心理统计

第二十六讲：脑影像统计1
——脑影像数据分析原理

严超赣

Chao-Gan Yan, Ph.D.

yancg@psych.ac.cn
http://rfmri.org/yan

Institute of Psychology, Chinese Academy of Sciences

1

1

Outline

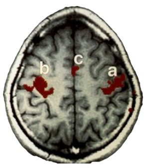
- 脑影像统计1：脑影像数据分析原理
- 脑影像统计2：脑影像数据处理与DPARSF程序实践
- 脑影像统计3：脑影像数据统计分析

2

2

脑功能磁共振成像


任务态功能磁共振成像



静息态功能磁共振成像

3

3

中科院心理所磁共振成像研究中心

GE MR750 3T磁共振成像仪

儿童脑与认知发育体验中心

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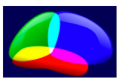
脑成像数据处理软件

OsiriX



MRIcron

Chris Rorden dcm2nii

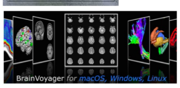
NITRC NeuroImaging Tools & Resources Collaboratory

https://www.nitrc.org/plugins/mwiki/index.php/dcm2nii:MainPage

DICOM to NiFTI converter

FSL

SPM



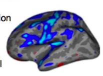
AFNI

FreeSurfer

FreeSurfer Software Suite

An open source software suite for processing and analyzing (human) brain MRI images.

- Skullstripping
- Image Registration
- Subcortical Segmentation
- Cortical Surface Reconstruction
- Cortical Segmentation
- Cortical Thickness Estimation
- Longitudinal Processing
- fMRI Analysis
- Tractography
- FreeView Visualization GUI
- and much more...



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5

DPARSF

Yan and Zang, 2010.
Front Syst Neurosci.
Cited: > 3000 times

Haris I. Sair
Johns Hopkins University

COMMUNICATION

Reporting of Resting-State Functional Magnetic Resonance Imaging Preprocessing Methodologies

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.

6

DPARSF Citations

Cited for more than 3000 times

7

7

DPARSF

Data Organization

ProcessingDemoData.zip

FunRaw

Sub_001

Sub_002

Sub_003

Functional DICOM data

T1Raw

Sub_001

Sub_002

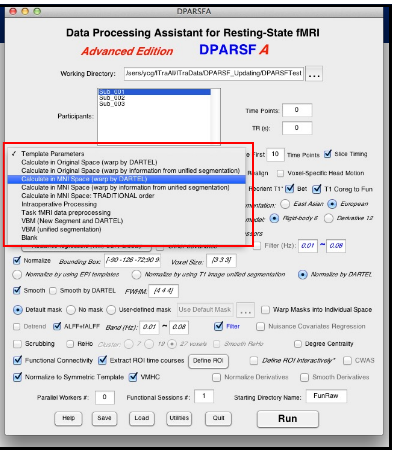
Sub_003

Structural DICOM data

8

8

Resting State fMRI Data Processing



Template Parameters

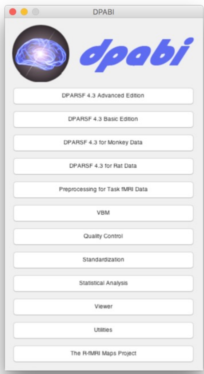
9

DPABI

Yan et al., 2016. Neuroinformatics

ESI Top 1% Highly Cited Paper

Cited > 2000 times



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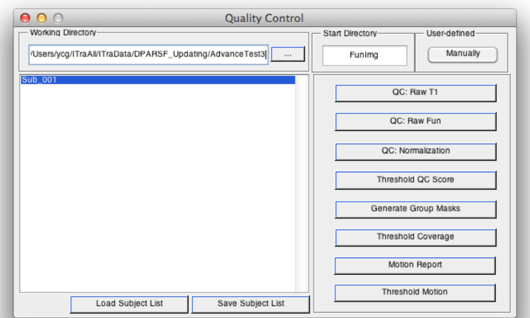
10

Quality Control



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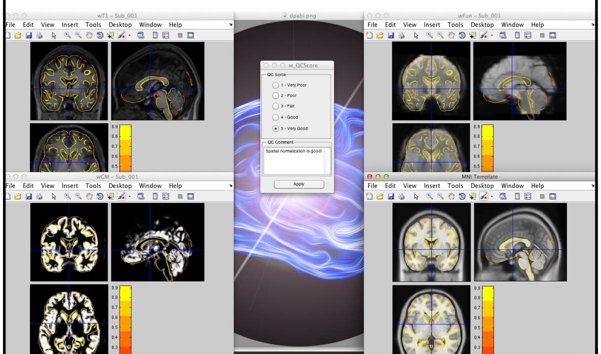
Quality Control



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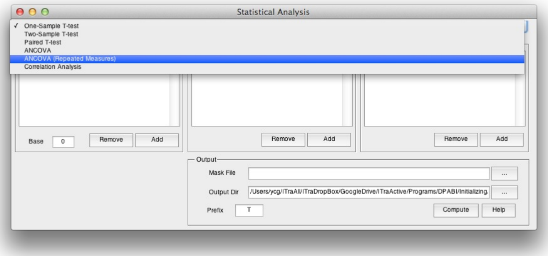
12

Statistical Analysis



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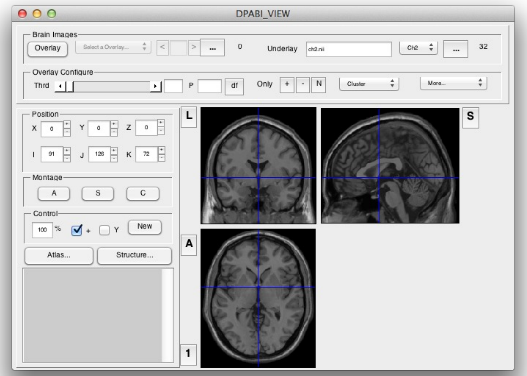
13

DPABI Viewer



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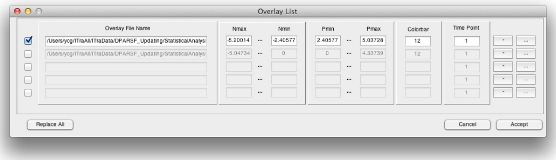
14

DPABI Viewer



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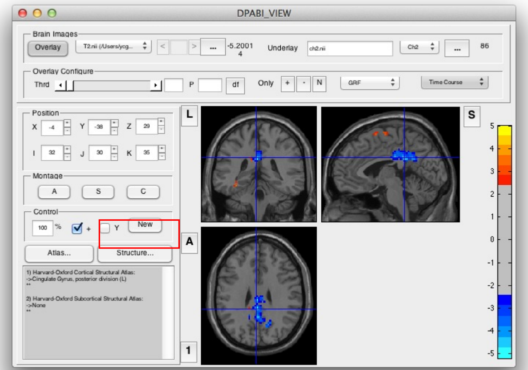
DPABI Viewer



16

16

Outline

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

17

17

Resting-State fMRI: Principles

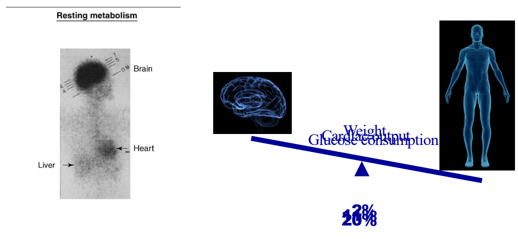
All of the human high mental functions such as thinking, emotion and consciousness rely on brain, an extremely complex system (Singer, 1999)

18

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

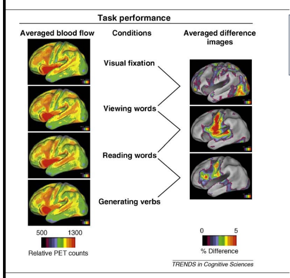
18

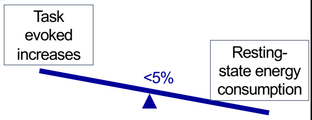
Resting-State fMRI: Principles



Raichle et al., 2010. Trends Cogn Sci

Resting-State fMRI: Principles



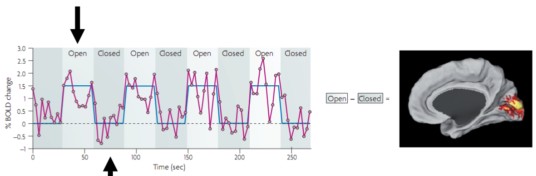


There are very important activities in the brain during resting-state (Fox and Raichle, 2007; Zhang and Raichle, 2010)

Raichle et al., 2010. Trends Cogn Sci

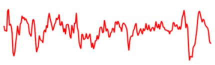
Resting-State fMRI: Principles

Task



Baseline

• **Traditional fMRI analysis**



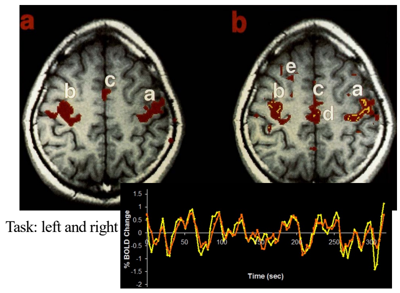
→ **Noise?**

Activities in the baseline state (usually resting-state)

Fox and Raichle, 2007. Nat Rev Neurosci

Resting-State fMRI: Principles

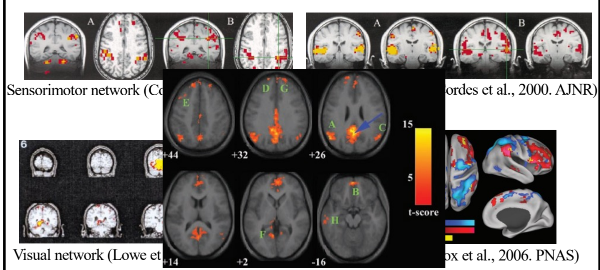
• **Temporal synchrony of spontaneous fluctuations**



Biswal et al., 1995. Magn Reson Med

Resting-State fMRI: Principles

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

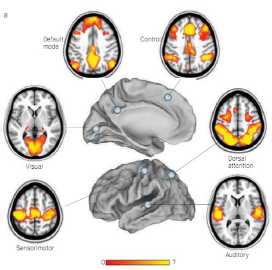


Sensorimotor network (C... ...ordes et al., 2000. AJNR)

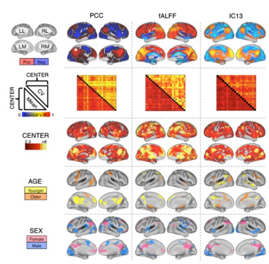
Visual network (Lowe et... ...ox et al., 2006. PNAS)

DMN (Greicius et al., 2003. PNAS)

Resting-State fMRI: Principles



Zhang and Raichle, 2010. Nat Rev Neurol



Biswal et al., 2010. PNAS

Resting-State fMRI: Principles

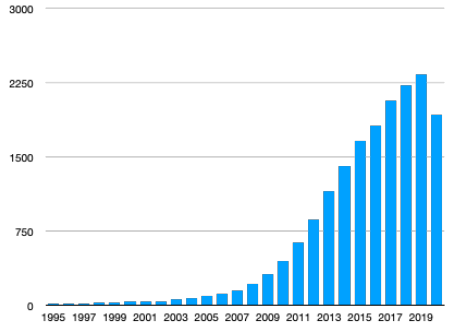


Figure 1. Number of R-fMRI related studies in PubMed (key words: “resting+state+fmri”).

25

25

Outline

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

26

26

Computational Methodology

- Integration approach
- Regional approach
- Graphical approach

27

27

Computational Methodology

Integration approach

- Functional Connectivity
-

a

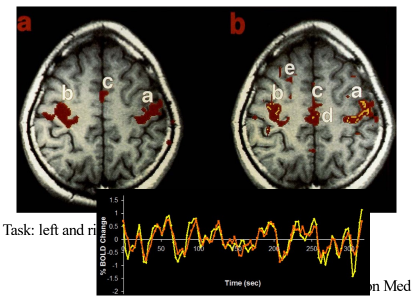
- Effective Connectivity: (Friston et al., 2002)
- Hierarchical Clustering: (Cordes et al., 2000; Salvador et al., 2005)
- Self Organization Map: (Peltier et al., 2003)
- ....

28

28

Computational Methodology

- **Correlation: Temporal synchrony of spontaneous fluctuations**



Task: left and ri

n Med

29

29

Computational Methodology

The “Resting” Brain

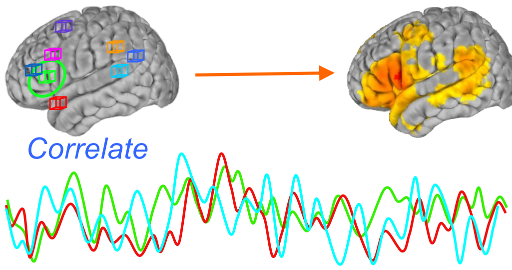
Courtesy of Dr. Daniel Margulies

30

Computational Methodology

How do we detect organized patterns of intrinsic activity?

Resting State Functional Connectivity

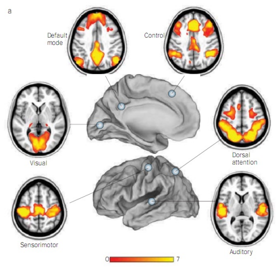


31

31

Computational Methodology

- **Correlation**



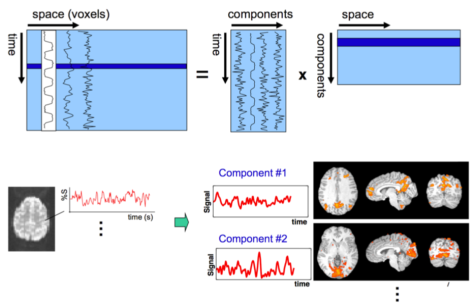
Zhang and Raichle, 2010. Nat Rev Neurol

32

32

Computational Methodology

- **Independent Component Analysis**



Birn 2015

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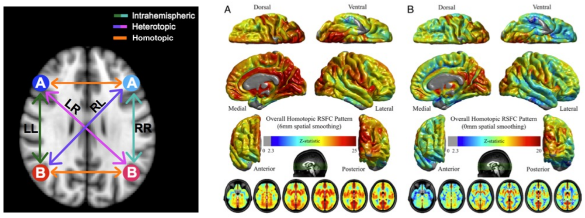
33

Computational Methodology

- **Voxel-mirrored homotopic connectivity (VMHC)**



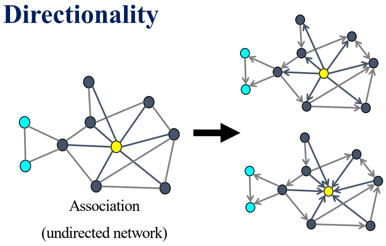
Gee et al., 2011 **Zuo et al., 2010**

34

34

Computational Methodology

Directionality



Association (undirected network)

Directionality Causality (directed network)

35

35

Computational Methodology

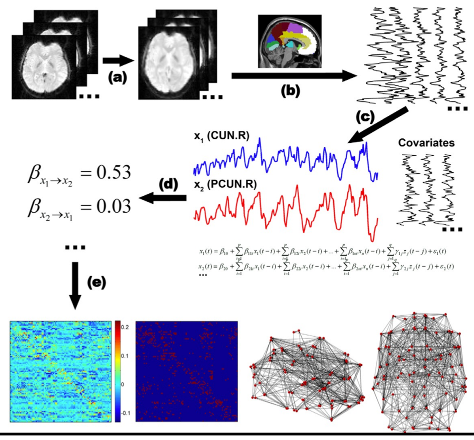
Directionality

- 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

36

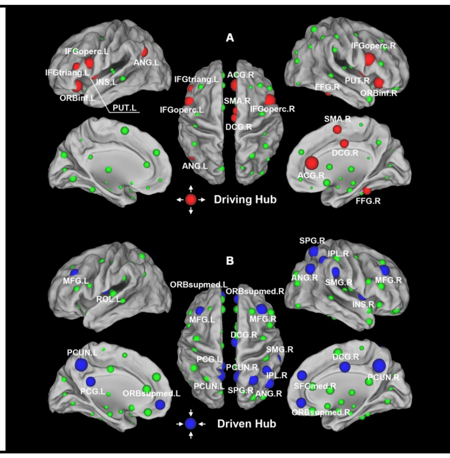
36



Yan et al., 2011. PLoS ONE

37

37

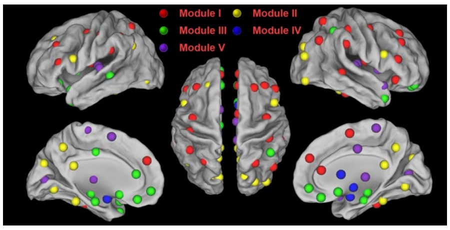


Yan et al., 2011. PLoS ONE

38

38

Computational Methodology



Yan et al., 2011. PLoS ONE

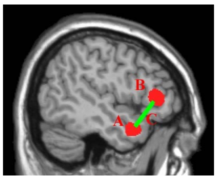
39

39

Computational Methodology

Regional approach

"Integrative" is really good, but:



Decreased functional connectivity

Question: Is A, B, C, or……abnormal?

40

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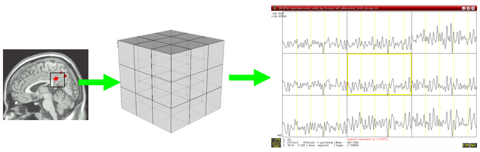
Computational Methodology

Regional Homogeneity (ReHo)

Similarity or coherence of the time courses within a functional cluster



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

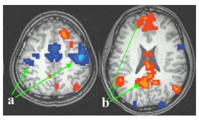
(Zang et al., 2004)

41

41

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)*

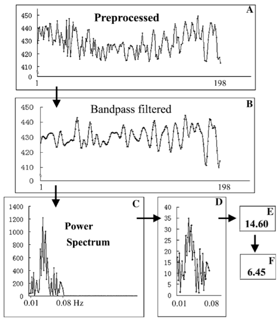
(Zang et al., 2004)

42

42

Computational Methodology

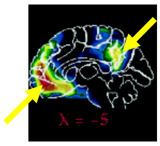
Amplitude of low frequency fluctuations



Zang et al., 2007

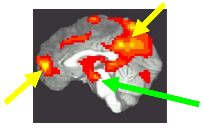
Computational Methodology

ALFF



PET

(Raichle et al., 2001)



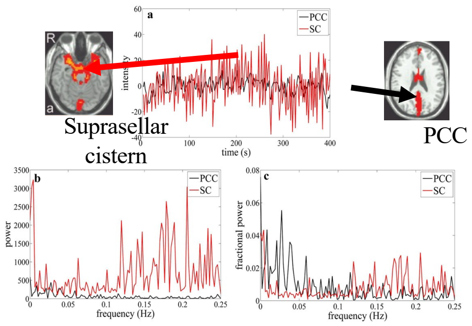
ALFF

(Zang et al., 2007)

noise

Computational Methodology

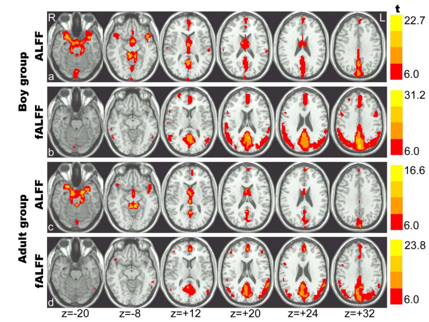
Improvement: fractional ALFF



Zou et al., 2008. J Neurosci Methods

Computational Methodology

Improvement: fractional ALFF



Zou et al., 2008. J Neurosci Methods

Computational Methodology

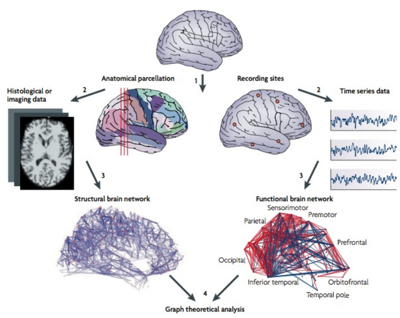
Graphical approach

- Graph theoretical analysis: (Salvador et al., 2005, Bullmore and Sporns, 2009)
  - Degree connectivity, functional connectivity density, degree centrality: (Buckner et al., 2009; Tomasi et al., 2010; Cole et al., 2010; Zuo et al., 2012)
- …

Computational Methodology

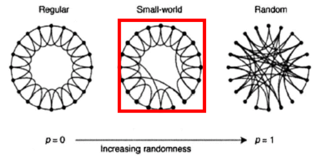
Graph theoretical analysis

Bullmore and Sporns, 2009



Computational Methodology

Graph theoretical analysis



Node: brain region
Link: connection

Watts and Strogatz, 1998. Nature

Regular:
high C_p
high L_p

Small-world:
high C_p
low L_p

Random:
low C_p
low L_p

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

Cp: average clustering of a network
Lp: average shortest path length of a network

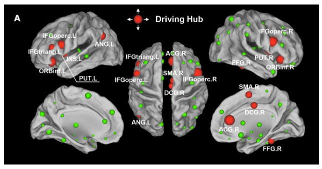
49

49

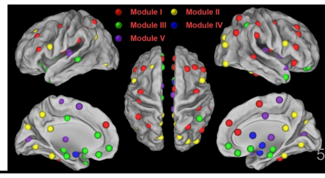
Computational Methodology

Graph theoretical analysis

Hub



Module



Yan et al., 2011. PLoS ONE

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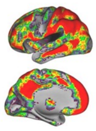
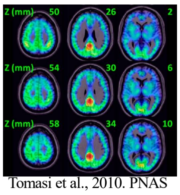
Computational Methodology

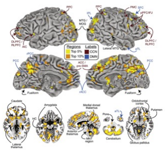
Degree centrality



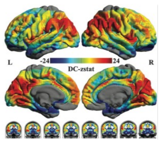
Buckner et al., 2009. J Neurosci



Tomasi et al., 2010. PNAS



Cole et al., 2010. Neuroimage



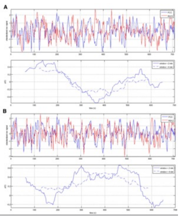
Zuo et al., 2011. Cereb Cortex

51

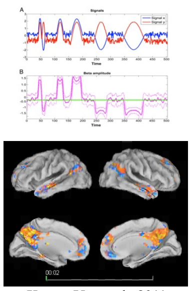
51

Computational Methodology

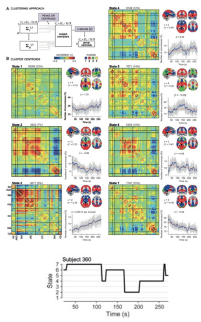
Dynamic perspective



Chang and Glover, 2010. Neuroimage



Kang, , Yan et al., 2011. Neuroimage



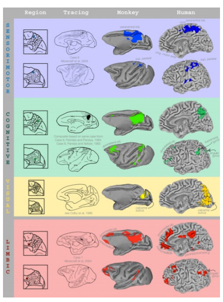
Allen et al., 2013. Cereb Cortex

52

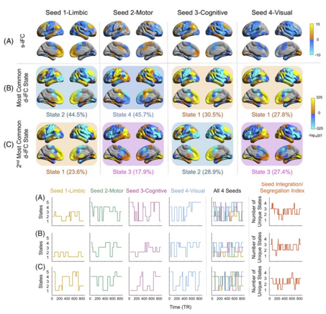
52

Computational Methodology

Dynamic perspective



Margulies et al., 2009. PNAS



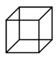
Yang, , Yan, Milham, 2014. Neuroimage

53

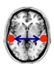
53

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

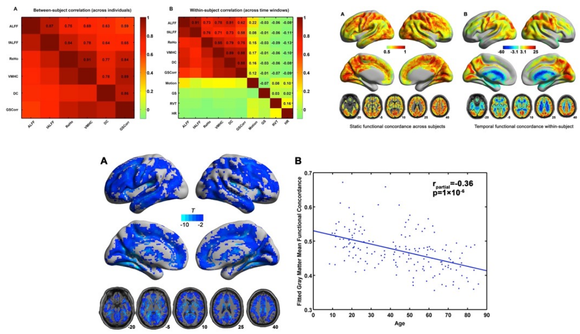
 Global Signal Correlation

54

54

Computational Methodology

Concordance Among Indices of Intrinsic Brain Function

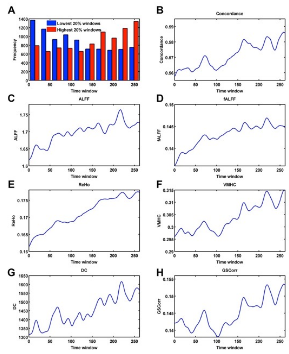


Yan et al., 2017. Science Bulletin

55

55

Computational Methodology



Yan et al., 2017. Science Bulletin

56

56

Outline

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

57

57

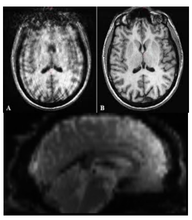
Methodological Issues

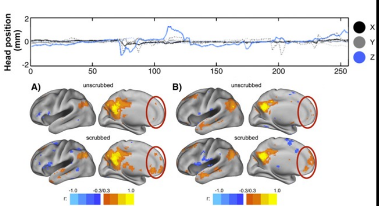
- Head motion — *Yan et al., 2013a. Neuroimage; Yan et al., 2013. Front Hum Neurosci*
- Standardization — *Yan et al., 2013b. Neuroimage*
- Multiple-comparison correction — *Chen, Lu, Yan*, 2017. Human Brain Mapping*
- And many many more…

58

58

Methodological Issues: Head Motion





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

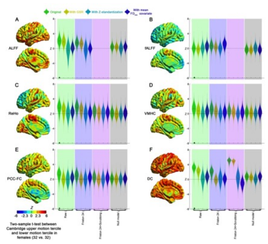
Head motion is a critical factor in R-fMRI data processing.

Need an effective motion correction strategy!

59

59

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: 1303 times
- ESI Top 0.1% highly cited paper

Yan et al., 2013a. Neuroimage

60

60

Methodological Issues: Standardization

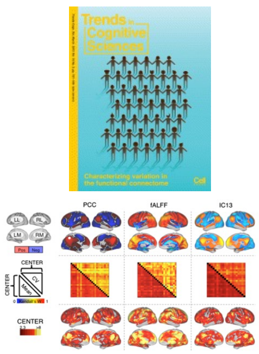


Table 1. Factors can introduce unintended variations in fMRI measurement.

Category	Factor
1. Acquisition-related variations	Scanner make and model (Friedman and Glover, 2006b), sequence type (spiral vs. echo planar; single-echo vs. multi-echo) (Klarhofer et al., 2002), parallel vs. conventional acquisition (Feinberg et al., 2010; Lin 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/gaps, slice prescription) (Friedman and Glover, 2006a)
2. Experimental-related variations	Participant instructions (Hartstra et al., 2011), eyes-open/eyes-closed (Yan et al., 2009; Yang et al., 2007), visual displays, experiment duration (Fang et al., 2007; Van Dijk et al., 2010)
3. Environment-related variations	Sound attenuation measures (Cho et al., 1998; Elliott et al., 1999), attempts to improve participant comfort during scans (e.g., music, videos) (Cullen et al., 2009), head-motion restraint techniques (e.g., vacuum pad, foam pad, bite-bar, plaster cast head holder) (Edward et al., 2000; Menon et al., 1997), room temperature and moisture (Vanhoutte et al., 2006).
4. Participant-related variations	Circadian cycle (Shannon et al., 2012), prandial (Haase et al., 2009), caffeine (Rack-Gomer et al., 2009), and nicotine status (Tanabe et al., 2011), sleepiness / arousal (Horovitz et al., 2008), sleep deprivation (Samann et al., 2010), scanner anxiety (de Bie et al., 2010), and menstrual cycle status (for women) (Protopopescu et al., 2005).

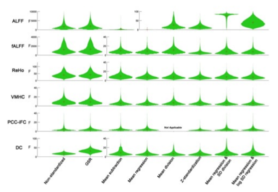
Yan et al., 2013b. Neuroimage

Biswal et al., 2010, PNAS

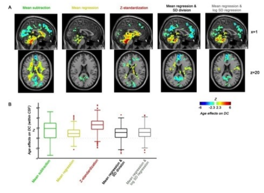
61

61

Methodological Issues: Standardization



The Impact of Standardization Procedures on Confound Variables: Site Effects



The Impact of Standardization Procedures on Variables of Interest: Age Effects

Proposed an effective standardization strategy

Mean regression + SD division

- Cited: 375 times
- ESI Top 1% highly cited paper

Yan et al., 2013b. Neuroimage

62

62

Our Updated Work

We choose 3 representative dataset to assess 10 methods along the harmonization spectrum, including popular ComBat series and advanced domain adaptation technique SMA and deep learning technique ICVAE, from 5 perspectives.

Step1:
Extract brain connectome

ReHo, ALFF, fALFF, DC, FC

Step2:
Harmonize

Methodology choices

- Linear Regression Series
- Empirical Bayesian ComBat/CovBat
- SMA
- Deep Learning-ICVAE

Step3:
Evaluate

Efficiency: Residual site effect
Identifiability: Individual identification
Test-retest reliability: Sex difference between sessions
Replicability: Sex difference across datasets
Extreme case: Sex confounds with sites.

Wang et al., 2023. Neuroimage

63

63

Methods

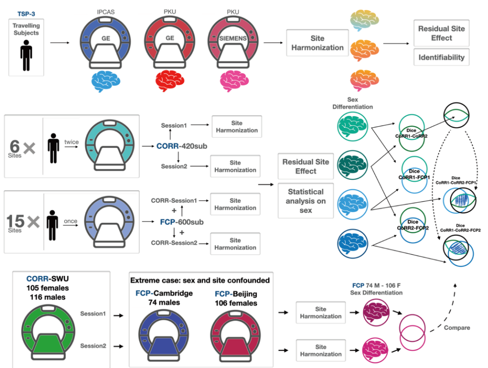
Harmonization Methodology			Addresses additive noise	Addresses multiplicative noise	Addresses Covariance	Addresses nonlinear effects	Non-parametric	Formular
Linear regression	without covariates		x					$Reg: y = \alpha + X_s\beta_s + \epsilon$
	with biological covariates		x					$Adj: y = \alpha + X_b\beta_b + X_s\beta_s + \epsilon$
	mixed model with covarites		x					$LMM: y = \alpha + X_b\beta_b + Z_s u_s + \epsilon$
ComBat	parametric	Adjusted	x	x				$y^* = \frac{\sigma_m}{\hat{\delta}^*_{im}}(Z_{ijm} - \hat{\gamma}^*_{im}) + \hat{\alpha} + X_b\hat{\beta}_b$
		Unadjusted	x	x				$y^* = \frac{\sigma_m}{\hat{\delta}^*_{im}}(Z_{ijm} - \hat{\gamma}^*_{im}) + \hat{\alpha}$
	nonparametric	Adjusted	x	x			x	$y^* = \frac{\sigma_m}{\hat{E}(\delta_{im})}(Z_{ijm} - \hat{E}(\gamma_{im})) + \hat{\alpha} + X_b\hat{\beta}_b$
		Unadjusted	x	x			x	$y^* = \frac{\sigma_m}{\hat{E}(\delta_{im})}(Z_{ijm} - \hat{E}(\gamma_{im})) + \hat{\alpha}$
CovBat			x	x	x			$y* = (y_{ComBat} - e_{ComBat}) + \sum_{k=1}^{K}(\lambda_k\Phi_k)_{ComBat}\Phi_k^T + \sum_{l=K+1}^{\min(N_{sub}, N_{feature})} \lambda_l\Phi_l\Phi_l^T$
Subsampling Maximum-mean-distance based Algorithm			x	x	x	x	x	$y^*_{source} = SMA(\underset{\lambda \subseteq \Omega_\lambda}{argmin}\widehat{MMD}(h^\lambda(y_{source}), y_{target}))$
Invariant Conditional Variational Auto-Encoder			x	x	x	x	x	$\vec{y^*} = ICVAE(\vec{y})$

Wang et al., 2023. Neuroimage

64

64

Evaluation Process



Wang et al., 2023. Neuroimage

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Application Guidance

Summary

- SMA performs the best overall.
- We provide a heuristic formula to assist choose target site when applying SMA to harmonize.
- We have opened our data and codes, and easy-to-use module specialized for harmonization shall be implemented in the next release of DPABI, including SMA, CovBat, ComBat and ICVAE etc.
- Together with the replication and validation efforts from other researchers, we hope this work would encourage better harmonization methods and reach consensus for the field.

Wang et al., 2023. Neuroimage

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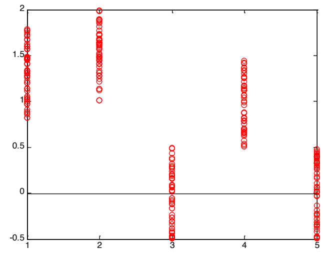
Eklund et al., 2016. PNAS

67

67



P=0.05 P=0.05 P=0.05 P=0.05 P=0.05

0.95 0.95 0.95 0.95 0.95

Probability of not getting a false positive result:

1 - 0.05 = 0.95

$0.95^5 = 0.774$

68

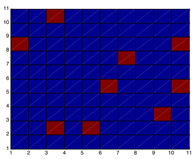
68

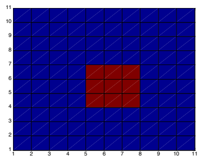
Reproducibility and Multiple Comparison Correction

Multiple Comparisons

Gaussian Random Field Theory Correction

Monte Carlo simulations (AlphaSim)





69

69

Reproducibility and Multiple Comparison Correction

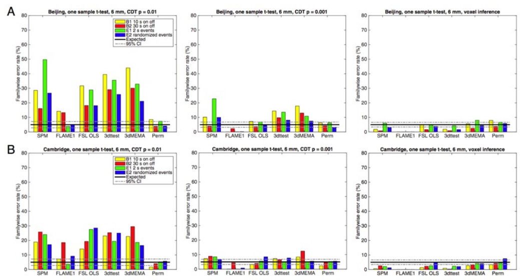


Fig. 1. Results for one-sample *t* test, showing estimated FWE rates for (*A*) Beijing and (*B*) Cambridge data analyzed with 6 mm of smoothing and four different activity paradigms (B1, B2, E1, and E2), for SPM, FSL, AFNI, and a permutation test. These results are for a group size of 20. The estimated FWE rates are simply the number of analyses with any significant group activation divided by the number of analyses (1,000). From *Left* to *Right*: Cluster inference using a cluster-defining threshold (CDT) of $P = 0.01$ and a FWE-corrected threshold of $P = 0.05$, cluster inference using a CDT of $P = 0.001$ and a FWE-corrected threshold of $P = 0.05$, and voxel inference using a FWE-corrected threshold of $P = 0.05$. Note that the default CDT is $P = 0.001$ in SPM and $P = 0.01$ in FSL (AFNI does not have a default setting).

Eklund et al., 2016. PNAS

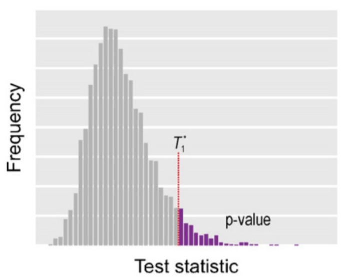
70

70

Reproducibility and Multiple Comparison Correction

Permutation Test

Permutations



Winkler et al., 2016. Neuroimage

71

71

Reproducibility and Multiple Comparison Correction

Threshold-Free Cluster Enhancement (TFCE)

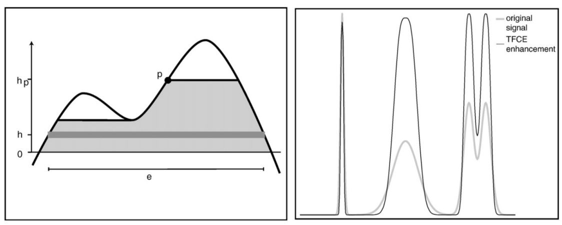


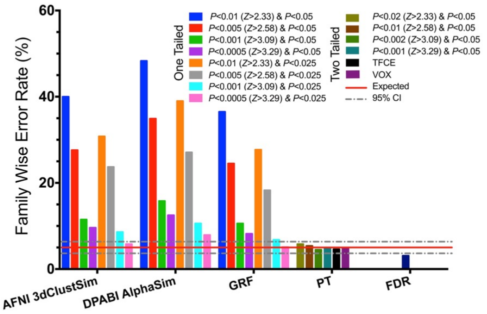
Fig. 1. Illustration of the TFCE approach. Left: the TFCE score at voxel *p* is given by the sum of the scores of all incremental supporting sections (one such is shown as the dark-grey band) within the area of "support" of *p* (light grey). The score for each section is a simple function of its height *h* and extent *e*. Right: example input image and TFCE-enhanced output. The input contains a focal, high signal, a much more spatially extended, lower, signal and a pair of overlapping signals of intermediate extent and height. The TFCE output has the same maximal values for all three cases, and preserves the distinct local maxima in the third case.

Smith et al., 2009. Neuroimage

72

72

Family wise Error Rate



Different Multiple Comparison Correction Strategies

20 vs. 20 Permutation 1000 times

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

73

73

Family wise Error Rate

TABLE I. FWER and cluster size of ALFF (smoothness: 7.94 × 7.31 × 6.86) without GSR under corrections of GRF Theory, AFNI 3dClustSim, and DPABI AlphaSim

(One-tailed twice)		AFNI 3dClustSim		DPABI AlphaSim		GRF	
Voxel threshold	Cluster threshold	FWER	Cluster size	FWER	Cluster size	FWER	Cluster size
$P < 0.01$ ($Z > 2.33$)	$P < 0.05$	40.0%	66.05 ± 0.73	48.3%	60.24 ± 1.68	36.5%	69.35 ± 1.09
$P < 0.005$ ($Z > 2.58$)	$P < 0.05$	27.6%	43.59 ± 0.42	34.9%	39.45 ± 1.13	24.5%	46.70 ± 0.75
$P < 0.001$ ($Z > 3.09$)	$P < 0.05$	11.5%	19.98 ± 0.34	15.8%	18.40 ± 0.61	10.6%	21.29 ± 0.46
$P < 0.0005$ ($Z > 3.29$)	$P < 0.05$	9.6%	14.53 ± 0.25	12.5%	13.93 ± 0.54	8.2%	15.82 ± 0.39
$P < 0.01$ ($Z > 2.33$)	$P < 0.025$	30.8%	74.50 ± 1.14	39.0%	67.72 ± 2.36	27.7%	78.96 ± 1.24
$P < 0.005$ ($Z > 2.58$)	$P < 0.025$	23.7%	47.01 ± 0.59	27.1%	44.48 ± 1.60	18.3%	53.48 ± 0.85
$P < 0.001$ ($Z > 3.09$)	$P < 0.025$	8.6%	22.63 ± 0.25	10.6%	21.00 ± 0.87	6.8%	24.94 ± 0.41
$P < 0.0005$ ($Z > 3.29$)	$P < 0.025$	5.8%	17.33 ± 0.22	7.9%	16.03 ± 0.71	5.1%	18.51 ± 0.50

20 vs. 20 Permutation 1000 times

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

74

74

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	fALFF	ReHo	DC	VMHC	ALFF with GSR	fALFF with GSR	ReHo with GSR	DC with GSR	VMHC with GSR	ALFF (8 mm smoothed)
Smoothness (mm, x×y×z)			7.94 × 7.31 × 6.86	7.34 × 7.42 × 7.20	9.36 × 8.72 × 8.39	7.86 × 7.97 × 7.81	6.31 × 6.87 × 6.61	7.99 × 7.31 × 6.84	7.32 × 7.41 × 7.19	9.24 × 8.56 × 8.18	8.06 × 8.16 × 8.09	6.11 × 6.61 × 6.37	11.88 × 11.53 × 11.68
AFNI 3dClustSim (one-tailed)	$P < 0.0005$ ($Z > 3.29$)	$P < 0.025$	5.8%	6.1%	7.3%	8.5%	6.0%	5.3%	6.6%	6.9%	6.8%	6.4%	5.5%
DPABI AlphaSim (one-tailed)			7.9%	8.3%	8.5%	10.2%	9.0%	7.8%	7.7%	7.8%	8.3%	9.6%	6.9%
GRF (one-tailed)			5.1%	5.5%	4.9%	7.4%	5.2%	4.8%	5.9%	5.3%	5.1%	6.4%	4.4%
PT cluster extent correction (two-tailed)	$P < 0.02$ ($Z > 2.33$)	$P < 0.05$	5.8%	3.6%	5.8%	4.6%	5.2%	4.8%	3.9%	5.5%	5.2%	4.3%	5.3%
	$P < 0.01$ ($Z > 2.58$)	$P < 0.05$	5.4%	4.0%	5.7%	4.6%	5.5%	5.3%	3.8%	5.3%	5.0%	4.5%	5.4%
	$P < 0.002$ ($Z > 3.09$)	$P < 0.05$	4.5%	4.1%	5.3%	4.8%	4.2%	4.5%	5.0%	5.1%	4.7%	4.3%	4.4%
	$P < 0.001$ ($Z > 3.29$)	$P < 0.05$	4.8%	4.5%	4.5%	4.9%	3.4%	4.3%	4.8%	5.4%	4.2%	3.9%	4.1%
PT TFCE			4.6%	3.9%	5.7%	5.0%	4.3%	5.3%	4.2%	5.5%	4.7%	4.8%	4.6%
PT VOX			4.9%	4.9%	5.7%	3.9%	4.7%	6.0%	4.5%	5.6%	4.0%	4.6%	3.9%
FDR correction			3.1%	3.4%	4.4%	2.4%	3.9%	4.1%	2.8%	3.6%	2.4%	3.5%	1.6%

The smoothness in the second row is the estimated effective smoothness of the final metric maps feed to statistical analysis, and was different form the applied smoothness (4 mm FWHM) in pre-processing. The effective smoothness was used in 3 versions 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

75

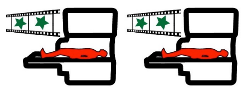
75

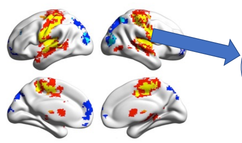
Test-retest Reliability

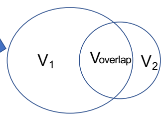
Test-retest reliability

Sex differences in test and retest

Time T1 Time T2







V_1: significant voxels in test

V_2: significant voxels in retest

$V_{overlap}$: voxels significant in both test and retest

Statistical significant voxels

$$Dice = \frac{2 \times V_{overlap}}{V_1 + V_2}$$

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

76

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	fALFF	ReHo	DC	VMHC	ALFF with GSR	fALFF 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 (two-tailed)	$P < 0.02$ ($Z > 2.33$)	$P < 0.05$	0.65	0.70	0.56	0.45	0.40	0.62	0.68	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 VOX			0.66	0.34	0.48	0.37	0.22	0.65	0.31	0.38	0.11	0.14
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, fALFF, ReHo are better than DC and VMHC

212 M vs. 208 F × 2 times

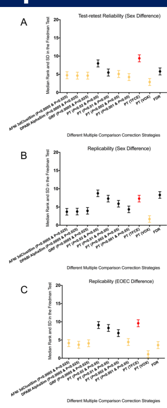
Chen, Lu, Yan*, 2018. Human Brain Mapping

77

77

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



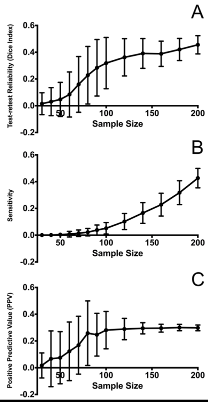
Chen, Lu, Yan*, 2018. Human Brain Mapping

78

78

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

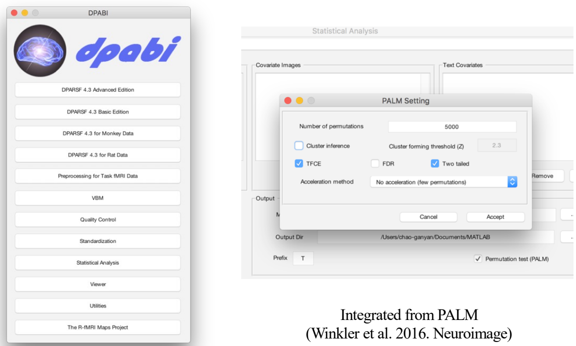
Reproducibility of R-fMRI Metrics on the Impact of Different Strategies for Multiple Comparison Correction and Sample Sizes

- 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 242 times
  - ESI Top 1% highly cited

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

Permutation Test with TFCE

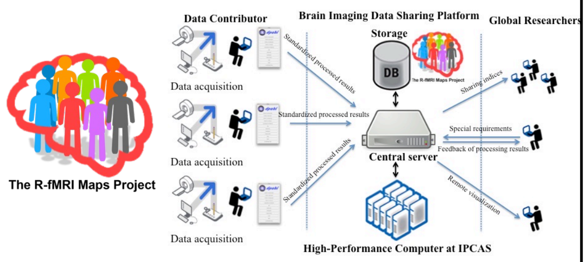


Integrated from PALM
(Winkler et al. 2016. Neuroimage)

Yan* et al., 2016. Neuroinformatics

ESI Top 0.1% highly cited (>2000 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 parcelations
   e. Dosenbach's 160 functional ROIs

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

Downloaded by
593 researchers

Outline

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

85

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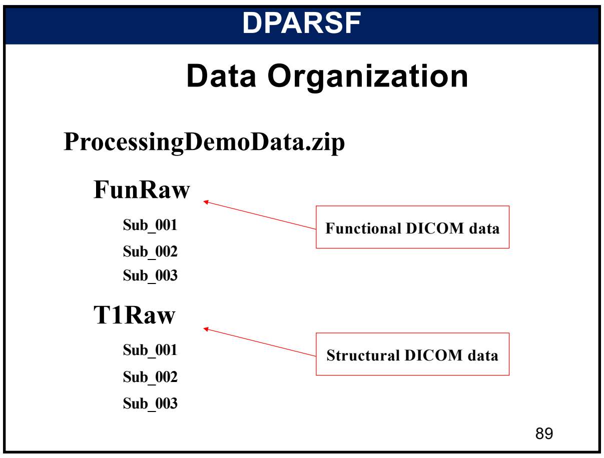

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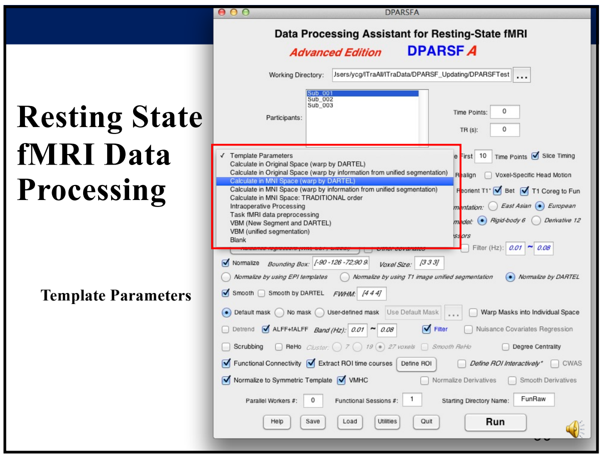

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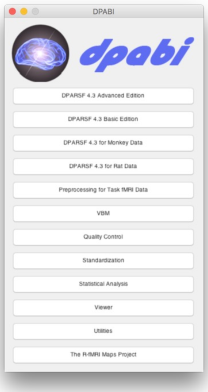
DPABI

Yan et al., 2016. Neuroinformatics

ESI Top 0.01% Highly Cited Paper



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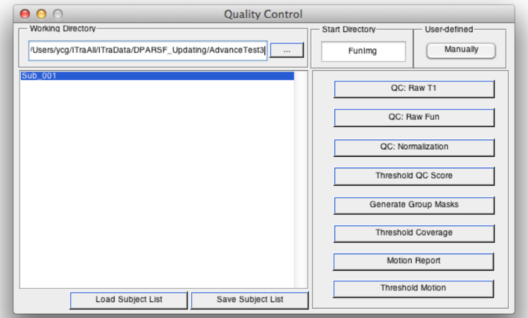
Quality Control



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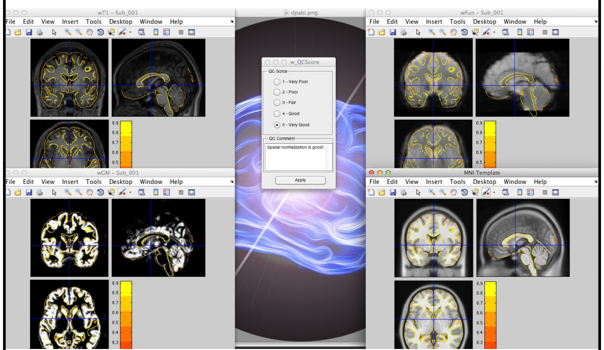

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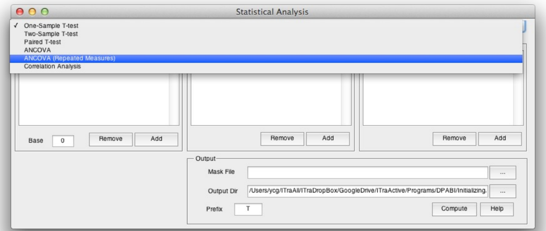
Statistical Analysis



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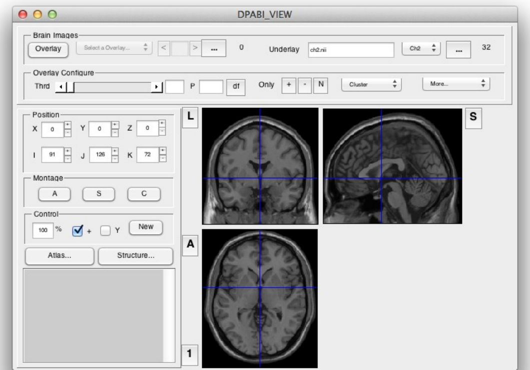
DPABI Viewer



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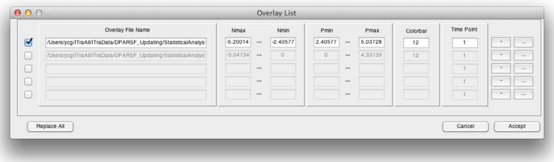

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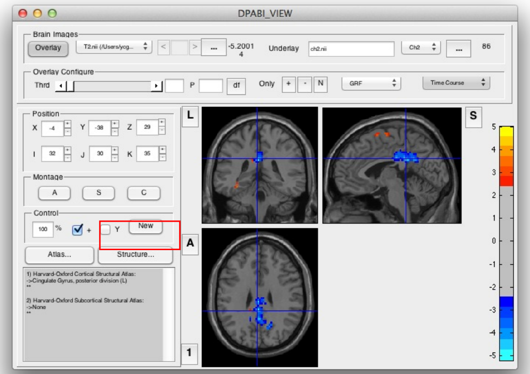

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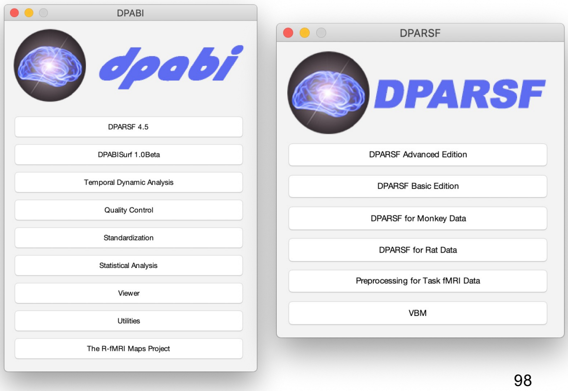

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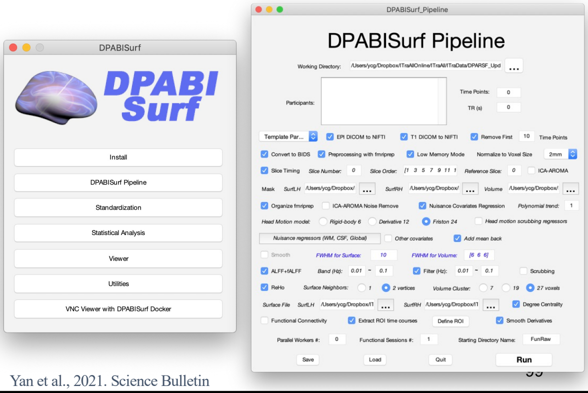

Yan et al., 2021. Science Bulletin

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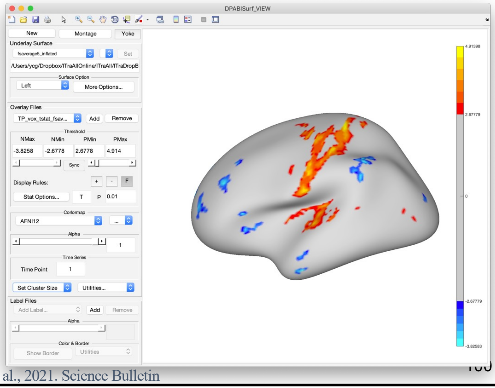
DPABISurf



Yan et al., 2021. Science Bulletin

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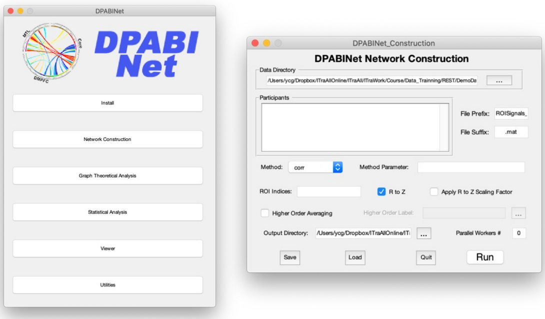
DPABINet



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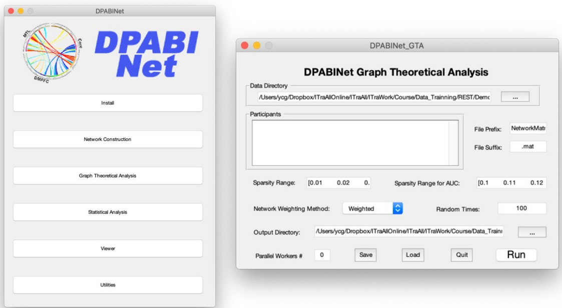

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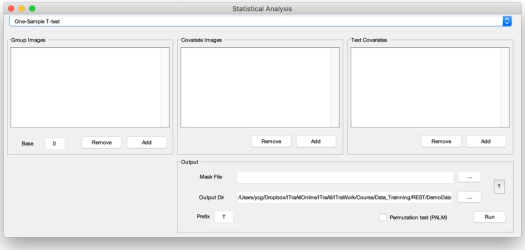

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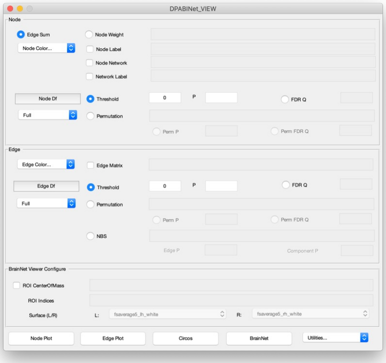

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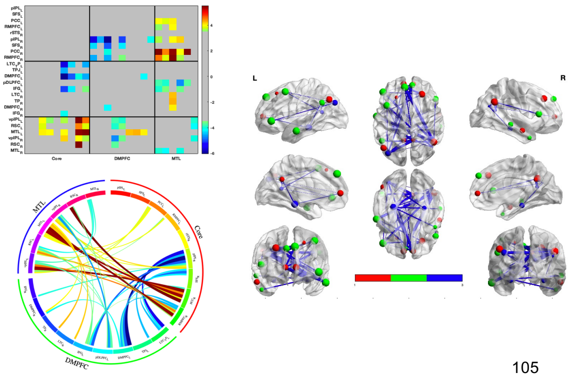

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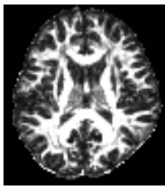
DPABIFiber



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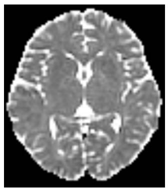
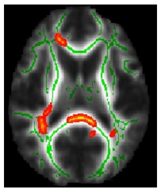


ADC (MD)



TBSS

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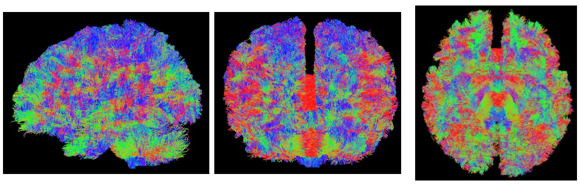
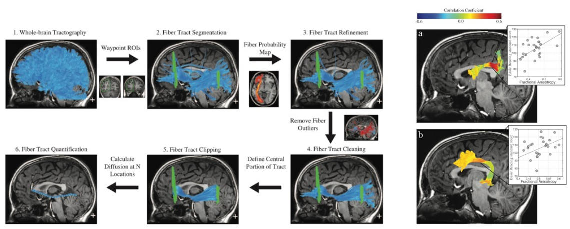


全脑纤维连接重建

107

107

DPABIFiber



AFQ

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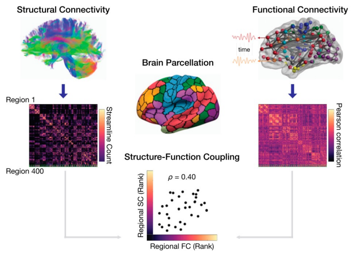
DPABIFiber

结构连接网络分析

结构/功能耦合分析



109

109

Future Directions

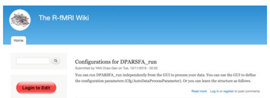
- R-fMRI methodology
- Mechanism of R-fMRI: electrophysiology/fMRI recording
- Modulation and intervention: medication and brain stimulation
- Application to brain disorders

110

110

Further Help

http://rfmri.org/Course



http://rfmri.org/wiki

The R-fMRI Journal Club

Official Account: RFMRILab

111

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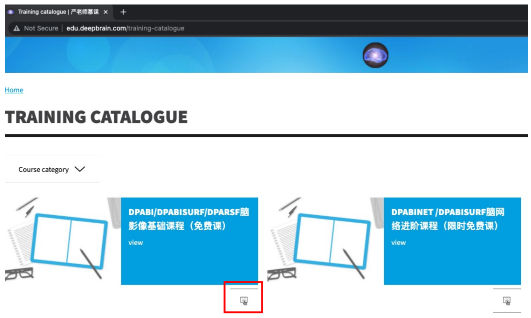
严老师慕课



http://edu.deepbrain.com/

112

112

严老师慕课

http://edu.deepbrain.com/

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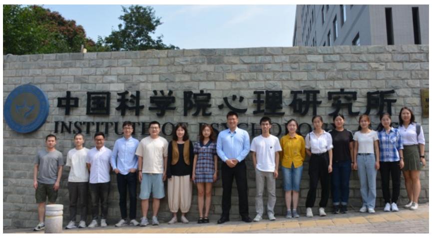
The R-fMRI Lab

WeChat Official Account: RFMRILab

微信添加**rfmriorg2**为好友，加入The R-fMRI Journal Club微信群

114

Acknowledgments



Chinese Academy of Sciences
Xi-Nian Zuo
Wei-Wen Wang
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F. Xavier Castellanos

Peking University Sixth Hospital
Tian-Mei Si
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Funding
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- National Key R&D Program of China
- Chinese Academy of Sciences

115

115

Thanks for your attention!

116

116

The DIRECT consortium and the REST-meta-MDD project: towards neuroimaging biomarkers of major depressive disorder

严超赣

Chao-Gan Yan, Ph.D.

yancg@psych.ac.cn
http://rfmri.org/yan

Institute of Psychology, Chinese Academy of Sciences

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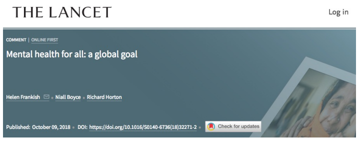
Outline

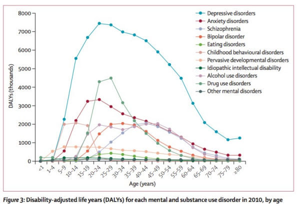
2

2

Global Health Crisis: MDD

"Black Dog"



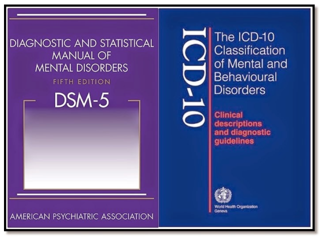


- Over 300 million MDD patients worldwide
- Prevalence in China: 3.4%
- Most heavily burdened disorder
- Potential suicide risk

Frankish, et al., 2018. Lancet. GBD, 2017. Lancet. Whiteford et al., 2013. Lancet. WHO 3

3

Diagnose of MDD



The current diagnostic criteria for MDD are mainly based on symptoms, calling for objective biomarkers

Oquendo et al., 2014. Depress Anxiety 4

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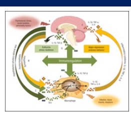
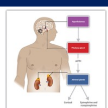
Biomarkers of MDD

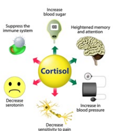


Proinflammatory cytokine?

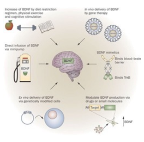
MDD



HPA axis?

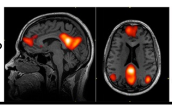


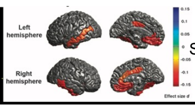
Cortisol?



BDNF?

Functional MRI?





Structural MRI?

5

fMRI Studies on MDD

ANALYSIS

Power failure: why small sample size undermines the reliability of neuroscience

Button et al., 2013. Nat Rev Neurosci

ANALYSIS

Scanning the horizon: towards transparent and reproducible neuroimaging research

Poldrack et al., 2017. Nat Rev Neurosci

- Small sample size and restricted power
- Flexibility in data analysis and inconsistent findings
- Inappropriate statistical thresholding leads to high false positive rates

Not a suitable biomarker for MDD now!

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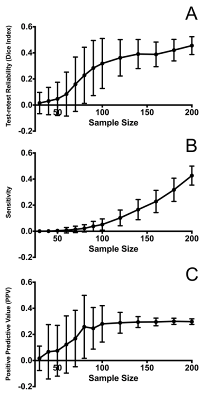
Sample Size

Sample size matters

Between-subject designed study cannot get reliable results if its sample size is less than 80

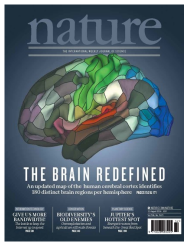


Chen, Lu, Yan*, 2018. Human Brain Mapping

Big Data Research is the Future!

Article

Reproducible brain-wide association studies require thousands of individuals



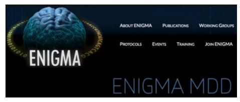
CONNECTOME COORDINATION FACILITY

Adolescent Brain Cognitive Development

Teen Brains. Today's Science. Brighter Future.

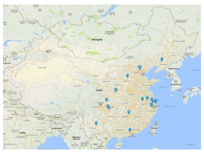
biobank uk

Improving the health of future generations



DIRECT I: REST-meta-MDD Project

Started a consortium for big data sharing on MDD. Connected by the preprocessing pipeline, DPARSF, cited for > 5000 times



北京大学第六医院、北京安定医院、中南大学湘雅二医院、四川大学华西医院、上海精神卫生中心、东南大学附属中大医院、浙江大学医学院附属第一医院与附属邵逸夫医院、南京脑科医院、苏州广济医院、暨南大学附属第一医院、中国医学科学研究院、无锡市精神卫生中心、中国医学科学院、中国医科大学、重庆医科大学、安徽医科大学、山西医科大学、昆明医学院、西安交通大学、西南大学、复旦大学、杭州师范大学……

25 MDD research groups over China

编号	参与研究单位	样本量	
		MDD 总数	NC 总数
1	安徽医科大学	51	36
2	北京大学第六医院	74	74
3	重庆医科大学附属第一医院	111	79
4	东南大学附属中大医院	139	113
5	暨南大学第一临床医学院	50	50
6	昆明医学院第一附属医院	32	31
7	山西医科大学第一医院	50	33
8	上海交通大学医学院附属精神卫生中心	28	26
9	首都医科大学附属北京安定医院	86	70
10	四川大学华西医院	63	61
11	苏州市广济医院	30	30
12	西安市中心医院	25	17
13	西南大学心理学部	282	251
14	浙江大学医学院附属第一医院	21	20
15	浙江大学医学院附属邵逸夫医院	38	49
16	中国医科大学第一临床医院	75	75
17	中南大学湘雅二医院	145	113
	合计	1300	1128

REST-meta-MDD consortium contains neuroimaging data of 1,300 depressed patients and 1,128 normal controls from 25 research groups in China, forming the word's largest MDD R-fMRI dataset

Outline

1. Introduction of DIRECT
2. **DIRECT Phase I Research Output**
3. DIRECT Phase II Research Progress
4. DIRECT Phase III Research Plan

Roadmap for Applying fMRI in MDD

Neuroimaging biomarkers for MDD

Big data of MDD brain imaging + deep learning

Ongoing Work

Neural underpinnings of MDD

Computational sharing platform

Head Motion

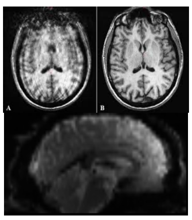
Standardization

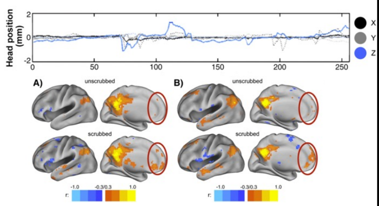
Multiple comparison correction

Prior Work

Validating fMRI methodology

Methodological Issues: Head Motion



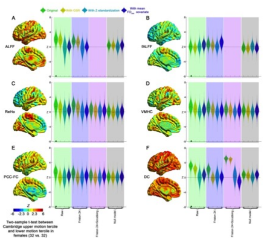


Power et al, 2012. Neuroimage
Van Dijk et al, 2012. Neuroimage

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

Need an effective motion correction strategy!

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**

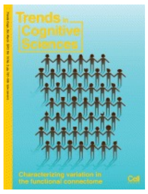
- Cited: 1303 times
- ESI Top 0.1% highly cited paper

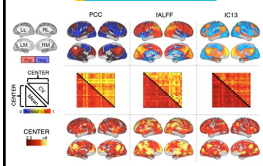
Yan et al., 2013a. Neuroimage

13

13

Methodological Issues: Standardization





Biswal et al., 2010, PNAS

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

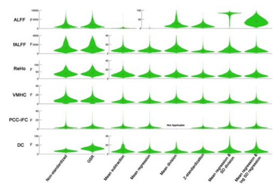
Category	Factor
1. Acquisition-related variations	Scanner make and model (Friedman and Glover, 2006b), sequence type (spiral vs. echo planar; single-echo vs. multi-echo) (Klarhofer et al., 2002), parallel vs. conventional acquisition (Feinberg et al., 2010; Lin et al., 2005), coil type (surface vs. volume, number of channels, orientation), repetition time, number of repetitions, flip angle, echo time, and acquisition volume (field of view, voxel size, slice thickness/gaps, slice prescription) (Friedman and Glover, 2006a)
2. Experimental-related variations	Participant instructions (Hartstra et al., 2011), eyes-open/eyes-closed (Yan et al., 2009; Yang et al., 2007), visual displays, experiment duration (Fang et al., 2007; Van Dijk et al., 2010)
3. Environment-related variations	Sound attenuation measures (Cho et al., 1998; Elliott et al., 1999), attempts to improve participant comfort during scans (e.g., music, videos) (Cullen et al., 2009), head-motion restraint techniques (e.g., vacuum pad, foam pad, bite-bar, plaster cast head holder) (Edward et al., 2000; Menon et al., 1997), room temperature and moisture (Vanhoutte et al., 2006).
4. Participant-related variations	Circadian cycle (Shannon et al., 2012), prandial (Haase et al., 2009), caffeine (Rack-Gomer et al., 2009), and nicotine status (Tanabe et al., 2011), sleepiness / arousal (Horovitz et al., 2008), sleep deprivation (Samann et al., 2010), scanner anxiety (de Bie et al., 2010), and menstrual cycle status (for women) (Protopopescu et al., 2005).

Yan et al., 2013b. Neuroimage

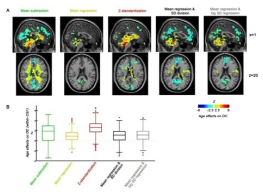
14

14

Methodological Issues: Standardization



The Impact of Standardization Procedures on Confound Variables: Site Effects



The Impact of Standardization Procedures on Variables of Interest: Age Effects

Proposed an effective standardization strategy
Mean regression + SD division

- Cited: 375 times
- ESI Top 1% highly cited paper

Yan et al., 2013b. Neuroimage

15

15

Reproducibility and Multiple Comparison Correction

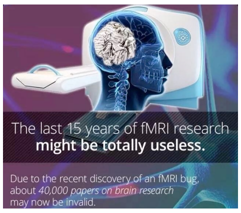
PNAS

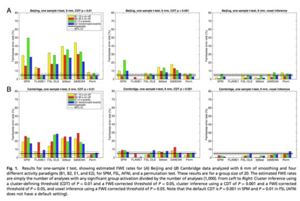
Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

Anders Eklund[a,b,c,1], Thomas E. Nichols[d,e], and Hans Knutsson[a,c]

[a]Division of Medical Informatics, Department of Biomedical Engineering, Linköping University, S-581 85 Linköping, Sweden; [b]Division of Statistics and Machine Learning, Department of Computer and Information Science, Linköping University, S-581 83 Linköping, Sweden; [c]Center for Medical Image Science and Visualization, Linköping University, S-581 83 Linköping, Sweden; [d]Department of Statistics, University of Warwick, Coventry CV4 7AL, United Kingdom; and [e]WMG, University of Warwick, Coventry CV4 7AL, United Kingdom

Edited by Emery N. Brown, Massachusetts General Hospital, Boston, MA, and approved May 17, 2016 (received for review February 12, 2016)





Eklund et al., 2016. PNAS

16

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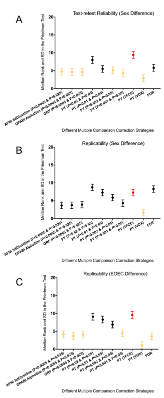
Reproducibility and Multiple Comparison Correction

Provided guideline for how to perform multiple comparison correction for resting-state fMRI, to best balance family-wise error rate and reproducibility, i.e., permutation test with TFCE

Cited: 242 times
Ranked ESI Top 1% of highly cited papers



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

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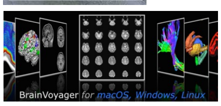
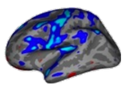
Traditional fMRI Preprocessing Toolbox

FSL SPM



AFNI

FreeSurfer



- Numerous steps and configurations
- High learning curve
- Big data era of neuroimaging calls for new pipelines

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Computational sharing platform for fMRI

- Incorporating DPARSF

Prior work, cited 3118 times

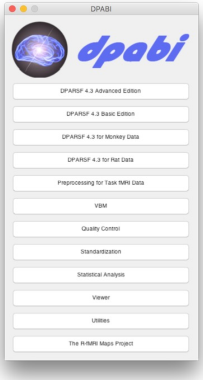
- Adapting methodological updates

Head motion (cited 1303 times)

Standardization (cited 375 times)

Multiple comparison correction (cited 242 times)

- Standardized preprocessing pipeline
- Statistical toolbox
- Platform for data sharing



Yan et al., 2016. Neuroinformatics

Corresponding author

19

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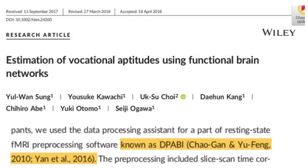
Peer Evaluation

Cited by 2136 times, ESI Top 0.01% top cited paper and hot paper


RESEARCH ARTICLE

WILEY

Estimation of vocational aptitudes using functional brain networks

Yul-Wan Sung[1] | Yousuke Kawachi[1] | Uk-Su Choi[2] | Daehun Kang[1] | Chihiro Abe[1] | Yuki Otomo[1] | Seiji Ogawa[1]

pants, 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

Inventor of fMRI BOLD

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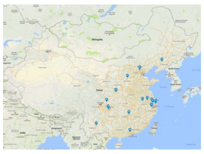
DIRECT I: REST-meta-MDD Project

Started a consortium for big data sharing on MDD. Connected by the preprocessing pipeline, DPARSF, cited for > 5000 times



北京大学第六医院、北京安定医院、中南大学湘雅二医院、四川大学华西医院、上海精神卫生中心、东南大学附属中大医院、浙江大学医学院附属第一医院与附属邵逸夫医院、南京脑科医院、苏州广济医院、暨南大学附属第一医院、中国医学科学研究院、无锡市精神卫生中心、中国医学科学院、中国医科大学、重庆医科大学、安徽医科大学、山西医科大学、昆明医学院、西安交通大学、西南大学、复旦大学、杭州师范大学……

25 MDD research groups over China

编号	参与研究单位	样本量 MDD 总数	样本量 NC 总数
1	安徽医科大学	51	36
2	北京大学第六医院	74	74
3	重庆医科大学附属第一医院	111	79
4	东南大学附属中大医院	139	113
5	暨南大学第一临床医学院	50	50
6	昆明医学院第一附属医院	32	31
7	山西医科大学第一医院	50	33
8	上海交通大学医学院附属精神卫生中心	28	26
9	首都医科大学附属北京安定医院	86	70
10	四川大学华西医院	63	61
11	苏州市广济医院	30	30
12	西安市中心医院	25	17
13	西南大学心理学部	282	251
14	浙江大学医学院附属第一医院	21	20
15	浙江大学医学院附属邵逸夫医院	38	49
16	中国医科大学第一临床医院	75	75
17	中南大学湘雅二医院	145	113
	合计	1300	1128

REST-meta-MDD consortium contains neuroimaging data of 1,300 depressed patients and 1,128 normal controls from 25 research groups in China, forming the word's largest MDD R-fMRI dataset

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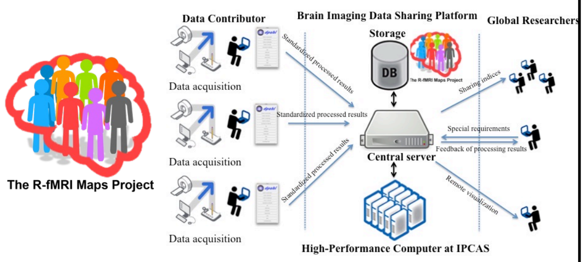
The R-fMRI Maps Project



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

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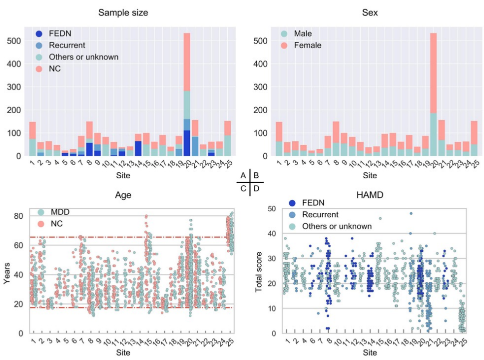
REST-meta-MDD



Yan et al., 2019, PNAS.

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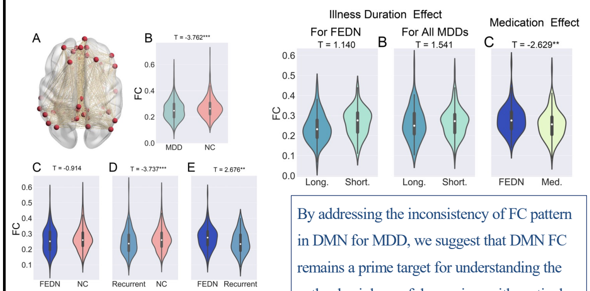
REST-meta-MDD



By addressing the inconsistency of FC pattern in DMN for MDD, we suggest that DMN FC remains a prime target for understanding the pathophysiology of depression, with particular relevance to revealing mechanisms of effective treatments

Yan et al., 2019, PNAS.

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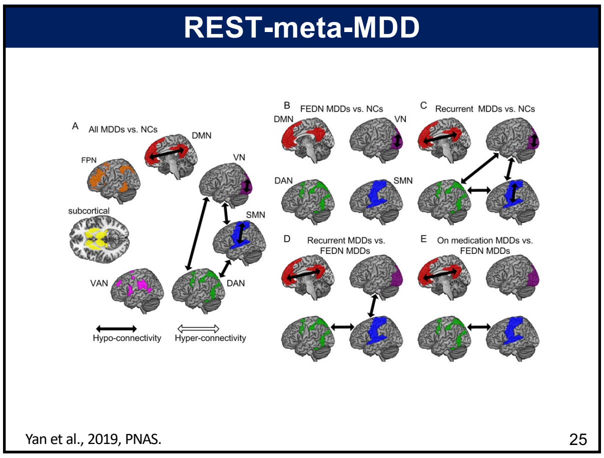

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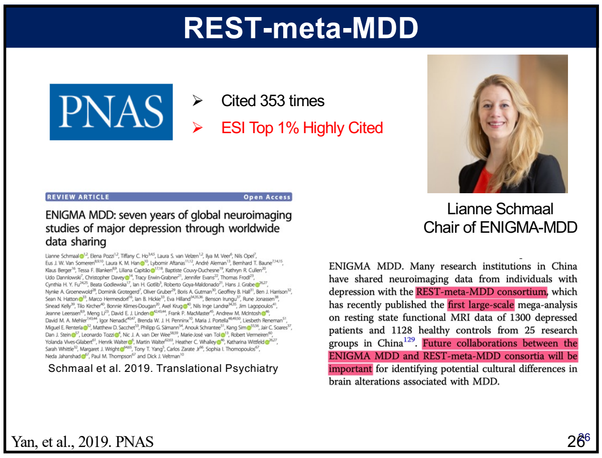

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Proposals

1	用静态功能磁共振研究抑郁症小世界属性的异常	浙江大学医学院附属第一医院
2	抑郁症大脑功能连接侧化研究	湘雅二医院
3	严重抑郁症内侧前额皮层局部脑活动与功能连接变化	杭州师范大学；华西医院；浙江大学
4	抑郁症症状亚型的大脑功能异常探讨：基于HAMD的项目分	西南大学心理学部
5	基于静息态影像和深度学习方法的抑郁症预测研究	西南大学心理学部
7	抑郁障碍患者突显网络结构和功能连接的研究	首都医科大学附属北京安定医院
8	抑郁症脑功能生物学亚型的研究-基于多中心静息态脑影像学数据分析	四川大学华西医院
9	Abnormal interhemispheric connectivity in major depressive disorder: an voxel mirrored homotopic connectivity analysis of 2428 individuals from REST-meta-MDD working group	上海市精神卫生中心
10	不同性别抑郁症患者静息态脑功能研究	苏州市广济医院
11	抑郁症动态功能网络连接模式研究	中南大学湘雅二医院
12	抑郁症基于脑网络整体功能的静息态功能影像研究	重庆医科大学附属第一医院
14	不同年龄发病抑郁症患者的脑功能影像学研究	昆明医科大学第一附属医院
15	抑郁症自杀相关神经环路	东南大学附属中大医院
16	MDD的脑网络异常机制研究	北京大学第六医院
17	基于图谱的时间序列脑有效连接分析	西安交通大学第一附属医院
18	抑郁症内疚静息态功能网络：基于HAMD的条目	中南大学湘雅二医院
19	情绪调节环路在首发未服药抑郁障碍伴发焦虑的脑影像学机制研究：基于独立样本验证	山西医科大学第一医院
20	基于网络控制的抑郁症脑功能网络特征分析	中国医科大学附属第一医院
21	Integrating graphic measures and deep learning technology to detect MDD at the individual level	四川大学华西医院华西MR研究中心
22	Changes in local brain activity and functional connectivity in major depressive disorder patients with insomnia	首都医科大学附属北京安定医院
23	The structural and functional alterations of brain in MDD with gastrointestinal symptoms	山西医科大学第一医院
24	Evolution of Brain Network in Depression: An Age and Illness Duration-associated Cross-sectional Study	四川大学华西医院
26	Abnormal resting-state functional connectivity of nucleus accumbens in patients with major depressive disorder	湘雅二医院
28	Resting-State Functional Connectivity of the Habenula in Depressive Disorder Patients With and Without Suicide-Related Behaviors	重庆医科大学附属第一医院
29	Baseline time variability and co-activation pattern based evaluation of severity in patient with MDD	东南大学附属中大医院
30	Common and different patterns of altered functional activities in drug-naive and treated first-episode depressive patients	苏州市广济医院
31	Relationship of brain structure of MDD patients and metabolome expression in classical rodent models of MDD	重庆医科大学

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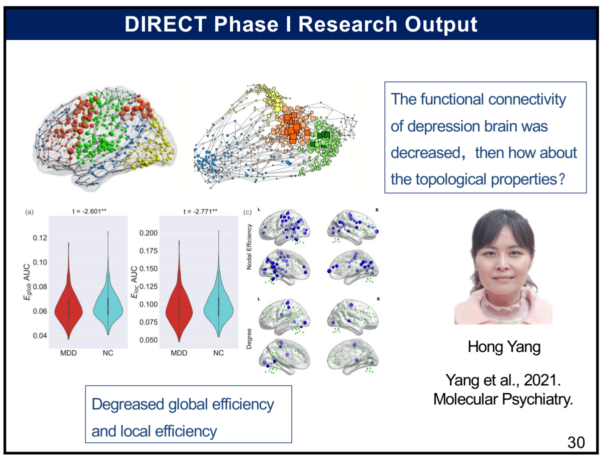

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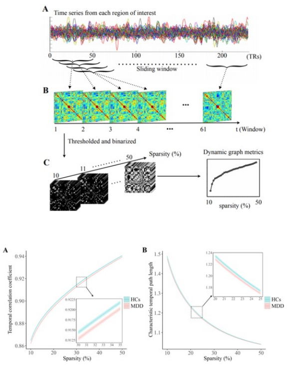
DIRECT Phase I Research Output



Disrupted Dynamic Functional Brain Networks in Major Depressive Disorder: Evidence from A Multi-site Resting-state fMRI Study

Yi-Cheng Long

Zhe-Ning Liu

Long et al., 2020. Neuroimage:Clinical

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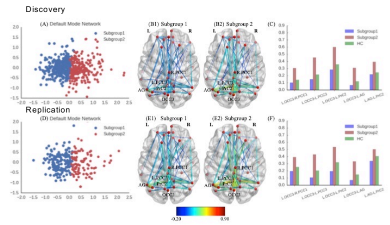
DIRECT Phase I Research Output



Biotypes of major depressive disorder: neuroimaging evidence from resting-state default mode network patterns

Su-Gai Liang

Tao Li

Liang et al., 2020. Neuroimage:Clinical

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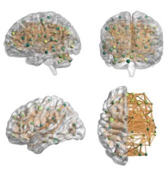
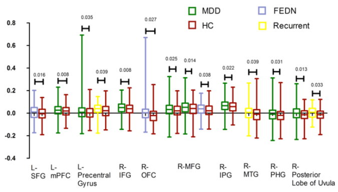
DIRECT Phase I Research Output

Disrupted hemispheric connectivity specialization in ventral attention network and cerebellum in patients with major depressive disorder





Yu-Dan Ding

Wen-Bin Guo

Ding et al., 2021. J Affect Disord.

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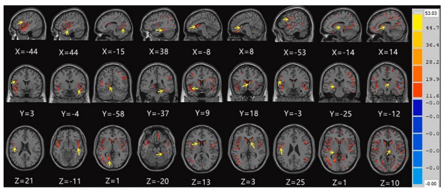
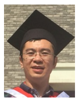
DIRECT Phase I Research Output

Brain structural alterations in MDD patients with gastrointestinal symptoms: Evidence from the REST-meta-MDD project





Peng-Hong Liu

Ke-Rang Zhang

Liu et al., 2021. Prog Neuropsychopharmacol Biol Psychiatry.

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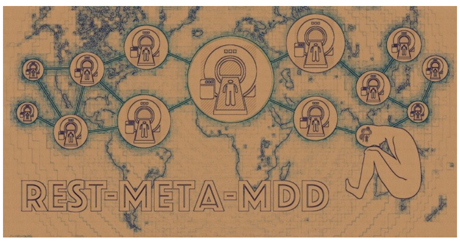
Open Access of REST-meta-MDD Data



http://rfmri.org/REST-meta-MDD

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Open Access of REST-meta-MDD Data

Number	PI Name	PI Email	Contact Name	Contact Email	Institute	Date
1	王一峰	wyf@sicnu.edu.cn	王一峰	wyf@sicnu.edu.cn	四川师范大学脑与心理科学研究院	2020.01.02
2	Yanpei Wang	wyp081412570@163.com	Yanpei Wang	wyp081412570@163.com	Jiangsu Province Key Constructive of Special Children's Impairment and	2020.01.02
3	Xijian Dai	xijiandai@cuhk.edu.hk	Xijian Dai	daixidoctor@126.com	The Chinese University of Hongkong	2020.01.06
4	Han Zhang	hanzhang@med.unc.edu	Guoshi Li	guoshi_li@med.unc.edu	University of North Carolina at Chapel Hill	2020.01.06
5	Zhiyong Zhao	zhaozhiyong_zju@zju.edu.cn	Zhiyong Zhao	zhaozhiyong_zju@zju.edu.c	Department of Biomedical Engineering, Zhejiang University, Hangzhou	2020.01.07
6	Bin Jing	bjing@ccmu.edu.cn	Bin Jing	bjing@ccmu.edu.cn	Capital Medical University	2020.01.07
7	Jinsong Tang	tangjingsong@zju.edu.cn	Jinsong Tang	tangjingsong@zju.edu.cn	Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University	2020.01.08
8	Kangcheng Wang	wangkangcheng.001@163.com	Kangcheng Wang	wangkangcheng.001@163.com	School of Psychology, Shandong Normal University	2020.01.07
9	Weifeng Luo	lwfwxxx@126.com	Erlei Wang	964078803@qq.com	The Second Affiliated Hospital of Soochow University	2020.01.08
10	程炜	wcheng.fdu@gmayl.com	程炜	wcheng.fdu@gmayl.com	Fudan University	2020.01.08
11	项艺珍	xyzxzj@csu.edu.cn	项艺珍	xyzxzj@csu.edu.cn	School of Computer Science and Engineering Central South University	2020.01.08
12	Hang Yu	hyu.hugo@ntu.edu.sg	Hang Yu	hyu.hugo@ntu.edu.sg	Nanyang Technological University	2020.01.09
13	Benjamin Becker	ben_becker@gmx.de	Xinqi Zhou	xinqizhou.uestc@outlook.c	neuSCAN Laboratory University of Electronic Science & Technology	2020.01.09
14	Junfeng Sun	jfsun@sjtu.edu.cn	Jie Zhou	zhoujie_sjtu@sjtu.edu.cn	Shanghai Jiao Tong University	2020.01.09
15	Hanqing Wang	1806594196@pku.edu.cn	Hanqing Wang	1806594196@pku.edu.cn	Peking University	2020.01.10
16	葛曼玲	gemanling@hebut.edu.cn	张夫一	2303639135@qq.com	State Key Laboratory of Reliability and Intelligence of Electrical Equ	2020.01.10
17	Guangyu Zhang	gyzhn@163.com	Guangyu Zhang	gyzhn@163.com	Shandong First Medical University & Shandong Academy of Medical Scienc	2020.01.13
18	朱朝喆	czzhu@bnu.edu.cn	曹正提	zcao@mail.bnu.edu.cn	北京师范大学认知神经科学与学习国家重点实验室（State Key Laboratory of	2020.01.14
19	Junhai Xu	jhxu@tju.edu.cn	Junhai Xu	jhxu@tju.edu.cn	Tianjin University	2020.01.17
20	Junzhong Ji	jjz01@bjut.edu.cn	Zhihui Chen	S201861411@email.bjut.edu	Beijing Artificial Intelligence Institute, Beijing University of Techn	2020.01.17
21	Alyssa Comising	pcomising@yahoo.com	Alyssa Comising	pcomising@yahoo.com	University of Maryland	2020.01.07
22	Tae-Eui Karn	karnte@korea.ac.kr	Tae-Eui Karn	karnte@korea.ac.kr	Korea University, Korea	2020.01.20
23	Bindiya.A.R	bindiyaramesh@sjce.ac.in	Bindiya.A.R	bindiyaramesh@sjce.ac.in	JSS Science and Technology University	2020.01.20
24	Forrest Wang	forrestw2005@hotmail.com	Forrest Wang	forrestw2005@hotmail.com	Middle Tennessee State University	2020.01.23
25	董建鑫	31392207@qq.com	董建鑫	31392207@qq.com	首都医科大学	2020.01.24
26	Mingxia Liu	mxliu@med.unc.edu	Dongren Yao	yaodongren2016@ia.ac.cn	University of North Carlina at Chapel Hill	2020.01.24
27	Tetsuya Iidaka	iidaka@met.nagoya-u.ac.jp	Tetsuya Iidaka	iidaka@met.nagoya-u.ac.jp	Nagoya University, Brain & Mind Research Center	2020.01.27
28	邓灵灵	307027521@qq.com	邓灵灵	307027521@qq.com	中南大学	2020.01.30
29	Peng Quan	QUANPENGO@GMAIL.COM	Peng Quan	QUANPENGO@GMAIL.COM	Guangdong Medical University	2020.02.01
30	Liang Gong	cd2gongling@126.com	Liang Gong	cd2gongling@126.com	Chengdu Second People's Hospital	2020.02.05
31	Simon Eickhoff	simon.b.eickhoff@gmail.com	Laura Waite	l.waite@fz-juelich.de	Institute of Neuroscience and Medicine (INM-7), Forschungszentrum Julic	2020.01.08
32	Leanne M. William	leawilliams@stanford.edu	Leonardo Tozzi	ltozzi@stanford.edu	Stanford University, Department of Psychiatry and Behavioral Science	2020.02.05
33	Prof. dr. Guido v	guidovanwingen@gmail.com	Dr. Selene Gall	gallo.selene@gmail.com	Academic Medical Center, University of Amsterdam, Amsterdam, The Nethe	2020.02.02
34	Qinmu Peng	pengqinmu@hust.edu.cn	Ziming Hong	hongzm@hust.edu.cn	Huazhong University of Science and Technology	2020.01.14
35	Wuxia	wuxia@bnu.edu.cn	Zhaodi Pei	peizd@mail.bnu.edu.cn	School of Artificial Intelligence, Beijing Normal University	2020.02.08
36	Ghdam-Ali Aossein	ghzadeh@ut.ac.ir	Morteza Fattahi	morteza.fattahi@ut.ac.ir	School of ECE, College of Eng., Univ. of Tehran	2020.02.09
37	Atif Riaz	atif.riaz@city.ac.uk	Atif Riaz	atif.riaz@city.ac.uk	City, University of London, UK	2020.02.14
38	Heung-Il Suk	hisuk@korea.ac.kr	Eunjin Jeon	eunjinjeon@korea.ac.kr	Korea University, Korea	2020.02.19
39	Peng Li	lipeng1986@bjmu.edu.cn	Peng Li	lipeng1986@bjmu.edu.cn	Pecking University Sixth Hospital	2020.02.21
40	魏安海	weianhai@126.com	杨利	1468159523@qq.com	陆军军医大学大坪医院	2020.02.25
41	Donglin Wang	wangdl@hznu.edu.cn	Xiaoran Lihan	lihanxiaoran@stu.hznu.edu	Institute of Psychological Science, Hangzhou Normal University	2020.03.12
42	Zhengjia Dai	Dai.CanLab@hotmail.com	Yadi Sun	u201415543@163.com	CAN Lab. Sun Yat-sen University	2020.01.08
43	Xinhua Yang	wolaiye1974@163.com	Xinhua Yang	wolaiye1974@163.com	Department of psychology, Hunan Agricultural University	2020.03.22
44	Tatia Mei-chun Le	tmclee@hku.hk	Mengxia Gao	mxgao@hku.hk	Department of psychology, The University of Hong Kong	2020.03.31
45	Liu Chenyang	liucy@eee.hku.hk	Tao Rongxin	u3566874@connect.hku.hk	The University of Hong Kong, Faculty of Engineering, Digital Signal Pr	2020.04.05
46	冯衍秋	foree@163.com	刘嘉明	liujiamingsmu@163.com	School of Biomedical Engineering, Southern Medical University	2020.04.05
47	Seung-Gul Kang	euphoric1@daum.net, kangsg	Seung-Gul Kang	euphoric1@daum.net	Department of Psychiatry, Gil Medical Center, Gachon University, Colle	2020.04.06
48	薛绍伟	xuesw@hznu.edu.cn	薛绍伟	xuesw@hznu.edu.cn	Center for Cognition and Brain Disorders, Institute of Psychological,	2020.04.12
49	周森玉	934130940@qq.com	周森玉	934130940@qq.com	South China Normal University	2020.04.16
50	Gustavo Deco	gustavo.deco@upf.edu	Josephine Cruza	josephine.curuzat@upf.edu	Universitat Pompeu Fabra	2020.04.17
51	Jin ZHANG	jinzhang@hunnu.edu.cn	Binjie CHENG	krischeng@smail.hunnu.edu	Hunan Normal University	2020.04.20
52	胡斌	bh@lzu.edu.cn	姚志军	yaozj@lzu.edu.cn	兰州大学	2020.04.27
53	Qing Lu	luq@seu.edu.cn	Xinyi Wang	wangxinyi@seu.edu.cn	Southeast University, China	2020.04.29
54	Yinyin Zang	Yinyin.Zang@pku.edu.cn	Yuxi Wang	yuxi.wang@pku.edu.cn	School of Psychology and Cognitive Sciences	2020.04.28
55	Jiaolong Qin	jiaolongq@njust.edu.cn	Jiaolong Qin	jiaolongq@njust.edu.cn	Nanjing University of Science and Technology, Nanjing, China	2020.04.30
56	乔立山	qiaolishanlcu@163.com	薛艳芳	hzxyanfang@163.com	聊城大学	2020.02.12
57	刘飞	17610866205@163.com	刘飞	17610866205@163.com	天津大学智算学部	2020.05.22
58	Zack shan	zshan@usc.edu.au	Zack shan	zshan@usc.edu.au	Sunshine Coast Mind & Neuroscience Institute, University of the Sunshi	2020.05.25
59	王莉	wangli@njtech.edu.cn	丁杰	dingjie@njtech.edu.cn	南京工业大学	2020.05.03
60	高婧婧	jingjing.gao@uestc.edu.cn	高婧婧	jingjing.gao@uestc.edu.cn	电子科技大学	2020.05.29

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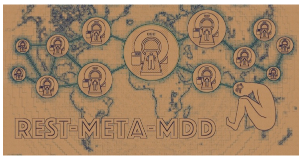
The DIRECT Consortium and the REST-meta-MDD Project



Chen et al., 2022. Psychoradiology

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The DIRECT Consortium and the REST-meta-MDD Project

OXFORD

Psychoradiology, 2(1), 2022, 32–42

https://doi.org/10.1093/psyrad/kkac005

Review

REVIEW

The DIRECT consortium and the REST-meta-MDD project: towards neuroimaging biomarkers of major depressive disorder

Xiao Chen[1,2,3,4], Bin Lu[2,3], Hui-Xian Li[2,3], Xue-Ying Li[1,2,3,4], Yu-Wei Wang[2,3], Francisco Xavier Castellanos[7,8], Li-Ping Cao[9], Ning-Xuan Chen[10], Wei Chen[11], Yu-Qi Cheng[12], Shi-Xian Cui[2,5,6], Zhao-Yu Deng[2,3], Yi-Ru Fang[13], Qi-Yong Gong[14,15], Wen-Bin Guo[16], Zheng-Jia-Yi Hu[2,3], Li Kuang[17], Bao-Juan Li[18], Le Li[19], Tao Li[20,21], Tao Lian[1,2,3], Yi-Fan Liao[1,2,3], Yan-Song Liu[22], Zhe-Ning Liu[16], Jian-Ping Lu[23], Qing-Hua Luo[17], Hua-Qing Meng[17], Dai-Hui Peng[13], Jiang Qiu[24], Yue-Di Shen[25], Tian-Mei Si[26], Yan-Qing Tang[27], Chuan-Yue Wang[28], Fei Wang[27], Hua-Ning Wang[18], Kai Wang[29], Xiang Wang[16], Ying Wang[30], Zi-Han Wang[2,3], Xiao-Ping Wu[31], Chun-Ming Xie[32], Guang-Rong Xie[16], Peng Xie[33,34,35], Xiu-Feng Xu[12], Hong Yang[36], Jian Yang[34], Shu-Qiao Yao[16], Yong-Qiang Yu[37], Yong-Gui Yuan[38], Ke-Rang Zhang[39], Wei Zhang[40], Zhi-Jun Zhang[32], Jun-Juan Zhu[41], Xi-Nian Zuo[42,43], Jing-Ping Zhao[16], Yu-Feng Zang[44,45], the DIRECT consortium[#] and Chao-Gan Yan[1,2,3,4,5,6,1]

Chen et al., 2022. Psychoradiology

38

38

Next steps of DIRECT

Box 1. Directions for future DIRECT research

(1) What are the differences regarding MDD abnormalities in different ethnic groups (e.g. Chinese vs. Caucasian)? What factors contribute such differences (e.g. response styles, thinking styles or genetic factors?)
(2) To what extent can it help improve the reproducibility of results to transfer preprocessing pipelines from volume-based approaches [i.e. DPSRSF (Yan & Zang, 2010) and SPM (Ashburner, 2012)] to surface-based approaches [e.g. DPABISurf (Yan et al., 2021) and fMRIPrep (Esteban et al., 2019)]?
(3) What are the differences and similarities among the neuroimaging alterations across different mental disorders?
(4) What are the longitudinal effects of antidepressant medications on the brain?
(5) What are the white matter alterations in MDD?
(6) Can we guide neuromodulation techniques (e.g. TMS) through brain network mechanisms we identified with fMRI?

Chen et al., 2022. Psychoradiology

39

39

Outline

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Go to Surface

PNAS

The impact of traditional neuroimaging methods on the spatial localization of cortical areas

Timothy S. Coalson[a], David C. Van Essen[a,1], and Matthew F. Glasser[a,b,1]

[a]Department of Neuroscience, Washington University School of Medicine, St. Louis, MO 63110; and [b]St. Luke's Hospital, St. Louis, MO 63017

Contributed by David C. Van Essen, May 17, 2018 (sent for review January 29, 2018; reviewed by Alexander L. Cohen, James V. Haxby, and Martin I. Sereno)

Localizing human brain functions is a long-standing goal in systems neuroscience. Toward this goal, neuroimaging studies have traditionally used volume-based smoothing, registered data to volume-based standard spaces, and reported results relative to volume-based parcellations. A novel 360-area surface-based cortical parcellation was recently generated using multimodal data from the Human Connectome Project, and a volume-based version of this parcellation has frequently been requested for use with traditional volume-based analyses. However, given the major methodological differences between traditional volumetric and Human Connectome Project-style processing, the utility and interpretability of such an altered parcellation must first be established. By starting from automatically generated individual-subject parcellations and processing them with different methodological approaches, we show that traditional processing steps, especially volume-based smoothing and registration, substantially degrade cortical area localization compared with surface-based approaches. We also show that surface-based registration using features closely tied to cortical areas, rather than to folding patterns alone, improves the alignment of areas, and that the benefits of high-resolution acquisitions are largely unexploited by traditional volume-based methods. Quantitatively, we show that the most common version of the traditional approach has spatial localization that is only 35% as good as the best surface-based method as assessed using two objective measures (peak areal probabilities and "captured area fraction" for maximum probability maps). Finally, we demonstrate that substantial challenges exist when attempting to accurately represent volume-based group analysis results on the surface, which has important implications for the interpretability of studies, both past and future, that use these volume-based methods.

mapping using Gaussian random-field theory requires volumetric smoothing to satisfy its underlying assumptions (e.g., ref. 8), resulting in the widespread adoption of smoothing in brain-imaging studies. Spatial smoothing has the seductive side effect of increasing the statistical significance of weak effects in small sample sizes, but at the expense of spatial localization precision (9, 10). Traditionally, smoothed group functional activations are then statistically thresholded and summarized by single 3D coordinates that may be assigned Brodmann's areas or gyral and sulcal designations. Unfortunately, these standard coordinates are imprecisely related to the underlying functional neuroanatomy—the cortical areas—whose neuronal populations generate the functional activations under study (9, 10).

Besides the reductions in precision from spatial smoothing and representing brain functional neuroanatomy with single 3D coordinates, another key issue is the approach used for cross-subject alignment. Because of the high degree of individual variability in cortical folding patterns, and in the location of many areal boundaries relative to folds (11, 12), traditional volume-based methods for aligning cortical areas are imprecise across much of the cerebral cortex (9). Progress in characterizing the functions of brain areas has been impeded by these factors, along with the distributed nature of many brain functions and the lack of an accurate map of human cortical areas.

Significance

Most human brain-imaging studies have traditionally used low-resolution images, inaccurate methods of cross-subject

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Why Surface-based Analysis

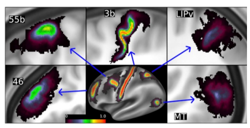
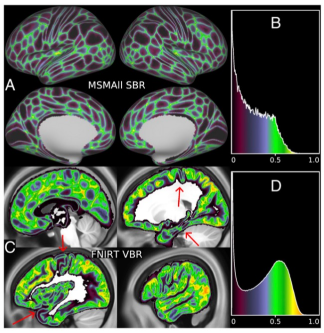


Fig. 1. Probabilistic maps for five areas using both MSMAll areal-feature-based surface registration and FNIRT volume alignment. The volume-based peak probabilities are all lower than the surface-based probabilities for these example areas. Each volume-based area is shown on a parasagittal slice through the peak volumetric probability. See SI Appendix, Supplementary Methods M2 and M3. Data are available at https://balsa.wustl.edu/xK0Z.



Coalson et al., 2018. PNAS

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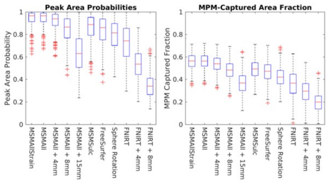
Why Surface-based Analysis



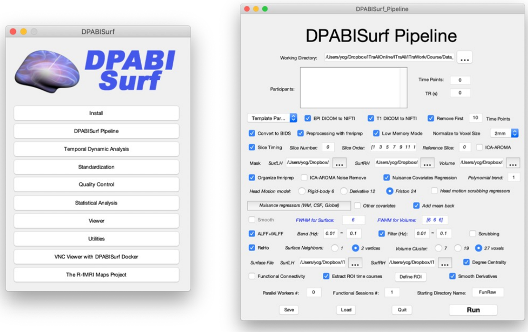
Widespread adoption of surface-based approaches has been slow: the desire to replicate or compare with existing studies that used the traditional volume-based approach; the relative lack of "turn-key" tools for running a surface-based analysis; the learning curve for adopting surface-based analysis methods; unawareness of the problems with traditional volume-based analysis; and uncertainty or even skepticism as to how much of a difference these methodological choices make.

Coalson et al., 2018. PNAS

43

43

Go to Surface



Based on fMRIPprep, FreeSurfer, ANTs, FSL, AFNI, PALM, GNU Parallel, MATLAB, Docker and DPABI.

Yan et al., 2021. Science Bulletin

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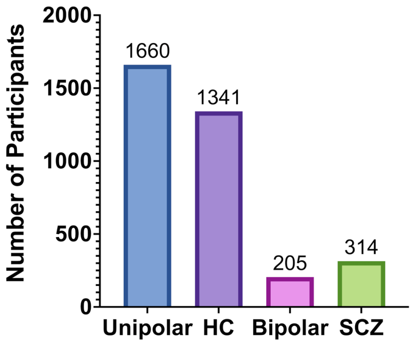
DIRECT Phase II Data



DIRECT II: Surface-based Data Sharing

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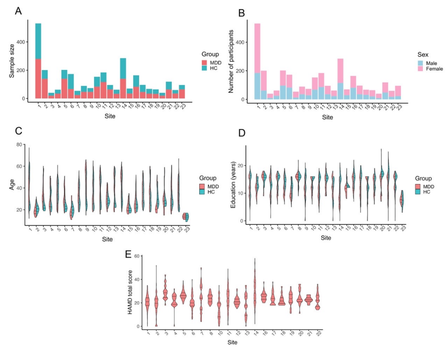
DIRECT Phase II Data



DIRECT II: Surface-based Data Sharing

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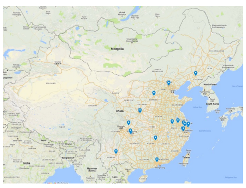
International Collaboration

International Conference on Brain Imaging of Depression



Cross-culture MDD data collection?

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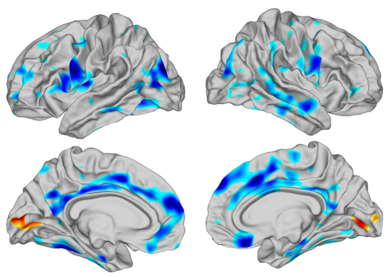
The difference of MDD related changes between Asians and Westerners

With Dr. Lianne Schmaal



Dx_Meta Thickness (DIRECT+ENIGMA: 5417 MDD vs. 6535 NC)

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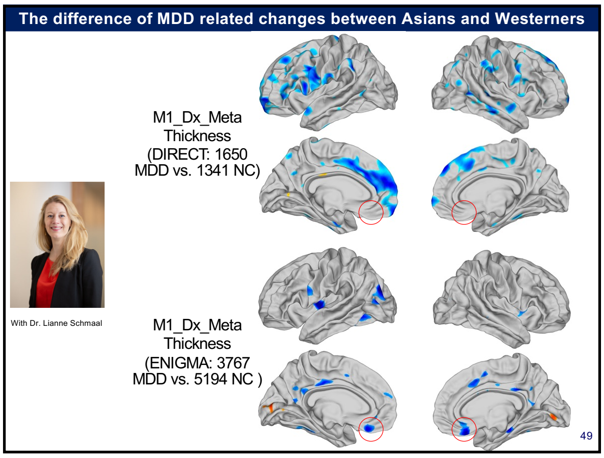

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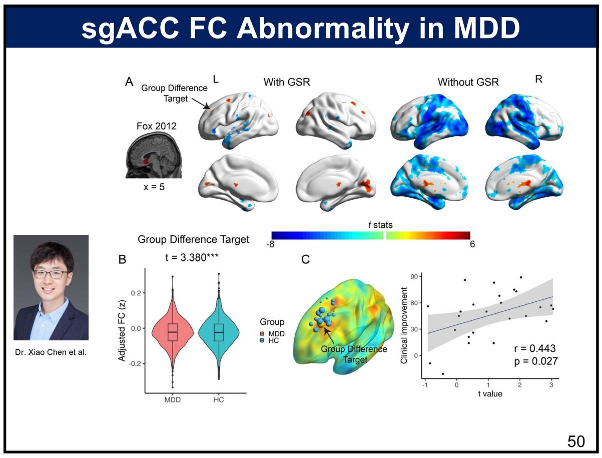

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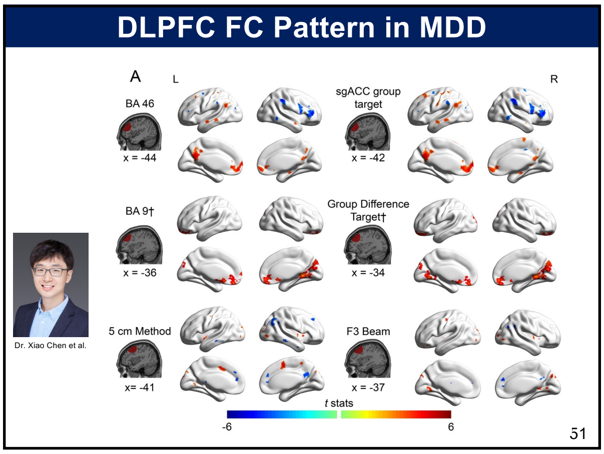

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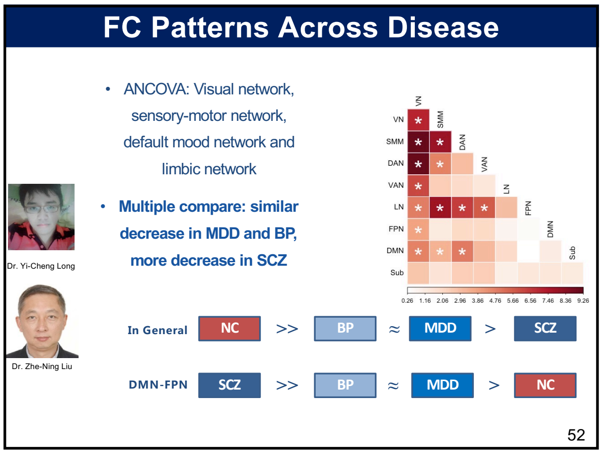

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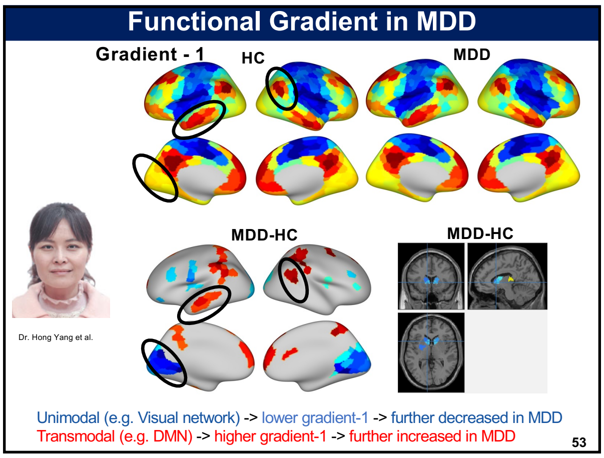

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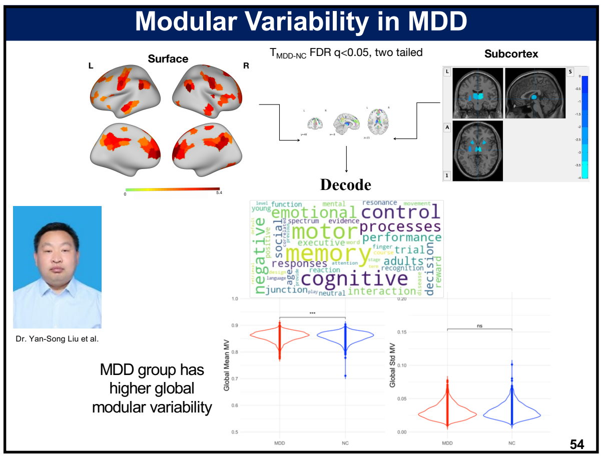

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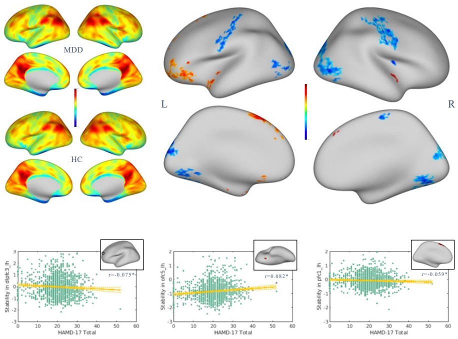
Functional Stability in MDD

Dr. Xiao-Ping Wu et al.



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Outline

1 Introduction of DIRECT

2 DIRECT Phase I Research Output

3 DIRECT Phase II Research Progress

4 **DIRECT Phase III Research Plan**

56

56

DIRECT Phase III Research Plan

1 DIRECT Individualized Precise TMS Study

2 Brain Mechanism of Antidepressants Study

3 Function/Structure (Fiber) Coupling Study

4 Rumination Spontaneous Thought Study

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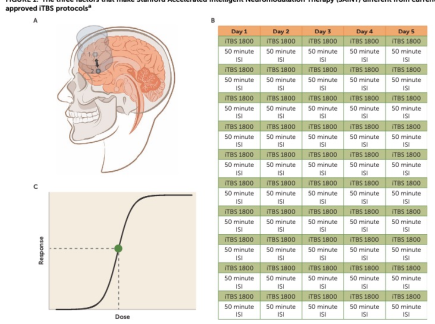
57

Stanford accelerated intelligent neuromodulation therapy (SAINT)

FIGURE 1. The three factors that make Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) different from current approved iTBS protocols



Cole et al,. 2020 and 2021. American Journal of Psychiatry

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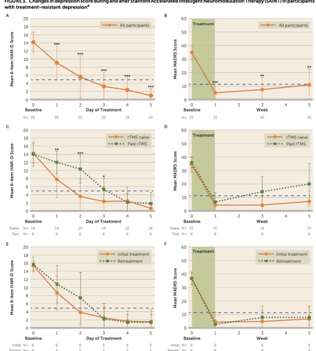
Stanford accelerated intelligent neuromodulation therapy (SAINT)

FIGURE 3. Changes in depression score during and after Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) in participants with treatment-resistant depression



Cole et al,. 2020. American Journal of Psychiatry

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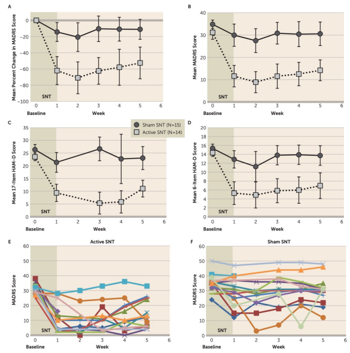
Stanford accelerated intelligent neuromodulation therapy (SAINT)



Cole et al,. 2021. American Journal of Psychiatry

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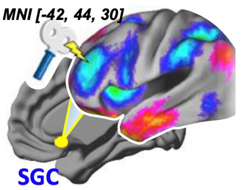
Algorithm 1. Fox 2012



MNI coordinates of our peak subgenual anticorrelation in the left DLPFC ($x = -42, y = 44, z = 30$), fall directly between two peak coordinates we reported previously ($x = -44, y = 38, z = 34$) and ($x = -38, y = 44, z = 26$) (27). The current coordinates should be considered an update of this previous work, because the current study used functional connectivity from 1000 subjects rather than 98. Whether intentionally

Weigand et al., 2018. Biol Psychiatry

Connectivity guided (SGC group target)

Fox et al., 2012; Weigand et al., 2018; Cash et a., 2020. Biol Psychiatry

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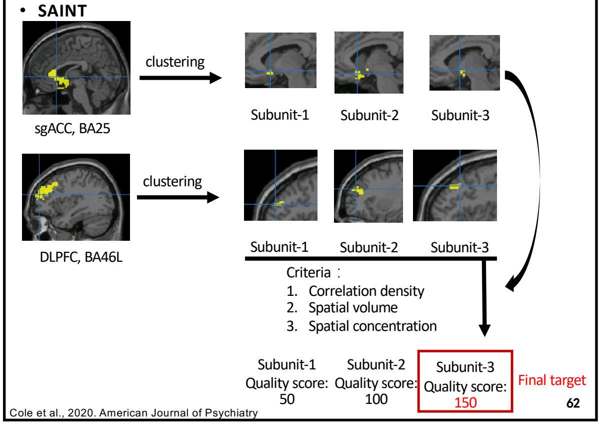
Algorithm 2. SAINT

- **SAINT**



Cole et al., 2020. American Journal of Psychiatry

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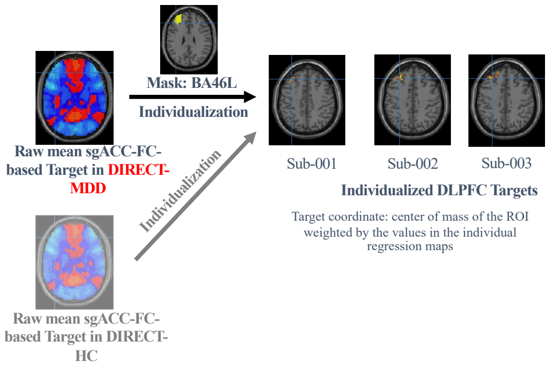
Algorithm 3. DIRECT Mean Map Guided Individualized Precise TMS



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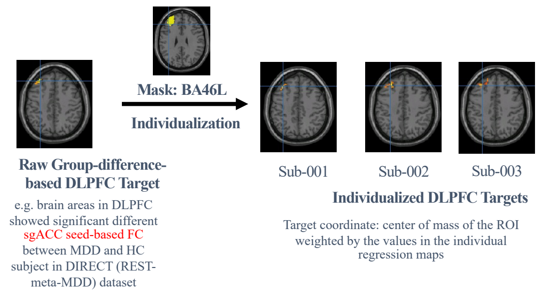
Algorithm 4. DIRECT Difference Map Guided Individualized Precise TMS



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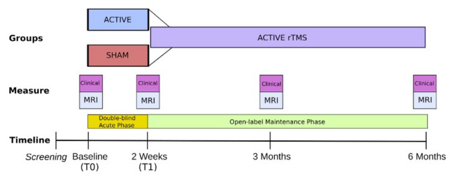
Open Data for TMS Targeting and HAMD Improvement

- **Justify the targets –** correlation between clinical outcome and targeting inaccuracy
- **Sample:** 16 cocaine-use-disorder participants whose HAMD scores at baseline were above 7
- **Clinical outcome:** all time HAMD score-reducing-rate during TMS treatment
- **Targeting inaccuracy :** Euclidean distance between the actual TMS targets and targets derived from MRI using our algorithms

Mexico data



- **The correlation was supposed to be negative (The less targeting inaccuracy, the better clinical outcome)**

Eduardo A. Garza-Villarreal and et al. (2021). Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.

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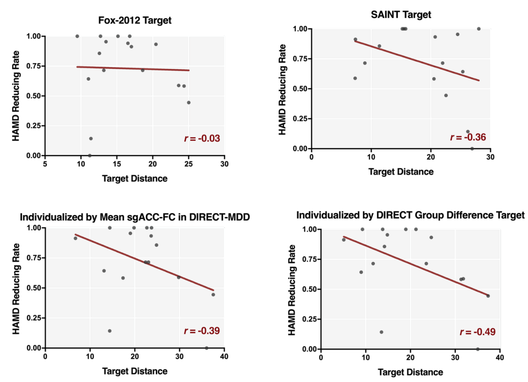
TMS Targeting Offset Distance and HAMD Improvement



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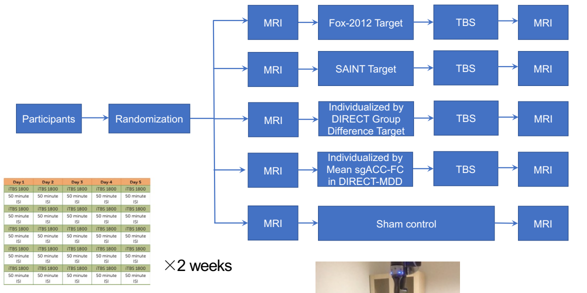
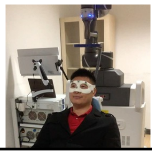
DIRECT Individualized Precise TMS Study



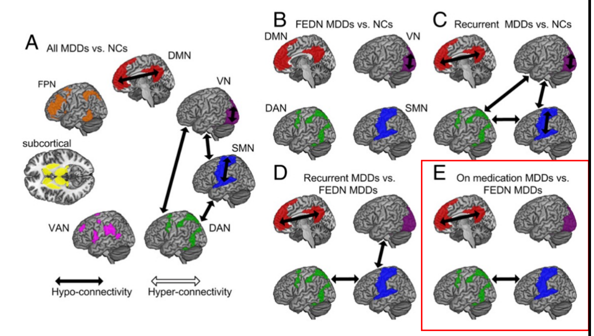
DIRECT will support each participating team for individualized target calculation!



DIRECT Phase III Research Plan

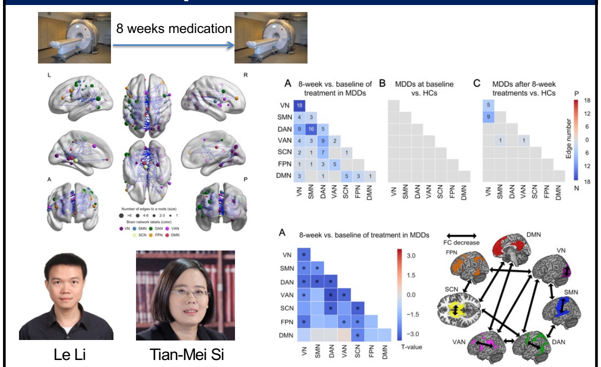
1. DIRECT Individualized Precise TMS Study
2. Brain Mechanism of Antidepressants Study
3. Function/Structure (Fiber) Coupling Study
4. Rumination Spontaneous Thought Study

Antidepressants Decrease FC



Yan et al., PNAS, 2019. ESI Top 1% Highly Cited

Antidepressants Decrease FC



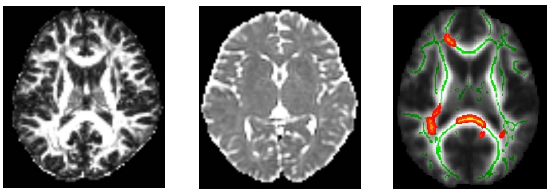
Li, et al., 2021. Hum Brain Mapp

DIRECT III: Brain Mechanism of Antidepressants Study

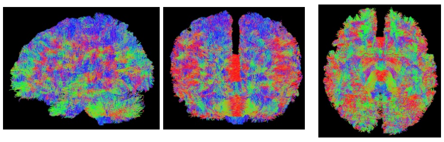
DIRECT Phase III Research Plan

1. DIRECT Individualized Precise TMS Study
2. Brain Mechanism of Antidepressants Study
3. Function/Structure (Fiber) Coupling Study
4. Rumination Spontaneous Thought Study

DPABIFiber



FA | ADC (MD) | TBSS



Whole Brain Fiber Reconstruction

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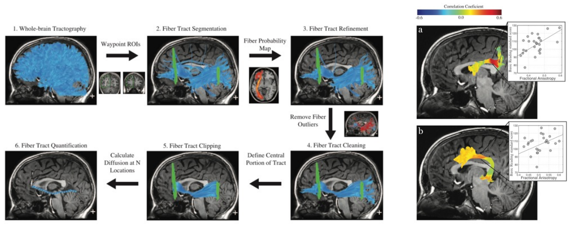
DPABIFiber



Automated Fiber Quantification

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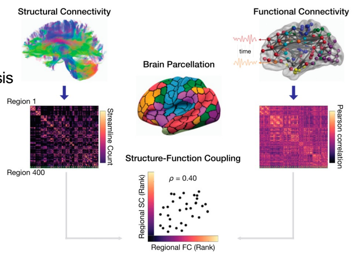
DPABIFiber

Structural Network Analysis



Structure-Function Coupling Analysis

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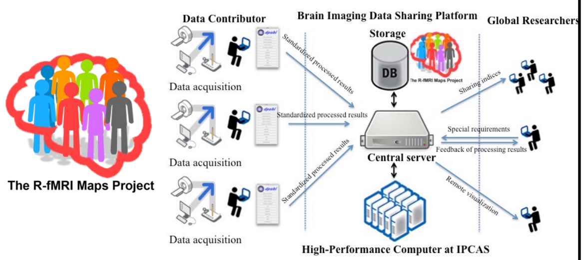
DIRECT III: Function/Structure (Fiber) Coupling Study



76

76

DIRECT Phase III Research Plan

1. DIRECT Individualized Precise TMS Study
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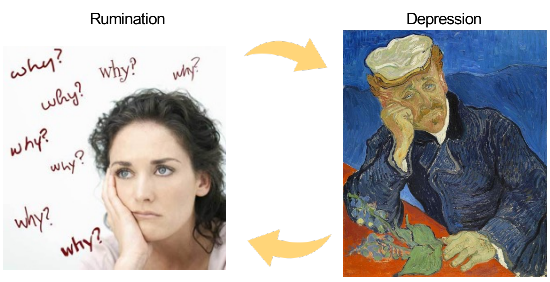
77

77

Rumination



Rumination is not only a feature, but also a risk factor for depression

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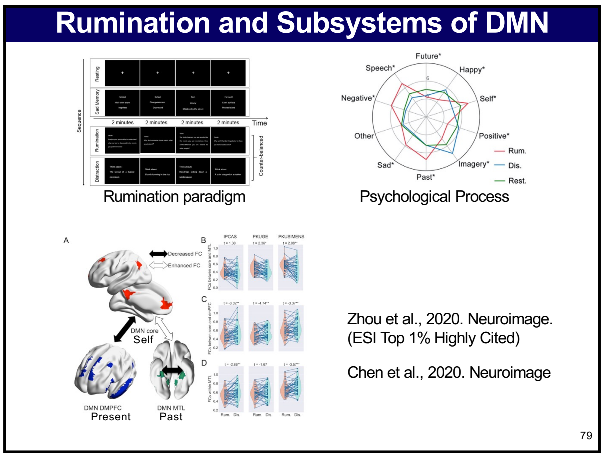
Koster et al., 2011. Clinical Psychol Rev

78



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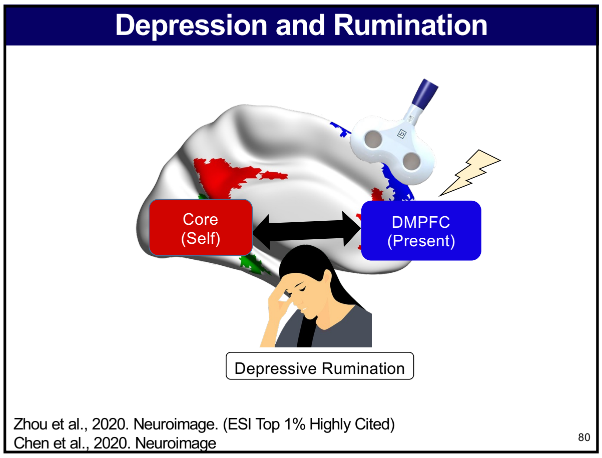

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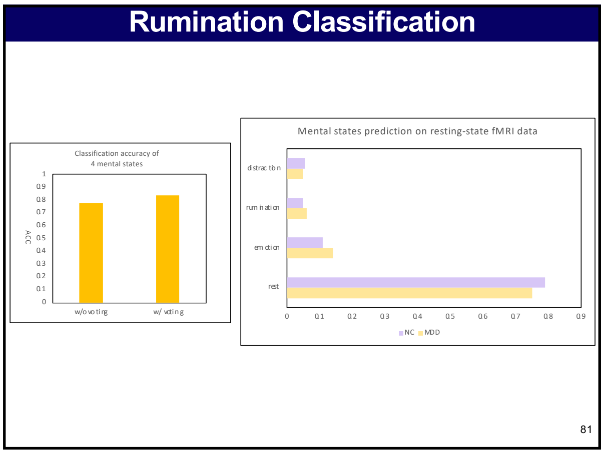

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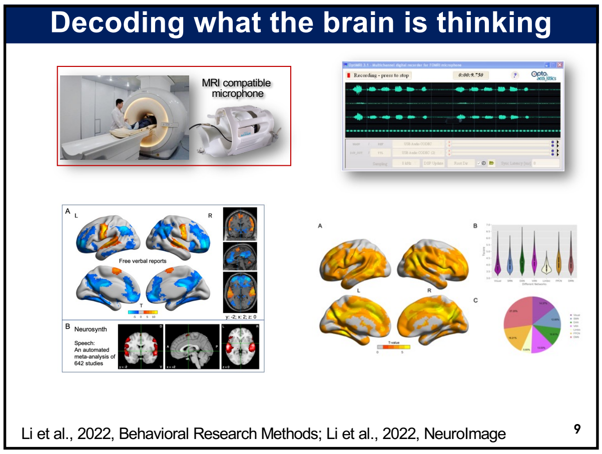

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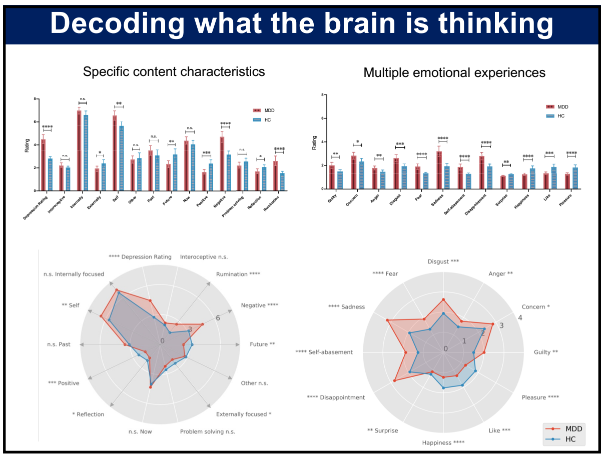
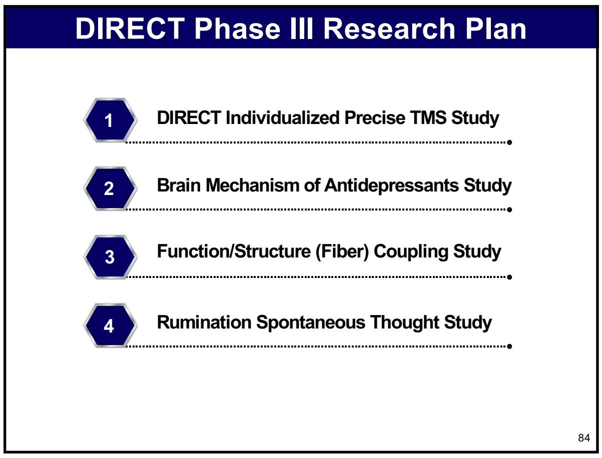


83



84

心花计划
2021-2030

活出心花怒放的人生！

中国科学院心理研究所
“心花计划”抑郁症研究项目

心花计划

- 采用脑影像等多种研究手段，建立抑郁症精准诊断和分型的客观生物标记
- 探索基于中国文化的新型心理干预技术
- 发展药物之外的无创神经调控新疗法

心花计划
2021-2030

IPCAS	医院
中度 遗传、免疫、脑影像 心理行为全面测查 心理干预、物理干预 药物治疗转介 10年跟踪	中重度 遗传、免疫、脑影像 临床测查 药物干预、物理干预 心理治疗转介 短期跟踪

心花计划预研究：总体设计

社区 → 问卷/电话筛选 → 被试120人

初测：
磁共振成像扫描
自评问卷

心理干预（一期）
移空技术（8周）
物理干预（三期）

后测：
磁共振成像扫描
自评问卷

- 所有被试最后将转入长期追踪

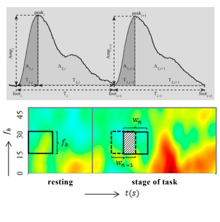
多模态人因感知系统

规格
- 尺寸
  - 终端：48.5mm*36.5mm*14mm
  - 腕带：25mm*260mm
  - 重量：20g
- 电池
  - 持续待机时长：168 小时
  - 持续采集时长：48 小时
  - 一次充电时长：2-3 小时
- 数据传输
  - 蓝牙 4.0
  - USB
- 内存
  - 256M
  - 满负荷使用支持 120 小时的数据存储

传感器
- 脉博PPG
  - 采样频率 100Hz
- 皮肤电阻EDA
  - 采样频率 4Hz ，交流激励源频率 24Hz
- 六轴加速度
  - 采样频率 20Hz
  - 输出 XYZ 三个方向上的加速度值和角速度值
- 皮温
  - 采样频率 1Hz
- 环境传感器 温度、湿度、气压
  - 采样频率 1Hz
- 事件标记按钮
  - 被试可主动打点，进行关键行为标记，打点信息会与生理数据同步记录

多模态人因感知系统

脉搏波	时域特征 (Time Domain)	心率（HR）
		心率变异性（HRV）：SDNN、RMSSD、N20、N50
	频域特征 (Frequency Domain)	低高频功率谱密度 (PSD_LF、PSD_HF、LHR)
皮肤电阻	时域特征 (Time Domain)	皮肤电导水平（SCL）
		皮肤电导反应（SCR）
六轴加速度/角速度	频域特征 (Time Domain)	运动加速度（ACC）
		运动角速度（GYRO）



Reference
Zhang, Y., Zhao, G., Ge, Y., Shu, Y., Zhang, D., Liu, Y. & Sun, X. (2021). CPED: A Chinese Positive Emotion Database for Emotion Elicitation and Analysis. *IEEE Transactions on Affective Computing*, 20, 1-14.
Liu, Y., Yu, M., Zhao, G., Song, J., Ge, Y., Shi, Y. (2018). Real-Time Movie-Induced Discrete Emotion Recognition from EEG Signals, *IEEE Transactions on Affective Computing*, 9(4): 550-562.

移空技术

一.静态作业	二.动态作业
1. 三调放松	6. 三调放松
2. 确定靶症状	7. 清洁与置放
3. 存想象征物	8. 移动与空境
4. 存想象承载物	9. 移回与评估
5. 填写移空记录纸A	10. 填写移空记录纸B

91

91

移空技术

92

92

“心花计划”心理支持专家

特级心理支持专家

刘天君

一级心理支持专家

冯晓东、高飞、和翊洽、梁翀、梁亚奇、龙迪、尚旻、孙晓军、王烜、须卫、杨雅清、周歆媛

二级心理支持专家

崔乔炜、董素兰、龚琳轩、郭艳霞、韩爽、毛力、毛曼、牛亚南、宋英朋、田菁、杨喆、张伏震、张莹波

93

93

初测流程

访谈

第一次磁共振成像扫描

心理干预：移空技术

第二次磁共振成像扫描

自评问卷
行为任务

94

94

磁共振成像设计

扫描：初测第一次

T1加权结构像 5分钟 → 静息态功能像 8分钟 → 反刍思维任务功能像 24分钟 → 出声思维功能像 10分钟 → DTI 11分钟

扫描：初测第二次

静息态功能像 8分钟

95

95

磁共振成像设计

扫描：后测

T1加权结构像 5分钟 → 静息态功能像 8分钟 → 反刍思维任务功能像 24分钟 → 出声思维功能像 10分钟

96

96

心花计划移空疗法心理干预

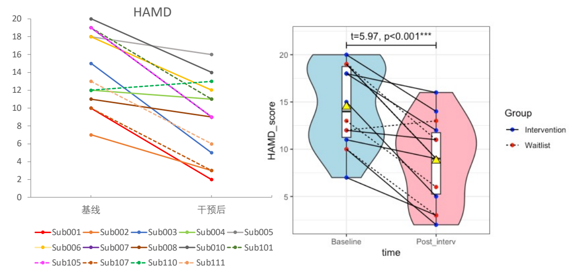
97

97

抑郁程度有效减低

汉密尔顿抑郁量表（HAMD）

心花计划入组基线 vs. 移空心理疗法干预后



注：汉密尔顿抑郁量表是对患者进行HAMD联合检查评定抑郁状态时医生使用的量表，本研究中由北大六院/深圳康宁医院的医生/医学研究生评定。

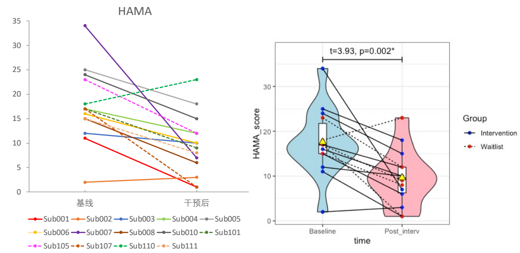
98

98

焦虑程度降低

汉密尔顿焦虑量表（HAMA）

总分≥29分，可能为严重焦虑；≥21分，肯定有明显焦虑；≥14分，肯定有焦虑；≥7分，可能有焦虑；如<7分，便没有焦虑症状。

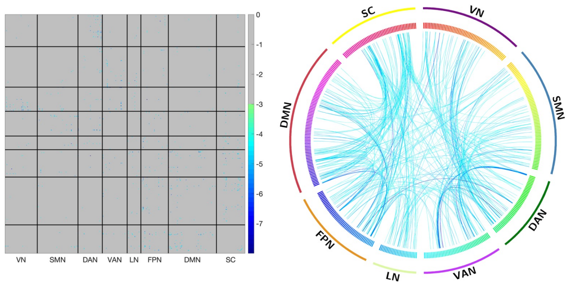


注：汉密尔顿焦虑量表是对患者进行HAMA联合检查评定焦虑状态时医生使用的量表，本研究中由北大六院/深圳康宁医院的医生/医学研究生评定。

99

99

大脑功能连接变化



NBS corrected: edge p < 0.001, cluster p < 0.05

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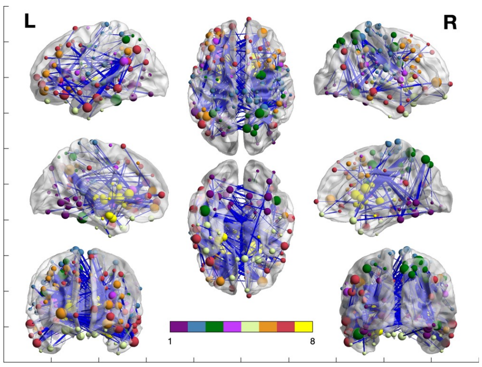
100

大脑功能连接变化

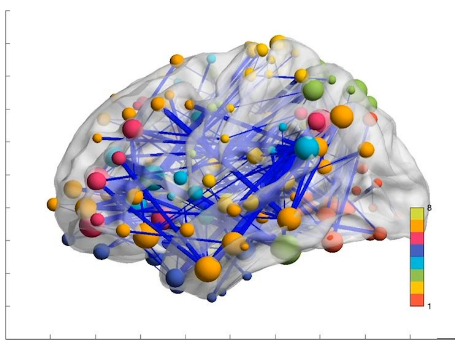


NBS corrected: edge p < 0.001, cluster p < 0.05

101

101

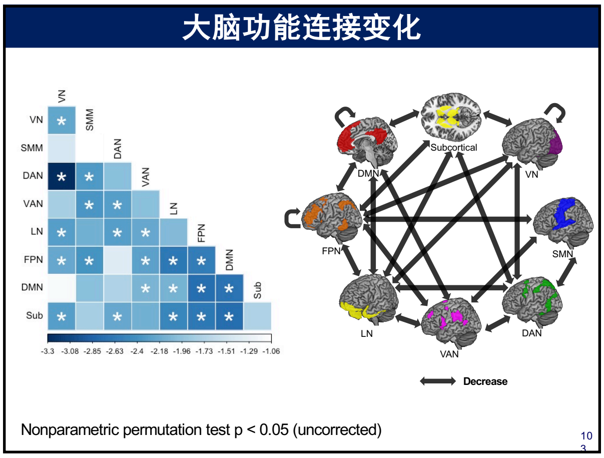
大脑功能连接变化



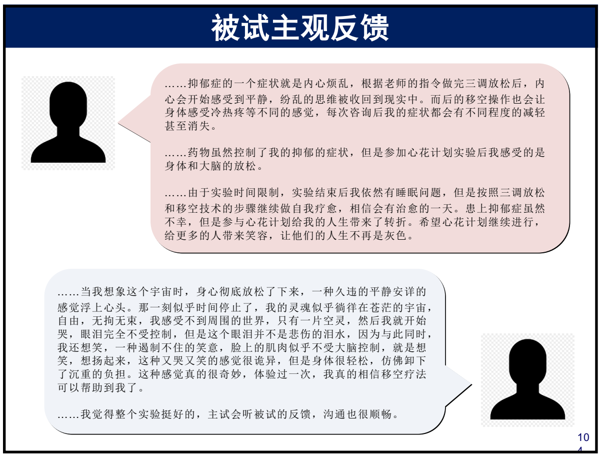
NBS corrected: edge p < 0.001, cluster p < 0.05

102

102



103

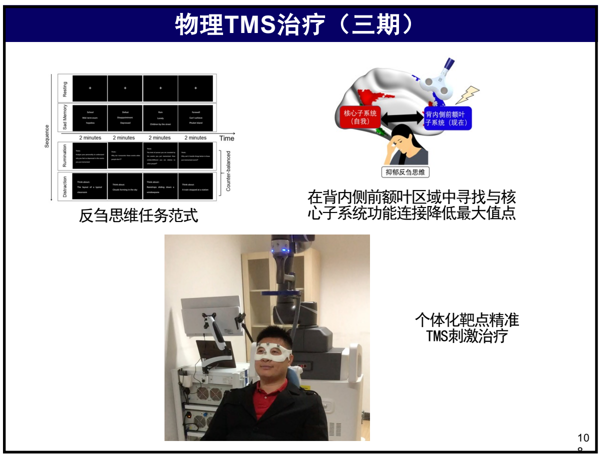


104

105

106

107



108

欢迎合作

CCTV-9《我们如何对抗抑郁》纪录片

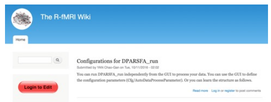
北京卫视《为你喝彩》纪录片

109

109

Further Help

http://rfmri.org/Course



http://rfmri.org/wiki

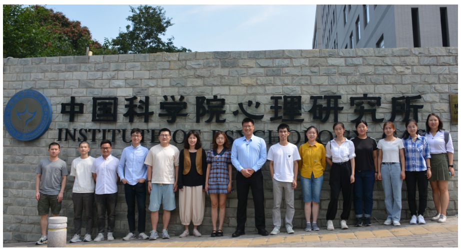
The R-fMRI Journal Club

Official Account: RFMRILab

110

110

Acknowledgments



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111

111

Thanks for your attention!

112

112