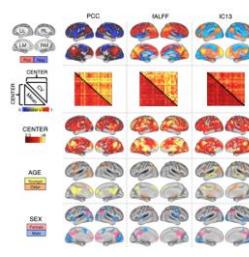
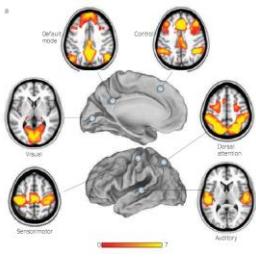


Resting-State fMRI: Principles

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



Resting-State fMRI: Principles



Resting-State fMRI: Principles

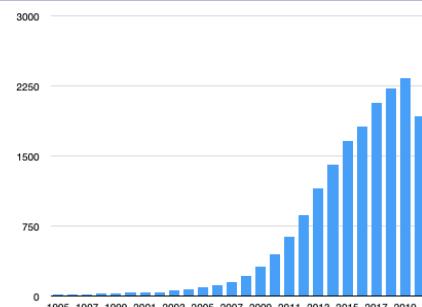


Figure 1. Number of R-fMRI related studies in PubMed (key words: "resting+state+fmri").

Outline

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



Computational Methodology

- Integration approach
- Regional approach
- Graphical approach



Computational Methodology

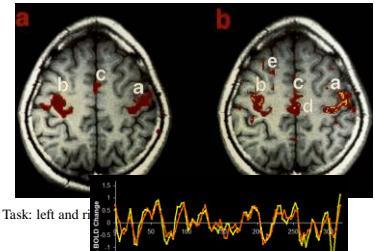
Integration approach

- 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

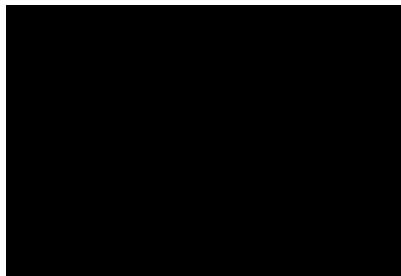


Task: left and right

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Computational Methodology

The “Resting” Brain



Courtesy of Dr. Daniel Margulies

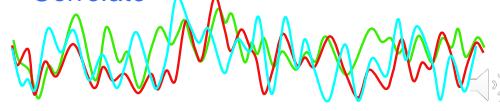
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Computational Methodology

- How do we detect organized patterns of intrinsic activity?



Correlate

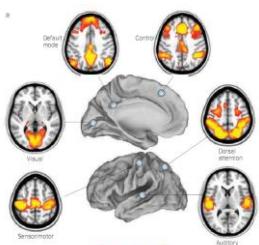


Resting State Functional Connectivity

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Computational Methodology

• Correlation

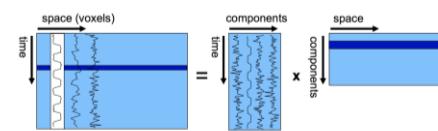


Zhang and Raichle, 2010. Nat Rev Neurol

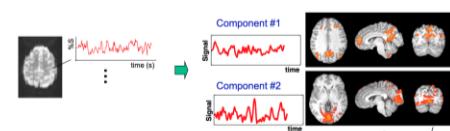
17

Computational Methodology

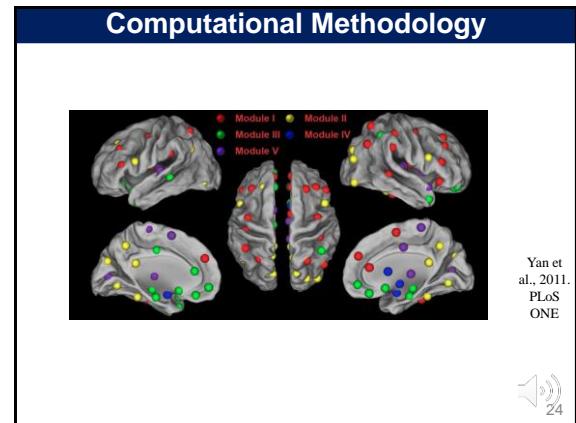
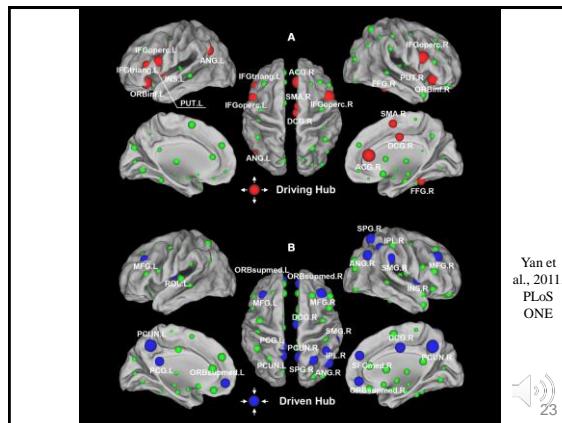
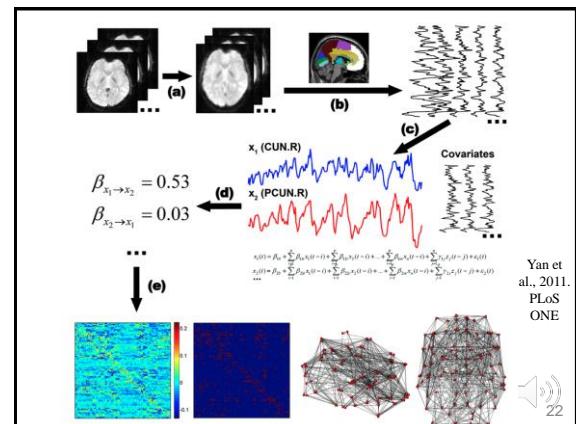
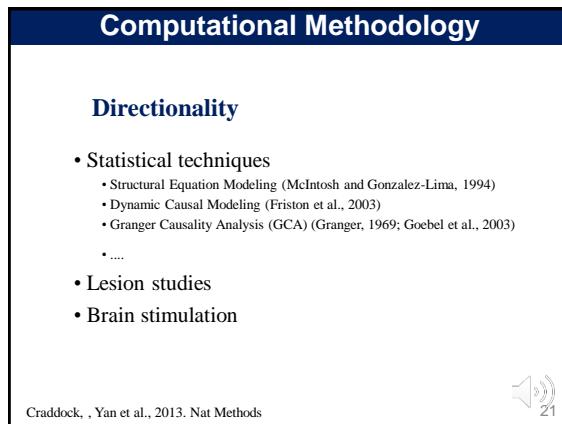
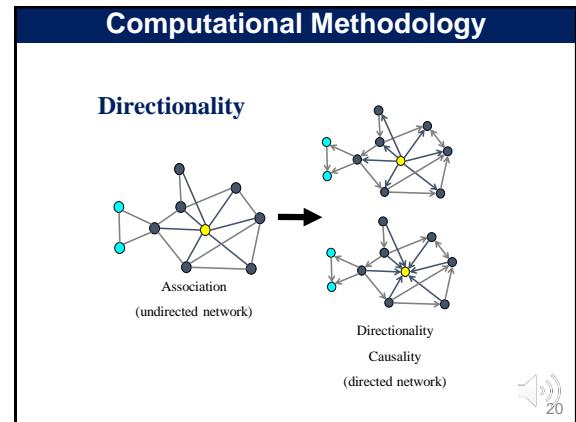
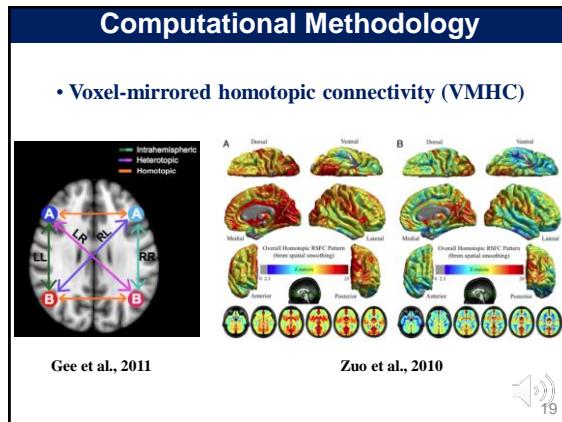
• Independent Component Analysis



Birn
2015



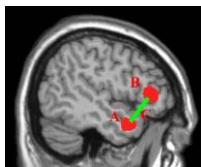
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Computational Methodology

Regional approach

“Integrative” is really good, but:



Decreased functional connectivity

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

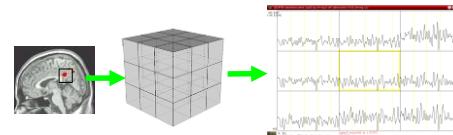


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Computational Methodology

Regional Homogeneity (ReHo)

Similarity or coherence of the time courses within a functional cluster



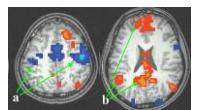
$$W = \frac{\sum(R_i)^2 - n(\bar{R})^2}{\frac{1}{12}K^2(n^3 - n)}$$

(Zang et al., 2004)



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)

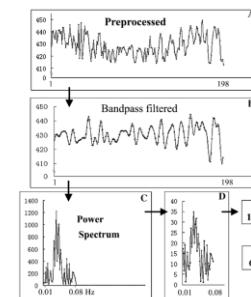
(Zang et al., 2004)



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Computational Methodology

Amplitude of low frequency fluctuations

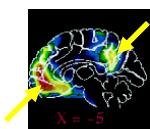


Zang et al., 2007



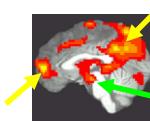
Computational Methodology

ALFF



PET

(Raichle et al., 2001)



ALFF

(Zang et al., 2007)

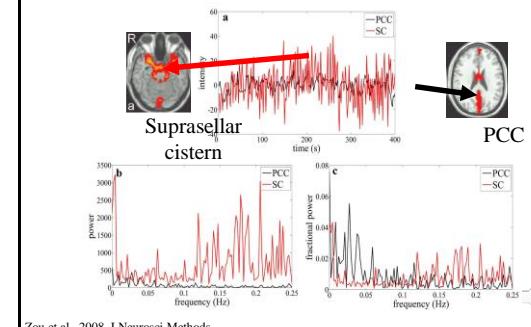
noise



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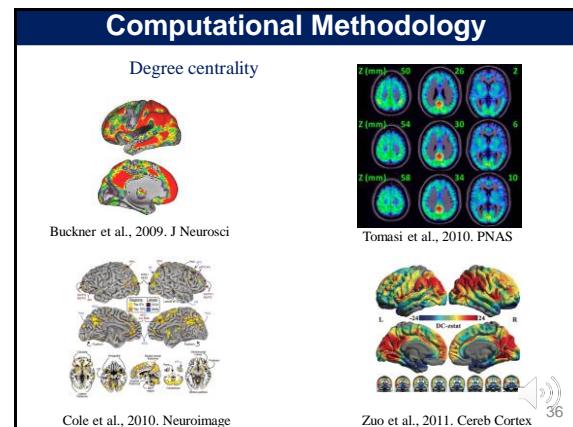
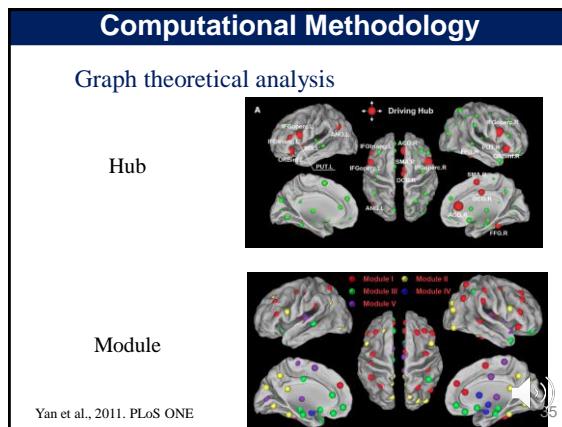
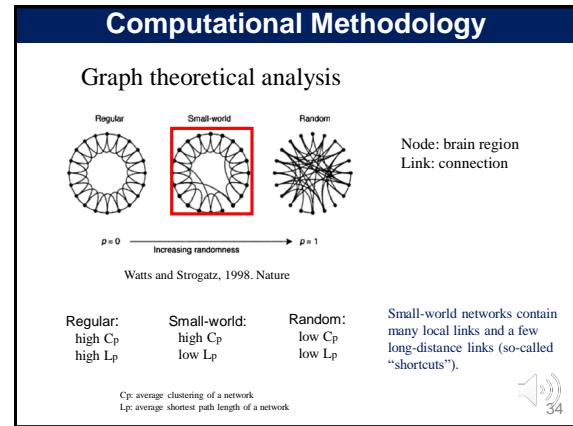
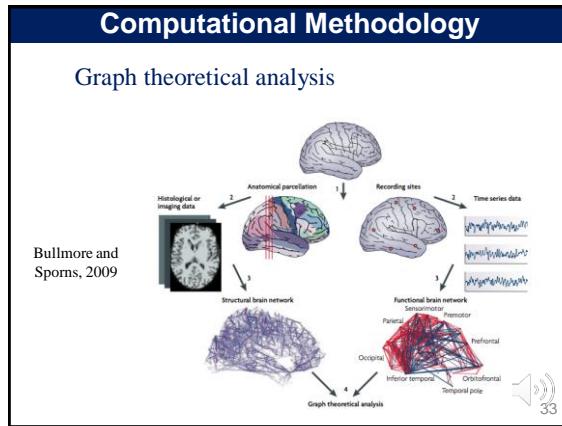
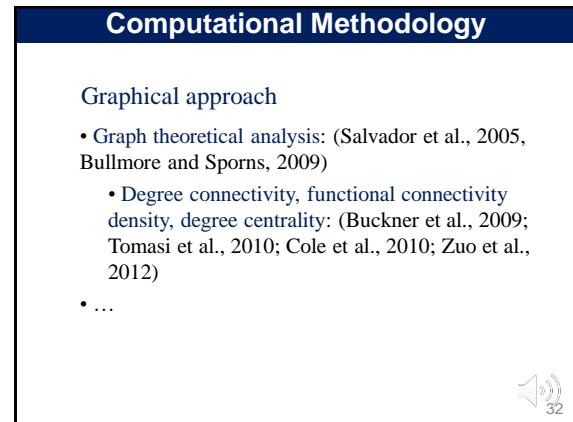
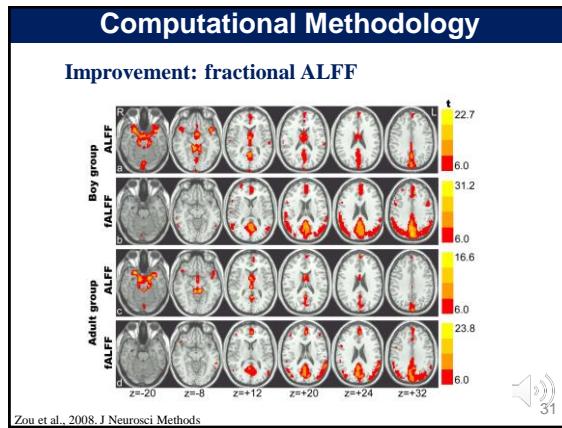
Computational Methodology

Improvement: fractional ALFF



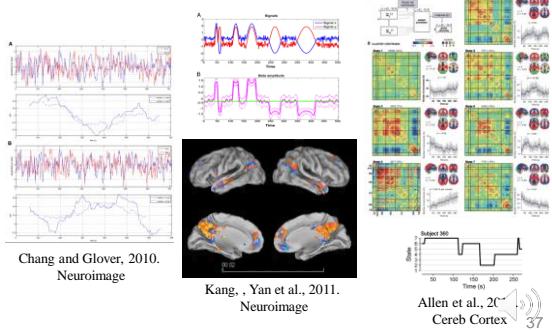
Zou et al., 2008, J Neurosci Methods

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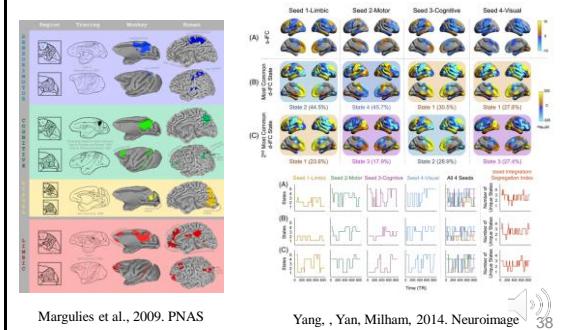
Computational Methodology

Dynamic perspective



Computational Methodology

Dynamic perspective



Computational Methodology

A Growing Range of R-fMRI Indices for Intrinsic Brain Function



Voxel strength: ALFF/fALFF



Regional synchronization: ReHo



Homotopic connectivity: VMHC



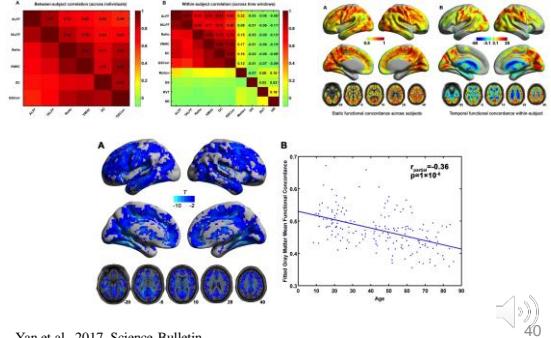
Global connectivity: Degree Centrality



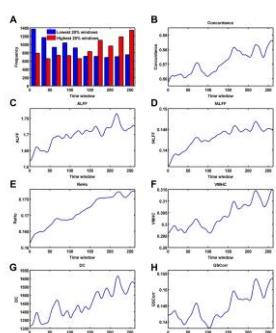
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Computational Methodology

Concordance Among Indices of Intrinsic Brain Function



Computational Methodology



Yan et al., 2017. Science Bulletin

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Outline

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



Methodological Issues

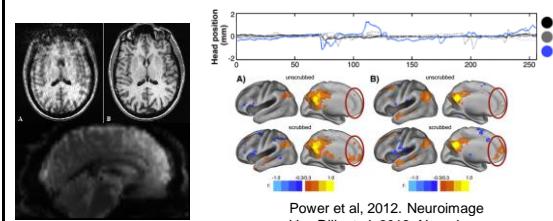
- Head motion
- Standardization
- Multiple-comparison correction
- And many many more...

*Yan et al., 2013a. Neuroimage
Yan et al., 2013. Front Hum Neurosci
Yan et al., 2013b. Neuroimage
Chen, Lu, Yan*. 2017. Human Brain Mapping*



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Methodological Issues: Head Motion



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

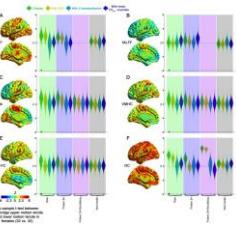
Head motion is a critical factor in R-fMRI data processing.

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: 970 times
- ESI Top 0.1% highly cited paper

Yan et al., 2013a. Neuroimage



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Methodological Issues: Standardization

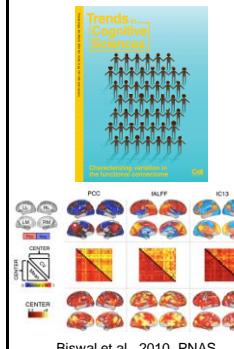


Table 1. Factors can introduce unintended variations in fMRI measurement.

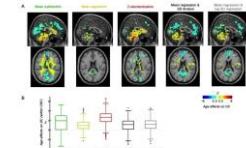
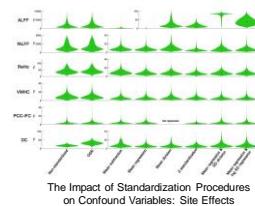
Category	Factor
1. Acquisition-related variations	Scanner make and model (Friedman and Glover, 2006b), sequence type (Eickhoff et al., 2005; Giedd et al., 2004; Giedd et al., 2002), parallel vs. conventional acquisition (Fischlberg et al., 2010; Lin et al., 2005), coil type (surface vs. volume; number of channels, orientation), field strength (1.5 T vs. 3 T), slice timing (inter-slice time), and acquisition volume (field of view, voxel size, slice thickness, and slice gap) (Fischlberg et al., 2010; Lin et al., 2005; Lin et al., 2006).
2. Experimental-related variations	Participant instructions (Harms et al., 2011), eyes-open/eyes-closed (Yan et al., 2013a; Yang et al., 2013), visual stimulus, experiment duration (Yan et al., 2013a; Yang et al., 2013), task (Yan et al., 2013a), video (Cohen et al., 2009), head-motion restraint techniques (e.g., vacuum bag, foam pad, bite-bar, plaster cast, or head holder) (Edward et al., 2000), and participant's age (Yan et al., 2013a), sex (Yan et al., 2006).
3. Environment-related variations	Sound attenuation measures (Cox et al., 1996; Elliott et al., 1996), room temperature (Yan et al., 2013a), room humidity (Yan et al., 2013a), room light (Yan et al., 2013a), room air pressure (Yan et al., 2006), and room air flow (Yan et al., 2013a).
4. Participant-related variations	Participant's age (Yan et al., 2013a), gender (Yan et al., 2006; Yannakakis et al., 2012), prandial (Vissers et al., 2009), caffeine (Nack-Gasser et al., 2009), and nicotine status (Tirabassi et al., 2011), sleep (Harms et al., 2011; Hommer et al., 2005), sleep deprivation (Suzuki et al., 2013), alcohol (Yan et al., 2013a), and menstrual cycle status (for women) (Popogrebscu 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: 284 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



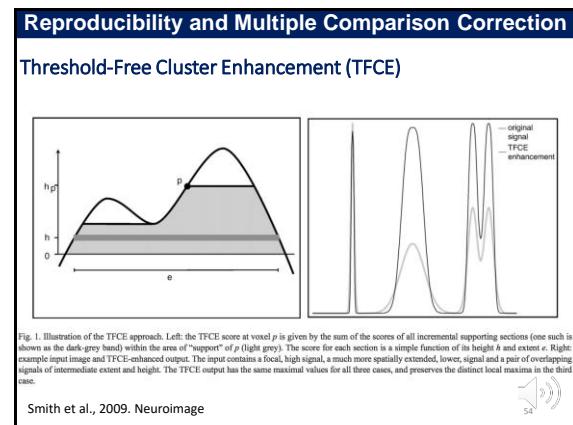
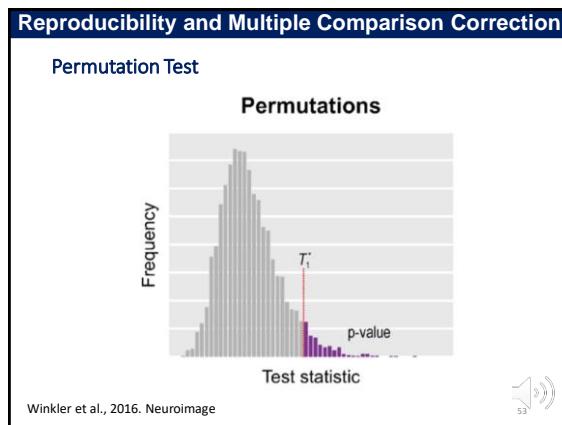
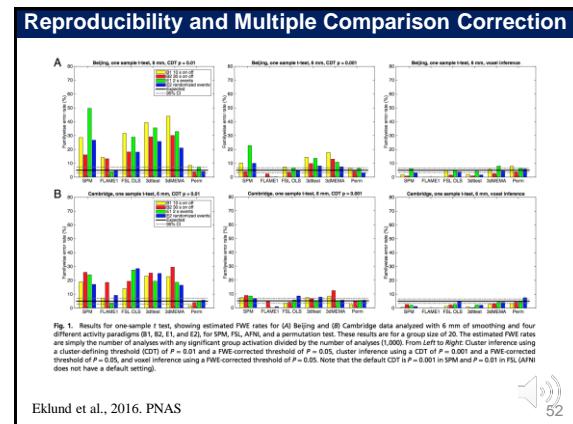
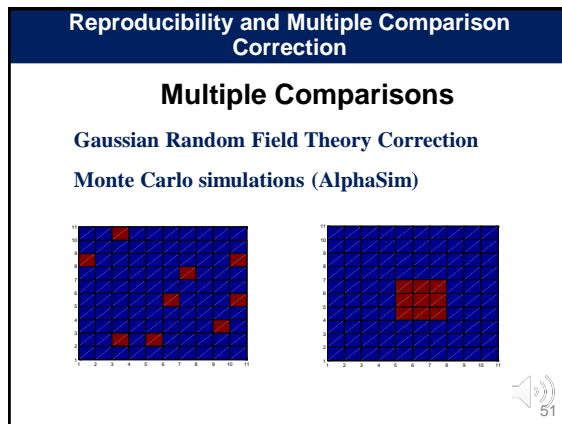
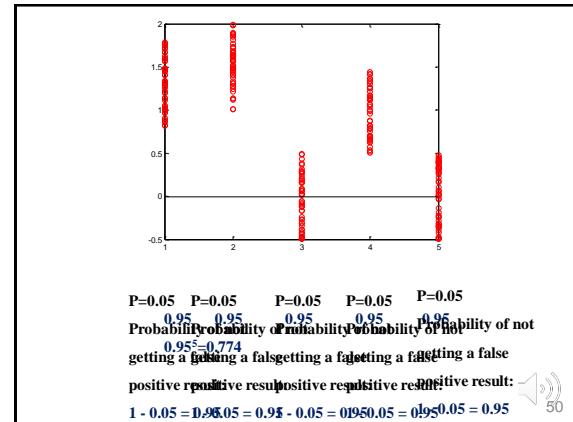
National Natural Science Foundation of China (81671774) (PI: Yan)

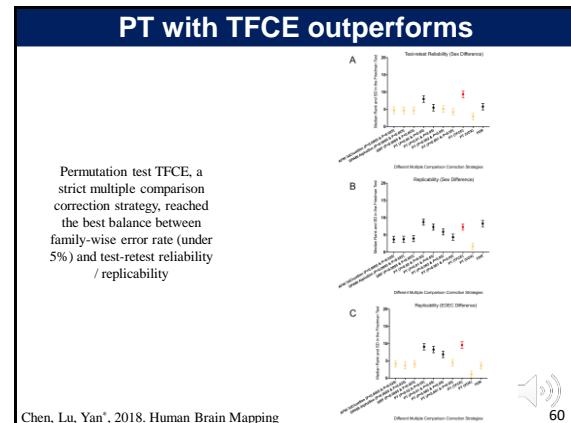
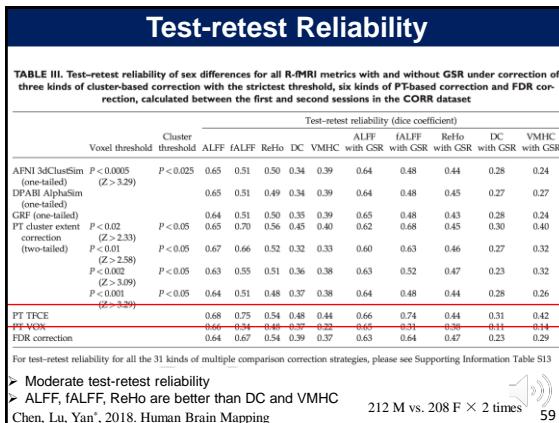
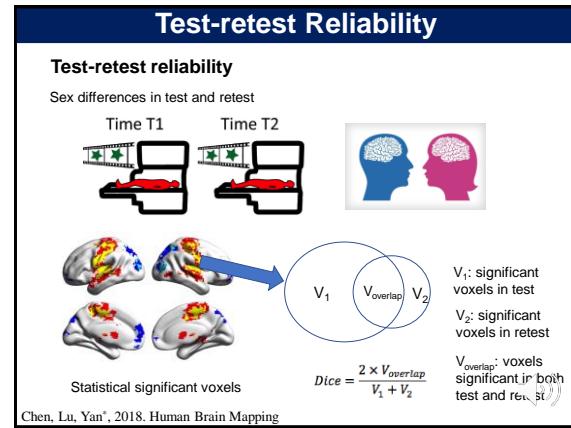
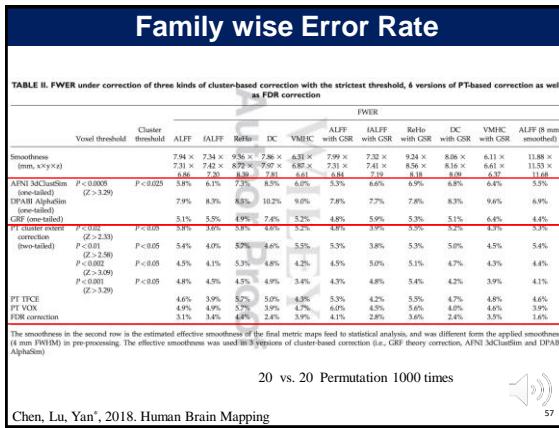
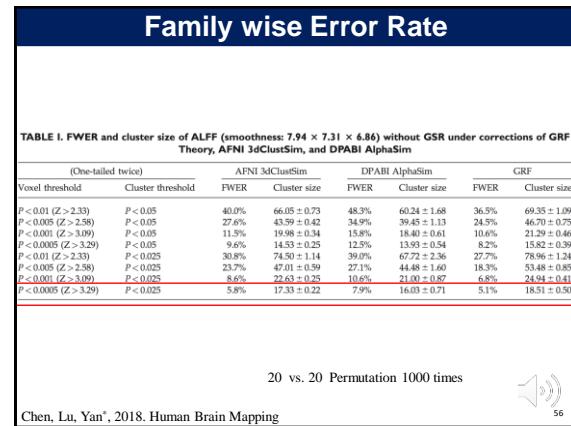
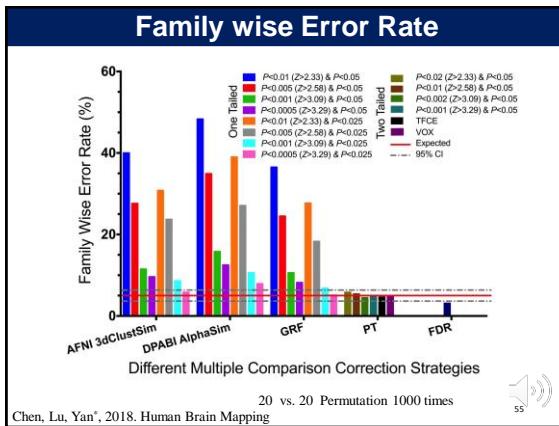
Beijing Municipal Science & Technology Commission (Z161100000216152) (PI: Gao)

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



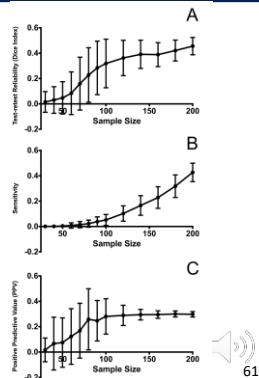
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Sample Size Matters

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

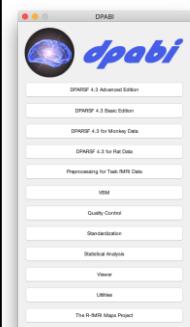
- Permutation test with TFCE reached the best balance between FWER and reproducibility
 - Although R-fMRI indices attained moderate reliabilities, they replicated poorly in distinct datasets (replicability < 0.3 for between-subject sex differences, < 0.5 for within-subject EOEC differences)
 - For studies 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).

- Cited 96 times
- ESI Top 1% highly cited



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Permutation Test with TFCE



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



Yan* et al., 2016. Neuroinformatics

ESI Top 0.1% highly cited (>850 times)

The R-fMRI Maps Project

Shared data of **4770** subjects:

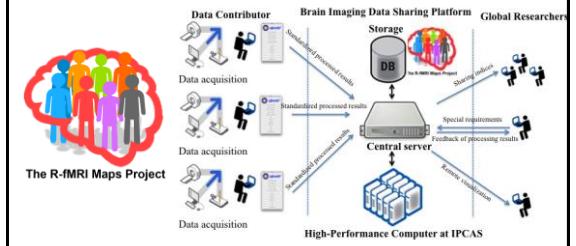
1. Amplitude of low frequency fluctuations (ALFF)
 2. Fractional ALFF (fALFF)
 3. Regional Homogeneity (ReHo)
 4. Voxel-mirrored homotopic connectivity (VMHC)
 5. Degree Centrality (DC)
 6. Functional Connectivity Matrices
 - a. Automated Anatomical Labeling (AAL) atlas
 - b. Harvard-Oxford atlas
 - 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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Part of the Human Brain Data Sharing Initiative (HBDSI), IPCAS



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同行评价及影响

BRAIN CONNECTIVITY
Volume 5, Number 9, 2016
ISSN: 1544-5303
DOI: 10.1089/brcn.2016.0448

COMMUNICATION

Reporting of Resting-State Functional Magnetic Resonance Imaging Preprocessing Methodologies

Syed Hanza Waheed,¹ Saeedeh Mirbagheri,² Shruti Agarwal,³ Arash Kamaei,² Nourishin Yahyaee-Fresu-Abadi,² Ammar Chaudhry,⁴ Michael DGivartos,⁵ Sartaj S. Guler,² Jay J. Pinto,² and Hafiz I. Sair²

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%) ...



Johns Hopkins University Professor



高效脑成像数据处理与共享平台

- 整合DPARSF
此前工作，被引2202次
- 整合方法学改进
头动（被引970次）
标准化（被引284次）
多重比较校正（被引96次）
- 处理流程规范化
- 统计分析
- 大数据共享平台

Yan* et al., 2016. Neuroinformatics



The screenshot shows the DPABI software interface. At the top is a circular logo with a brain scan and the word "dpabi". Below the logo is a menu bar with "DPABI" and "File". The main window contains several sections: "DPARSF 4.3 Advanced Edition", "DPARSF 4.3 Basic Edition", "DPARSF 4.3 for Memory Data", "DPARSF 4.3 for Rat Data", "Preprocessing for Task fMRI Data", "VBM", "Quality Control", "Standardization", "Statistical Analysis", "Viewer", and "Utilities". At the bottom right is a "The In-MRI Maps Project" logo with a speaker icon.

The slide features a world map with numerous blue and orange location markers indicating research sites. A portrait of Seiji Ogawa is positioned on the right side. A speaker icon is located in the bottom right corner.

同行评价及影响
引用850次, 为ESI Top 1%高被引论文

Journal: [Journal of Vocational Rehabilitation](#) | Volume: [Volume 51 Number 3](#) | DOI: [10.1007/s40261-020-00360-0](#)

RESEARCH ARTICLE

Estimation of vocational aptitudes using functional brain networks

Yui-Wan Sung¹ | Yousuke Kanewaki¹ | Uki-Su Choi¹ | Daehun Kang¹ |
Chihio Aso² | Yuki Otmoto³ | Seiji Ogawa⁴

In this study, we used the data processing assistant for a part of resting-state fMRI preprocessing software known as DPABI (Chao-Gan & Yu-Feng, 2010; Yan et al., 2016). The preprocessing included slice-scan time cor-

Seiji Ogawa
fMRI BOLD個人

DPARSF

Data Organization

ProcessingDemoData.zip

```
graph TD; PDZ[ProcessingDemoData.zip] --> FunRaw[FunRaw]; PDZ --> T1Raw[T1Raw]; FunRaw --> Sub001_1[Sub_001]; FunRaw --> Sub002_1[Sub_002]; FunRaw --> Sub003_1[Sub_003]; T1Raw --> Sub001_2[Sub_001]; T1Raw --> Sub002_2[Sub_002]; T1Raw --> Sub003_2[Sub_003];
```

FunRaw

- Sub_001
- Sub_002
- Sub_003

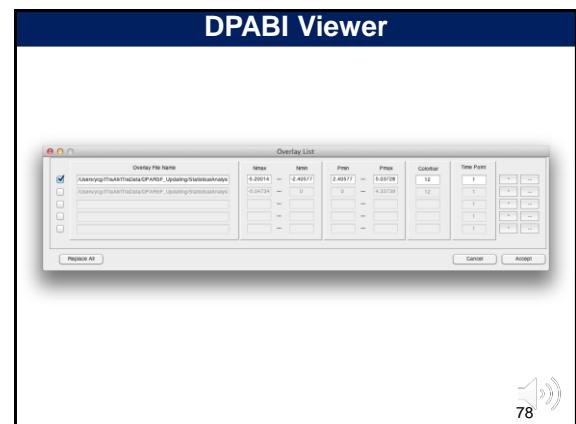
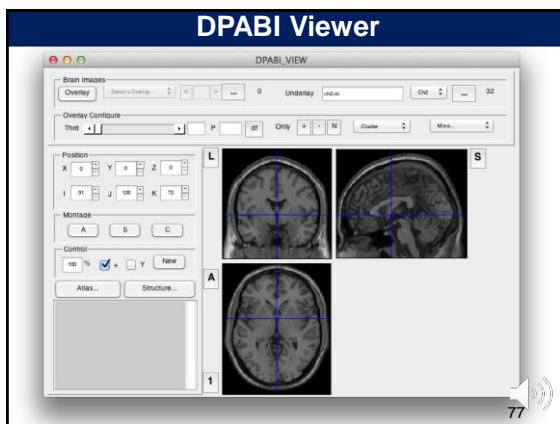
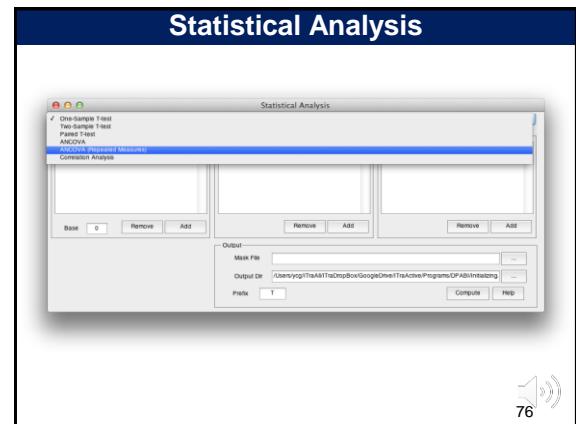
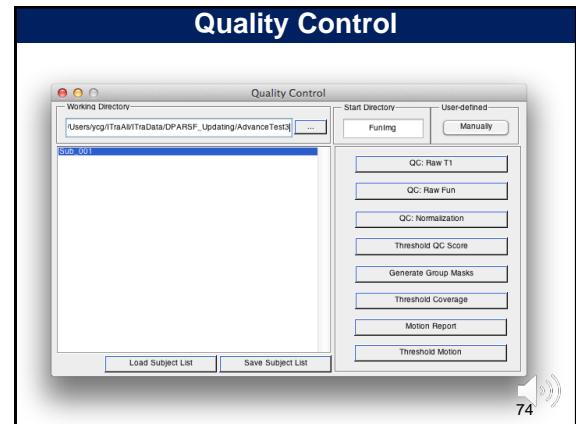
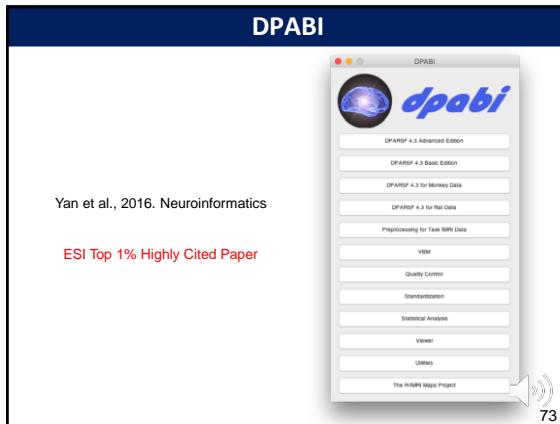
Functional DICOM data

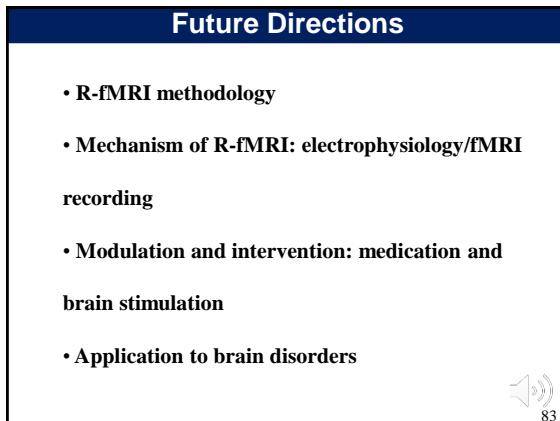
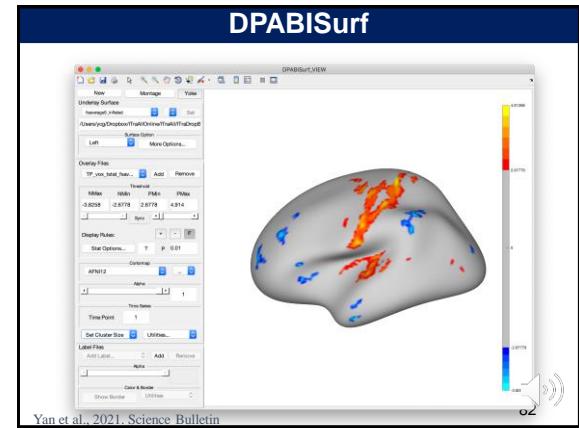
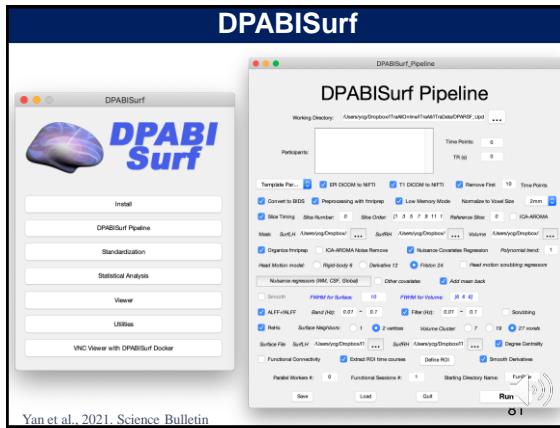
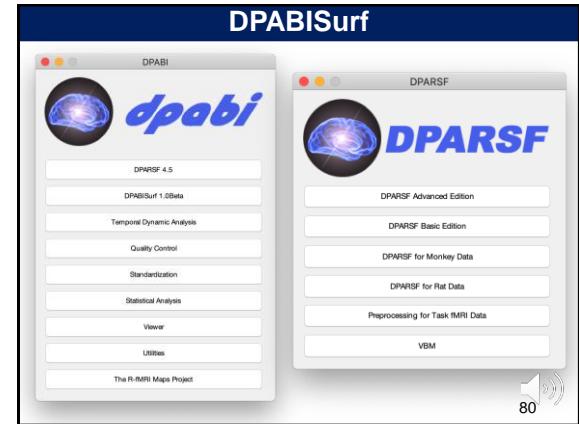
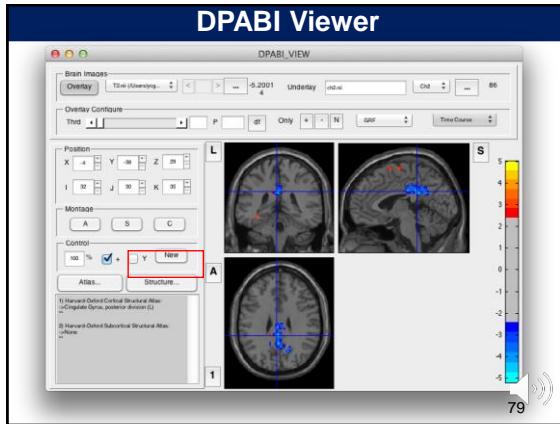
T1Raw

- Sub_001
- Sub_002
- Sub_003

Structural DICOM data

The screenshot shows the DPARSF Advanced Edition software window. The main title bar reads "Data Processing Assistant for Resting-State fMRI Advanced Edition DPARSF A". Below the title, the working directory is set to "J:\rest\yrgf\TrnMfTnsData\DPARSF\UpdatingDPARSFTest". The participants list contains "Sub-001" and "Sub-003". The time points are set to 0, and the TR (ms) is also 0. A red box highlights the "Template Parameters" section. This section includes dropdown menus for "Calculus by using SPM's template" (with options like "Calculus in MINI TRADITIONAL order" and "Calculus in MINI TRADITIONAL order from segmented"), "Calculus in MINI TRADITIONAL order", "Task fMRI data processing", "VBM (new segment and DARTEL)", and "Buck". There are also checkboxes for "Normalize", "Boundary Box", "Input Size", "Output Size", "Normality by using FEP template", "Normality by using T1 image unified segmentation", and "Normality by DARTEL". Other buttons include "Smooth", "Smooth by DARTEL", "Default mask", "No mask", "Overestimated mask", "Use Default Mask", "Warp Masks into Individual Space", "Delete ROI", "ROI", "Smooth ROI", "Smooth Amico", "Smooth Amico", "Delete ROI", "ROI", "Delete ROI", "Interactively", "CWAWS", "Dense Centrality", "Nonnegative Densities", and "Smooth Densities". At the bottom, there are buttons for "Parallel Workers #", "Functional Sessions #", "Starting Directory Name", "Run", "Help", "Save", "Load", "Utilities", "Quit", and a "Run" button with a yellow play icon.





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Thanks for your attention!



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