Resting-state fMRI for precise localization of abnormal brain activity

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Outline

- What is resting-state fMRI
- Analytic methods of resting-state fMRI
- Correlation of resting-state fMRI and FDG-PET
- Meta-analysis of resting-state fMRI in brain disorders
- Precise localization and brain stimulation

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MRI

- Anatomical: T1, T2……
- Diffusion MRI
- MRS
- Perfusion (ASL…)
- fMRI-BOLD
- ……

fMRI

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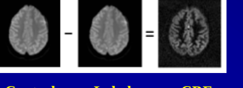
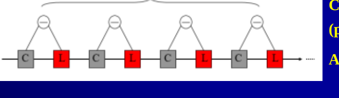
Arterial Spin Labeling (ASL) perfusion MRI



Control — Label = CBF

(Courtesy of Dr. Yihong Yang)



CBF timecourse (pseudo ~4s)

ASL timecourse (~2s)

Absolute quantification of CBF (ml/100g/min)

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Functional MRI BOLD

Blood Oxygenation Level Dependent (BOLD) deoxyhemoglobin

Seiji Ogawa et al, 1990, PNAS

(AT & T Bell Laboratory, NJ, USA)

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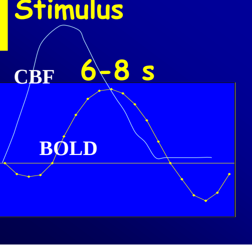
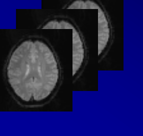
fMRI-BOLD





DeO_2Hb ↓

Signal change: ~1%

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Marcus E. Raichle

Fox P, Raichle ME (PNAS, 1986)

(Washington University St. Louis)

Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects

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BOLD vs. Arterial Spin Labeling (ASL)

	BOLD	ASL
Measure	deoxy-Hb	CBF
Quantification	No	Yes
Temporal resolution	0.2-3s	> 4s
SNR	high	low

fMRI

- Task fMRI
- Resting-state fMRI

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Experimental design for task fMRI

- Blocked-design — Every ~30 s
- Fast event-related — Every 3-5 s
- Slow event-related — Every ~15 s
- Mixed

Two or more conditions within a single run!

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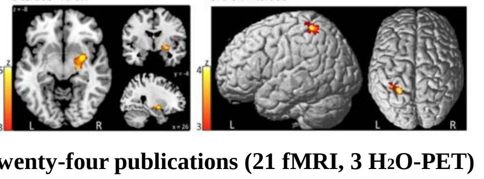
Task BOLD-fMRI meta-analysis

• Human Brain Mapping 35:3227–3237 (2014) •

Functional Neuroimaging of Motor Control in Parkinson's Disease: A Meta-Analysis

Damian M. Herz,[1*] Simon B. Eickhoff,[2,3] Annemette Løkkegaard,[4] and Hartwig R. Siebner[1]

[1]Danish Research Center for Magnetic Resonance, Center for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark
[2]Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine University, Duesseldorf, Germany
[3]Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany
[4]Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark

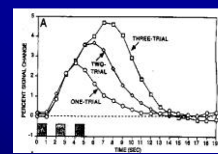


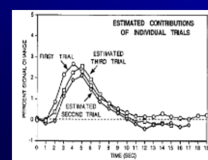
Twenty-four publications (21 fMRI, 3 H2O-PET)

Limitation: task paradigm varies so much:

- Internal vs., external
- Timing
- Selection
- Sequential
- In-phase, anti-phase,
- Unilateral vs bilateral
- Writing, finger, grip-force, joystick-movement, ankle

Individual statistical analysis Assumptions





Linearly additive

Problems & Questions

Time invariant

*(Figures from **Dale & Buckner, 1997**)*

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Linearly additive and time invariant for blocked and event-related task fMRI design

Not suitable to:

- Strong emotional stimuli or craving
- Natural, continuous, consecutive (natural language reading or listening, music, …)
- Sustained attention
- ……

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Experimental design for fMRI studies

- Blocked-design — Every ~30 s
- Fast event-related — Every 3-5 s
- Slow event-related — Every ~15 s
- Mixed
- **State-fMRI design** — Quite a few mins

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Natural "State" fMRI design

- A whole period of time (> a few minutes)
- Natural task-"State" design: on-going activity
- Resting-"State" design: spontaneous activity
- Computation: quite different from task general linear model (GLM) activation detection

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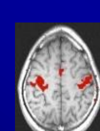
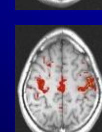
The first Resting-state fMRI paper

(Biswal et al., 1995, MRM)



Activation map of bilateral finger tapping (task vs. rest)



Higher functional connectivity or synchronization low frequency fluctuation (LFF, 0.01 – 0.08 Hz) of RS-fMRI

(Thanks to Dr. WENG Xu-Chu for showing me this paper on someday in 2003)

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Marcus E. Raichle

Fox P, Raichle ME (PNAS, 1986)

(Washington University St. Louis)

Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects

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A default mode of brain function

Marcus E. Raichle*†, Ann Mary MacLeod*, Abraham Z. Snyder*, William J. Powers‡, Debra A. Gusnard*§, and Gordon L. Shulman‡

*Mallinckrodt Institute of Radiology and Departments of ‡Neurology and §Psychiatry, Washington University School of Medicine, St. Louis, MO 63110

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected on April 30, 1996.

Contributed by Marcus E. Raichle, October 26, 2000

PNAS

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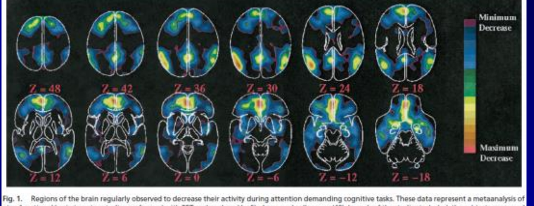

Fig. 1. Regions of the brain regularly observed to decrease their activity during attention demanding cognitive tasks. These data represent a metaanalysis of nine functional brain imaging studies performed with PET and analyzed by Shulman and colleagues (49). In each of the studies included, the subjects processed a particular visual image in the task state and viewed it passively in the control state. One hundred thirty-two individuals contributed to the data in these images. These decreases appear to be largely task independent. The images are oriented with the anterior at the top and the left side to the reader's left. The numbers beneath each image represent the millimeters above or below a transverse plane running through the anterior and posterior commissures (26).

49. Shulman, G. L., Fiez, J. A., Corbetta, M., Buckner, R. L., Miezin, F. M., Raichle, M. E. & Petersen, S. E. (1997) *J. Cognit. Neurosci.* **9,** 648–663.

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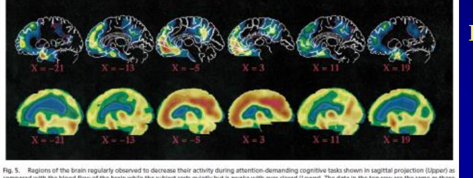

Fig. 5. Regions of the brain regularly observed to decrease their activity during attention-demanding cognitive tasks shown in sagittal projection (*Upper*) as compared with the blood flow of the brain while the subject rests quietly but is awake with eyes closed (*Lower*). The data in the top row are the same as those shown in Fig. 1, except in the sagittal projection, to emphasize the changes along the midline of the hemispheres. The data in the bottom row represent the blood flow of the brain and are the same data shown in horizontal projection in the top row of Fig. 2. The numbers below the images refer to the millimeters to the right (positive) or left (negative) of the midline.

Deactivation

Resting

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M&F: a default or intrinsic mode of functioning derives from the observation that "a consistent network of brain regions shows high levels of activity when no explicit task is performed and subjects are asked simply to rest."

A default mode of functioning was initially inferred on the basis of two related observations: first, certain areas of the brain consistently decrease activity when subjects engage in goal-directed tasks as compared to simply resting quietly with the eyes closed or visually fixating; and, second, this network of areas was not physiologically 'activated' in the resting state. While initially attributed specifically to a specific system, now often called the *default network*, we now appreciate that all parts of the brain exhibit a default mode of functioning that largely reflects their ongoing intrinsic activity.

(Raichle & Snyder, Neuroimage, 2007)

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Spontaneous Neuronal Activity (SNA)?

SNA is a common issue in electroneurophysiological studies and is of great physiological importance

(Review by McCormick 1999, Science)

The nature of spontaneous LFF?

It has been shown that many brain regions generate its own cyclical patterns that interact with those of other regions to which it interconnected

(Review by Steriade et al 1993, Science)

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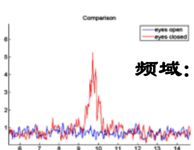
EEG, MEG

时间序列：波动大小
平均值：意义不大



频域：功率或者振幅

Power = a × Amplitude²

(Figures adapted from “Yahoo images”)

PET (glucose, CBF, transmitter…)

主要分析方法：一段时间的平均值（如10分钟）

fMRI

- BOLD
- ASL
- ……

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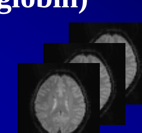
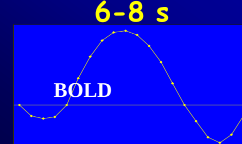
fMRI-BOLD (blood oxygenation level dependent) (sensitive to deoxyhemoglobin)



Stimulus

6-8 s



DeO_2Hb ↓

Signal change: ~1%

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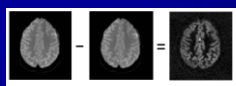
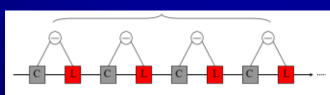
Arterial Spin Labeling (ASL) perfusion MRI



Control － Label ＝ CBF

(Courtesy of Dr. Yihong Yang)



CBF timecourse (pseudo ~4s)

ASL timecourse (~2s)

- 一段时间的平均血流量
- 时间序列的波动（如低频振幅）

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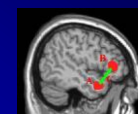
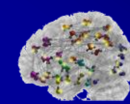
Resting-state fMRI BOLD 计算方法





- Functional integration功能整合
  - 脑区之间的关系
  - 功能连接
  - 网络
- Functional segregation
  (local activity of individual regions or voxels)

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Connectivity

- Functional connectivity
- ? connectivity

Connectivity

- Functional connectivity
- Effective connectivity?
- Structural connectivity?

功能整合的分析方法

- Un-directed:
  - Seed-based linear correlation
  - Independent Component Analysis
  - Graph theory (degree centrality,,,,,,)
  - …….
- Directed:
  - Structural Equation Modeling
  - Dynamic Causal Modeling
  - Granger Causality Analysis

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Most of resting-state fMRI studies : integration (connectivity)

- Correlation: *(Biswal et al., 1995; ……)*
- ICA: *(Kiviniemi et al., 2003; van de Ven et al., 2004; Greicius et al., 2004)*
- Graph theory, small world *(He et al., 2009)*
- Hierarchical Clustering: *(Cordes et al., 2000; Salvador et al., 2005)*
- Self Organization Map: *(Peltier et al., 2003)*
- ....

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BRAIN RESEARCH

ScienceDirect

www.elsevier.com/locate/brainres

ELSEVIER

Research Report

Abnormal resting-state functional connectivity patterns of the putamen in medication-naïve children with attention deficit hyperactivity disorder

Xiaohua Cao[a,b], Qingjiu Cao[a,b], Xiangyu Long[c], Li Sun[a,b], Manqiu Sui[a,b], Chaozhe Zhu[c], Xinian Zuo[c], Yufeng Zang[c,*], Yufeng Wang[a,b,*]

[a]Institute of Mental Health, Peking University, Beijing 100191, China
[b]Key Laboratory of Mental Health, Ministry of Health, Peking University, China
[c]State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China

Seed-based linear correlation

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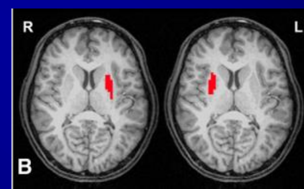

Left and right putamen seed ROIs

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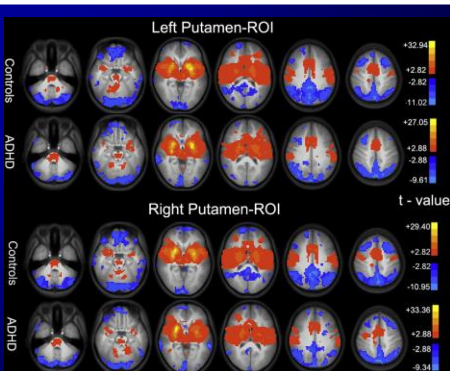

Functional connectivity patterns
Masks for two-sample t-tests

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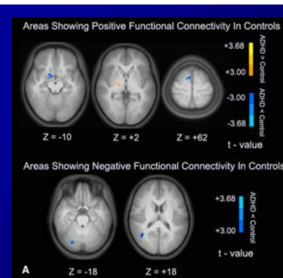
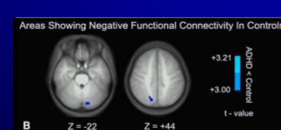


Two-sample t-test of left putamen-FC



Two-sample t-test of right putamen-FC

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Most of resting-state fMRI studies : integration (connectivity)

- **Correlation:** *(Biswal et al., 1995; ……)*
- **ICA:** *(Kiviniemi et al., 2003; van de Ven et al., 2004; Greicius et al., 2004)*
- **Graph theory, small world** *(He et al., 2009)*
- **Hierarchical Clustering:** *(Cordes et al., 2000; Salvador et al., 2005)*
- **Self Organization Map:** *(Peltier et al., 2003)*
- ....

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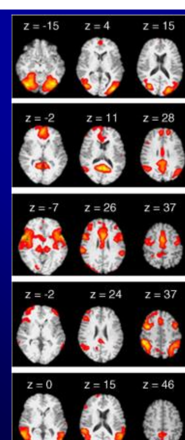

Spatial ICA

Visual cortex

Default mode network

Sensorimotor cortex

Attentional?

(De Luca et al., 2005)

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Most of resting-state fMRI studies: integration (connectivity)

- **Correlation:** *(Biswal et al., 1995; ……)*
- **ICA:** *(Kiviniemi et al., 2003; van de Ven et al., 2004; Greicius et al., 2004)*
- ➡ **Graph theory, small world** *(He et al., 2009)*
- **Hierarchical Clustering:** *(Cordes et al., 2000; Salvador et al., 2005)*
- **Self Organization Map:** *(Peltier et al., 2003)*
- ....

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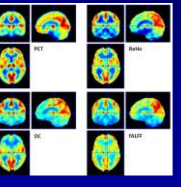
Graph
degree or degree centrality (DC)
voxel-wise whole-brain
(region-wise, part of brain)

Sum of linear correlation coefficients of the timecourse of a voxel with the timecourse of every voxel in the whole brain



(Aiello M, Salvatore E, Cachia A, PappatàS, Cavaliere C, Prinster A, Nicolai E, Salvatore M, Baron JC, Quarantelli M. Relationship between simultaneously acquired resting-state regional cerebral glucose metabolism and functional MRI: A PET/MR hybrid scanner study. Neuroimage. 2015 Mar 17;113:111-121)

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Functional integration or connectivity

- Un-directed: linear correlation, ICA…
- Directed: SEM, DCM, GCA… ➡

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Granger Causality Analysis (GCA)

GCA is a method based on multiple linear regression for investigating whether the past value of one time series could correctly predict the current value of another (Granger, 1969).

时间先后

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Granger Causality Analysis (GCA)

- Coefficient-based GCA (Chen et al., 2009)

$$Y_t = \sum_{k=1}^{p} A_k X_{(t-k)} + \sum_{k=1}^{p} B_k Y_{(t-k)} + CZ_t + E_t \qquad (1)$$

$$X_t = \sum_{k=1}^{p} A'_k Y_{(t-k)} + \sum_{k=1}^{p} B'_k X_{(t-k)} + C'Z_t + E'_t \qquad (2)$$

A_k: X to Y

A'_k: Y to X

Positive or negative effect of one to another

(Chen et al., 2009; Hamilton et al., 2011; Zang ZX et al., 2012)

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Granger Causality Analysis (GCA)

- Residual-based GCA (Geweke 1982)

$$Y_t = \sum_{k=1}^{p} b_k Y_{(t-k)} + cZ_t + \varepsilon_t \qquad \mathrm{var}(\varepsilon_t) = R_1$$

$$Y_t = \sum_{k=1}^{p} A_k X_{(t-k)} + \sum_{k=1}^{p} B_k Y_{(t-k)} + CZ_t + \mu_t \qquad \mathrm{var}(\mu_t) = R_2$$

$$F_{x \to y} = \ln \frac{R_1}{R_2}$$

Only positive effect of X to Y, or Y to X

(Modified from Zang ZX et al., 2012)

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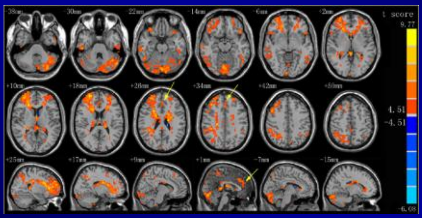
Granger Causality Analysis of the right fronto-insular cortex



the rFIC to all (x = 37, y = 25, z = −4 with radius = 5 mm), TR = 2s

(Zang ZX et al., 2012)

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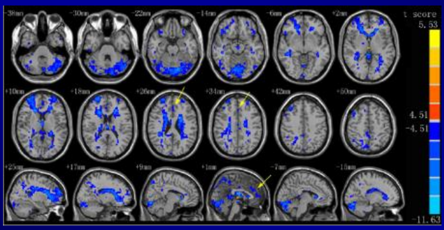
Granger Causality Analysis of the right fronto-insular cortex



all to the rFIC

(Zang ZX et al., 2012)

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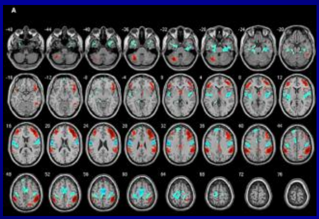
Granger Causality Analysis of the right anterior insula in schizophrenia



the rAI to all (x = 33, y = 21, z = -3 with radius = 6 mm), TR = 2.5s

(Palaniyappan et al., 2013, Neuron)

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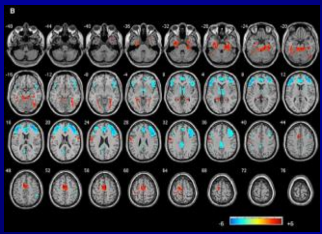
Granger Causality Analysis of the right anterior insula in schizophrenia



all to the rAI

(Palaniyappan et al., 2013, Neuron)

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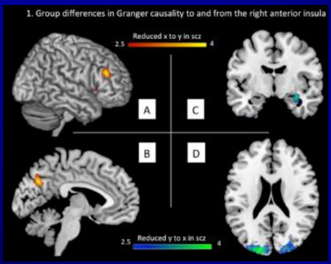
Granger Causality Analysis of the right anterior insula in schizophrenia



(Palaniyappan et al., 2013, Neuron)

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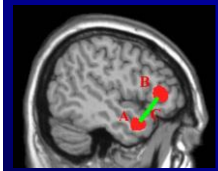
Functional connectivity between regions
vs.
Local activity of a specific region



Abnormal functional connectivity between A and B

Question: Is A, B, C, or……abnormal?

Local activity!

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Methods for local activity of RS-fMRI

- **Amplitude: rms, power spectrum, amplitude of low frequency fluctuation (ALFF):** *(Biswal et al., 1995; Li et al., 2000; Kiviniemi et al., 2000; Zang et al., 2007)*
- **Local synchronization: coefficients of spontaneous low frequency (COSLOF)** *(Li et al., 2002)*, **regional homogeneity (ReHo)** *(Zang et al., 2004)*, **integrated local correlation (ILC)** *(Deshpande et al., 2009)*
- **Temporal clustering analysis (TCA):** *(Liu et al., 2000; Morgan et al., 2004)*
- **Multiple Regressors:** *(Fransson, 2005)*
- **Autoregressive Noise Model:** *(Cordes et al., 2005)*
- **Fractal:** *(Maxim et al., 2005)*
- **Time delay:** *(Lv et al., 2013)*
- ……

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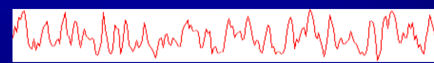
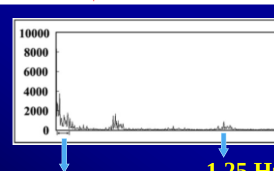
Amplitude of Low Frequency Fluctuation (ALFF) *(Zang et al., 2007, Brain Dev)*





TR

400 ms

1.25 Hz

0.01-0.08 Hz

Steps: square root, average of 0.01-0.08 Hz, standardization by global mean

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Root Mean Square (RMS)

white matter vs. gray matter = 0.6 : 1

(Biswal et al., 1995; Li et al., 2000)

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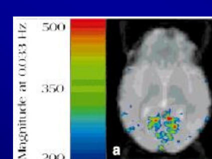
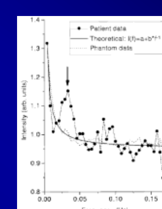
Power

- Power spectrum:





Higher power at 0.033Hz in the visual area *(Kiviniemi et al., 2000)*

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Power, Amplitude of Low Frequency Fluctuation (ALFF)

For a given frequency:

standard deviation
ALFF

Square root of the power

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Root Mean Square vs. Standard Deviation

Relationship to the arithmetic mean and the standard deviation [edit]

If $\bar{x}$ is the arithmetic mean and σ_x is the standard deviation of a population or a waveform then:[3]

$$x_{\mathrm{rms}}^2 = \bar{x}^2 + \sigma_x^2.$$

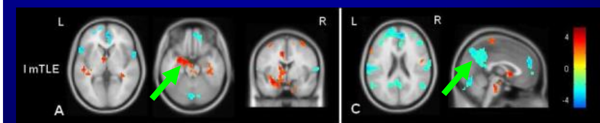
3. ^ Chris C. Bissell and David A. Chapman (1992). *Digital signal transmission* (2nd ed.). Cambridge University Press. p. 64. ISBN 978-0-521-42557-5.

http://en.wikipedia.org/wiki/Root_mean_square#Relationship_to_the_arithmetic_mean_and_the_standard_deviation

60

FMRI Study of Mesial Temporal Lobe Epilepsy using Amplitude of Low-Frequency Fluctuation Analysis

(Zhang et al., 2010, Human Brain Mapp)



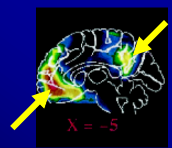
Left mTLE patients:

Increased in the left hippocampus

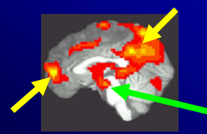
Decreased in the default mode network

61

ALFF



PET
(Raichle et al., 2001)

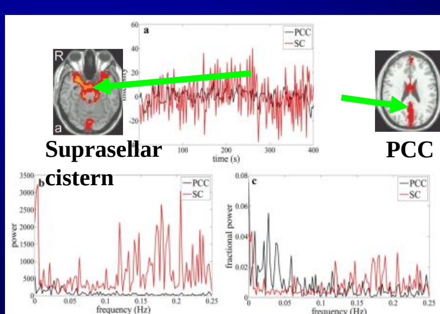


ALFF
(Zang et al., 2007)

noise

62

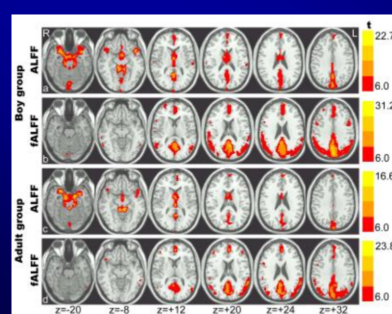
Improvement: fractional ALFF



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

63

Improvement: fractional ALFF ?



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

64

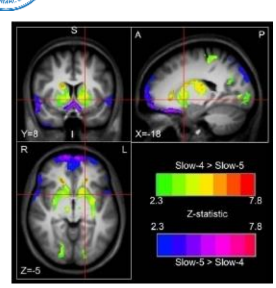
low frequency fluctuation
(0.01 – 0.08)

higher?

frequency-dependent amplitude of fluctuation

65

ALFF at different frequency band



Slow 4: 0.027-0.073 Hz
Slow 5: 0.01-0.027 Hz

Slow 4 is more specific to the basal gangalia

Zuo XN, Di Martino A, Kelly C, Shehzad ZE, Gee DG, Klein DF, Castellanos FX, Biswal BB, Milham MP. The oscillating brain: Complex and reliable. Neuroimage. 2010 Jan 15;49(2):1432-45.

Higher frequency bands

> 0.1 Hz

Amplitude of fluctuation eyes open vs. eyes closed, TR = 300 ms

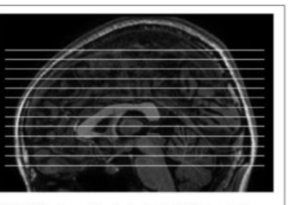
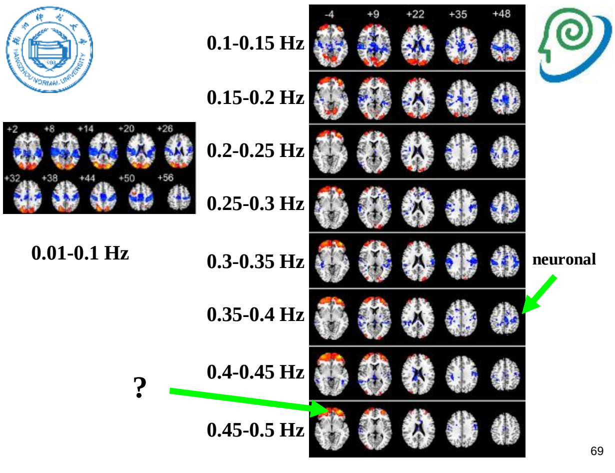


FIGURE 1 | The slice position for short-TR rs-fMRI data acquisition. TR = 400 ms, total number of slices = 13, thickness/gap = 6 mm/1 mm.

(Yuan BK, Wang J, Zang YF, Liu DQ. Amplitude differences in high-frequency fMRI signals between eyes open and eyes closed resting states. Front Hum Neurosci. 2014 Jul 8;8:503.)

68



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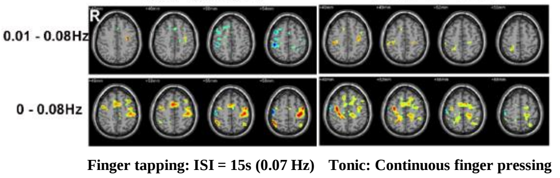
Very low frequency band

< 0.01 Hz

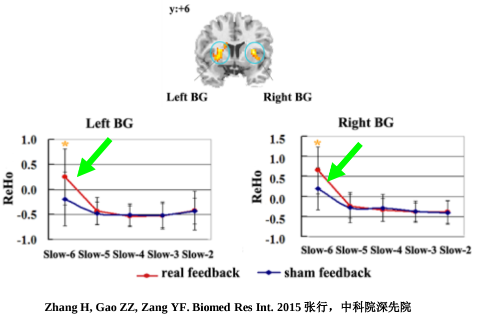
Effects of very low frequency on ReHo (< 0.01 Hz)



Finger tapping: ISI = 15s (0.07 Hz) Tonic: Continuous finger pressing

Lv Y, Margulies DS, Villringer A, Zang YF. Effects of finger tapping frequency on regional homogeneity of sensorimotor cortex. PLoS One. 2013 May 16;8(5):e64115. 吕亚婷，杭师大

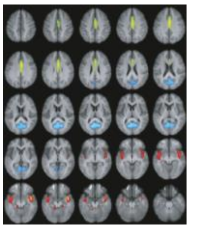
Effects of very low frequency on ReHo (< 0.01 Hz)



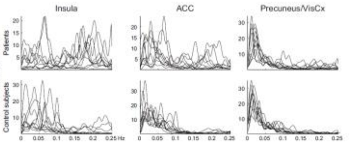
Zhang H, Gao ZZ, Zang YF. Biomed Res Int. 2015 张行，中科院深先院

Interaction of higher and lower frequency bands

Insular cortex, dACC, higher frequency, pain

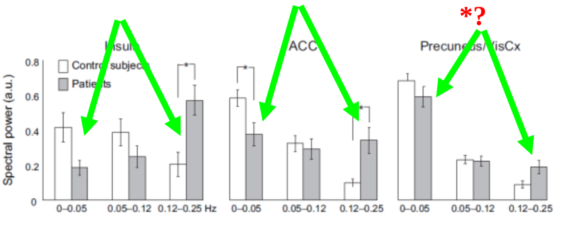


Power analysis of ICA



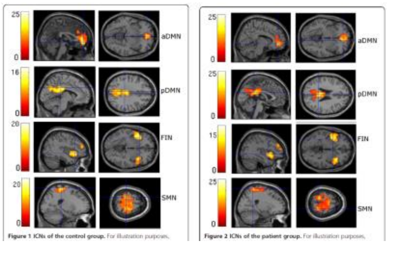
Malinen S, Vartiainen N, Hlushchuk Y, Koskinen M, Ramkumar P, Forss N, Kalso E, Hari R. Aberrant temporal and spatial brain activity during rest in patients with chronic pain. Proc Natl Acad Sci U S A. 2010 Apr 6;107(14):6493-7.

Interaction (not mentioned in the paper)



Malinen S, Vartiainen N, Hlushchuk Y, Koskinen M, Ramkumar P, Forss N, Kalso E, Hari R. Aberrant temporal and spatial brain activity during rest in patients with chronic pain. Proc Natl Acad Sci U S A. 2010 Apr 6;107(14):6493-7.

Anterior DMN, Frontal-insular network, higher frequency, pain



No significant differences in spatial functional connectivity between the patient and control groups

Otti A, Guendel H, Wohlschläger A, Zimmer C, Noll-Hussong M. Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder. BMC Psychiatry. 2013 Mar 13;13:84.

Interaction (not mentioned in the paper)

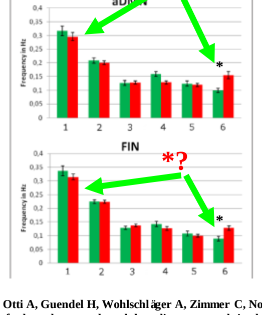


Figure 3 Power spectra of patients (red) and healthy controls (green). Intrinsic neural activity within the aDMN and the FIN show faster spontaneous fluctuations in patients with chronic pain disorder. Error bars represent the standard error of the mean. [1 ≡ 0–0.04 Hz, 2 ≡ 0.04 - 0.08 Hz, 3 ≡ 0.08 - 0.12 Hz, 4 ≡ 0.12 - 0.16 Hz, 5 ≡ 0.16 - 0.20 Hz, 6 ≡ 0.20 - 0.24 Hz].

Otti A, Guendel H, Wohlschläger A, Zimmer C, Noll-Hussong M. Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder. BMC Psychiatry. 2013 Mar 13;13:84. doi: 10.1186/1471-244X-13-84.

Medicine

OBSERVATIONAL STUDY

OPEN

Frequency-Specific Alterations of Local Synchronization in Idiopathic Generalized Epilepsy

Jue Wang, Zhiqiang Zhang, MD, Gong-Jun Ji, PhD, Qiang Xu, Yubin Huang, MD, Zhengge Wang, MD, Qing Jiao, MD, Fang Yang, MD, Yu-Feng Zang, MD, Wei Liao, PhD, and Guangming Lu, MD

王珏等，2015

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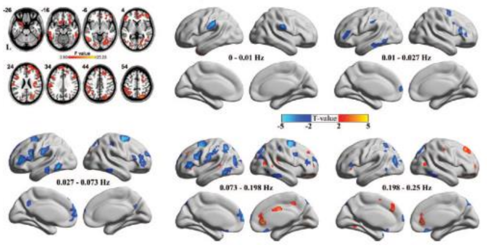
Main effect of group

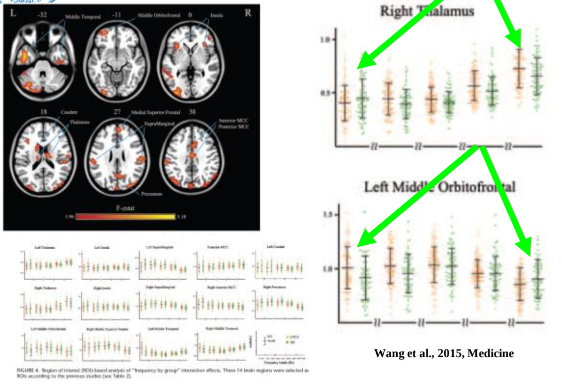
ANOV

t-tests



Wang et al., 2015, Medicine

Interaction effect of group*frequency



Wang et al., 2015, Medicine

Methods for local activity of RS-fMRI

- **Amplitude: rms, power spectrum, amplitude of low frequency fluctuation (ALFF):** *(Biswal et al., 1995; Li et al., 2000; Kiviniemi et al., 2000; Zang et al., 2007)*
- **Local synchronization: coefficients of spontaneous low frequency (COSLOF)** *(Li et al., 2002)*, **regional homogeneity (ReHo)** *(Zang et al., 2004)*, **integrated local correlation (ILC)** *(Deshpande et al., 2009)*
- **Temporal clustering analysis (TCA):** *(Liu et al., 2000; Morgan et al., 2004)*
- **Multiple Regressors:** *(Fransson, 2005)*
- **Autoregressive Noise Model:** *(Cordes et al., 2005)*
- **Fractal:** *(Maxim et al., 2005)*
- ……

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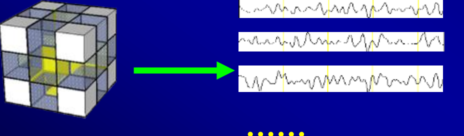
Regional Homogeneity (ReHo)

Similarity or synchronization of the time courses within a functional cluster (usually 27 neighboring voxels)

(Zang et al., 2004, NeuroImage)



……

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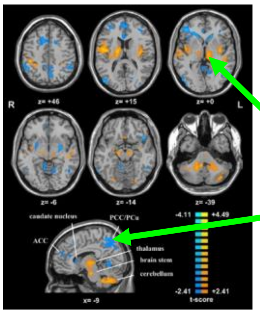
ReHo in epileptic patients with generalized tonic-clonic seizures



Increased ReHo in the thalamus, brain stem

Decreased ReHo in the DMN

(Zhong Y, Lu G, Zhang Z, Jiao Q, Li K, Liu Y. Altered regional synchronization in epileptic patients with generalized tonic-clonic seizures. Epilepsy Res. 2011 Nov;97(1-2):83-91.)

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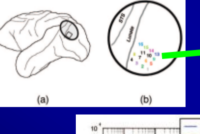
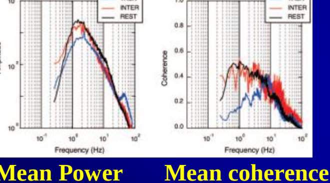
Regional Coherence of Local Field Potential *(Leopold et al., 2003, Cerebral Cortex)*



4 × 4 array

2.5 – 10.6 mm



Mean Power   Mean coherence

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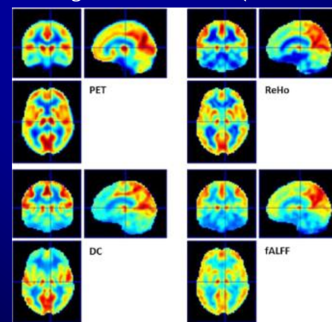
Outline

- What is resting-state fMRI
- Analytic methods of resting-state fMRI
- Correlation of resting-state fMRI and FDG-PET
- Meta-analysis of resting-state fMRI in brain disorders
- Precise localization and brain stimulation

PET glucose and BOLD (PET-MRI hybrid)



Similar

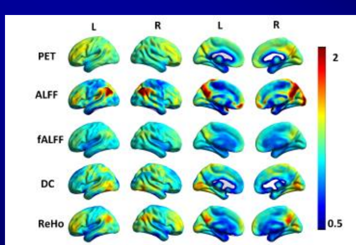
spatial

pattern

Higher in DMN

(Aiello M, Salvatore E, Cachia A, PappatàS, Cavaliere C, Prinster A, Nicolai E, Salvatore M, Baron JC, Quarantelli M. Relationship between simultaneously acquired resting-state regional cerebral glucose metabolism and functional MRI: A PET/MR hybrid scanner study. Neuroimage. 2015 Mar 17;113:111-121)

PET glucose vs. BOLD (PET and fMRI)



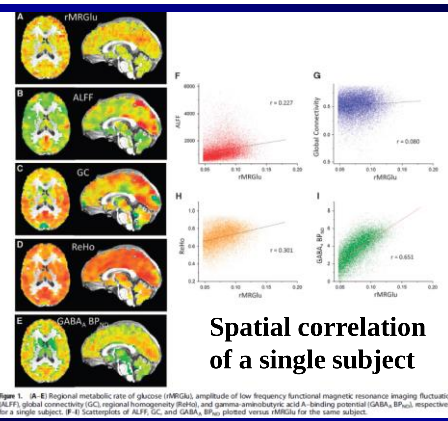
Similar

spatial

pattern

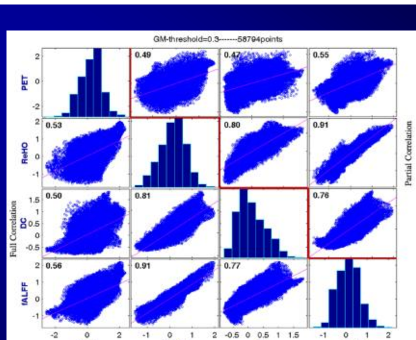
Higher in DMN

(Jiao, FY Gao ZZ, Jia XZ, „,Zang YF, Zuo CT, under review)



Spatial correlation of a single subject

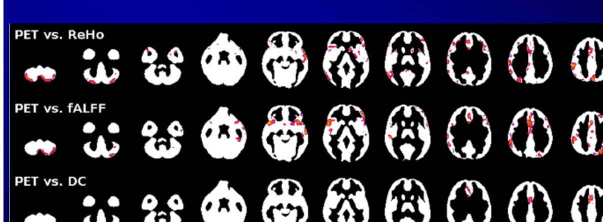
(Nugent AC, Martinez A, D'Alfonso A, Zarate CA, Theodore WH.. J Cereb Blood Flow Metab. 2015)



Spatial correlation (mean r value across subjects)

(Aiello M, Salvatore E, Cachia A, PappatàS, Cavaliere C, Prinster A, Nicolai E, Salvatore M, Baron JC, Quarantelli M. Relationship between simultaneously acquired resting-state regional cerebral glucose metabolism and functional MRI: A PET/MR hybrid scanner study. Neuroimage. 2015 Mar 17;113:111-121)

PET glucose vs. BOLD (PET-MRI hybrid)

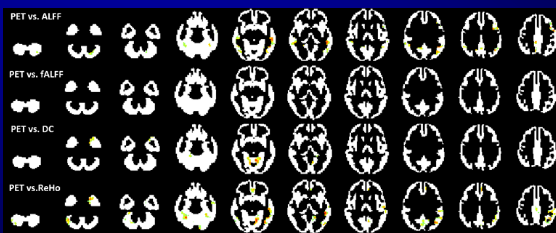


Across-subject correlation

(Aiello M, Salvatore E, Cachia A, PappatàS, Cavaliere C, Prinster A, Nicolai E, Salvatore M, Baron JC, Quarantelli M. Relationship between simultaneously acquired resting-state regional cerebral glucose metabolism and functional MRI: A PET/MR hybrid scanner study. Neuroimage. 2015 Mar 17;113:111-121)

PET glucose vs. BOLD (PET and fMRI)

Almost no correlation!



(Jiao, FY Gao ZZ, Jia XZ, ,,,Zang YF, Zuo CT, under review)

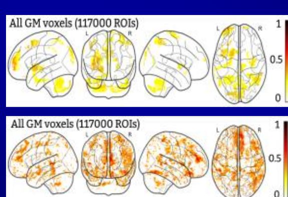
PET glucose, GABA vs. BOLD

Voxel-Wise Between-Subject Analyses
Across subjects, no significant correlations between rMRGlu and ALFFs, rMRGlu and GC, or rMRGlu and ReHo were observed within either group. However, in both healthy and TLE subjects, a relationship between rMRGlu and $GABA_A$ BP_{ND} was observed in

No correlation of BOLD with PET across subjects

(Nugent AC, Martinez A, D'Alfonso A, Zarate CA, Theodore WH.. J Cereb Blood Flow Metab. 2015)

Spatial distribution of resting-state BOLD regional homogeneity as a predictor of brain glucose uptake: A study in healthy aging

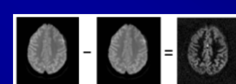


Young group

Aged group

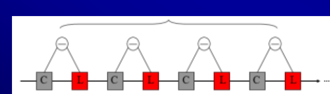
(Bernier M, Croteau E, Castellano CA, Cunnane SC, Whittingstall K. Neuroimage. 2017 Apr 15;150:14-22.)

Arterial Spin Labeling (ASL) perfusion MRI



Control － Label ＝ CBF

(Courtesy of Dr. Yihong Yang)

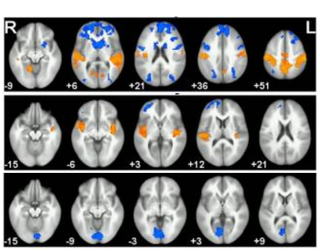


CBF timecourse (pseudo ~4s)

ASL timecourse (~2s)

- 一段时间的平均血流量
- 时间序列的波动（如低频振幅）

Difference between eyes closed and eyes open



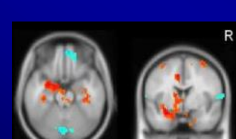
fMRI BOLD-ALFF

fMRI CBF-ALFF) (ASL)

fMRI CBF-mean (ASL)

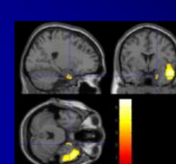
(Zou Q, Yuan BK, Gu H, Liu D, Wang DJ, Gao JH, Yang Y, Zang YF. Detecting Static and Dynamic Differences between Eyes-Closed and Eyes-Open Resting States Using ASL and BOLD fMRI. PLoS One. 2015 Mar 27;10(3):e0121757)

内侧颞叶癫痫
BOLD ALFF vs. FDG-PET?



ALFF增高

Zhang et al., 2010
Human Brain Mapp



Glucose减低

Guedjet al., 2015
Epilepsia

Correlation of PET and BOLD fMRI

- Spatial correlation within subject
  Very high!
- Voxel-wise correlation across subjects
  Very low!

不同的指标，有不同的意义！

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- What is resting-state fMRI
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meta-analysis for voxel-based neuroimaging

Based on comparison between groups of resting-state fMRI

Voxel-wise whole-brain analysis (ALFF, ReHo, degree centrality…)

vs.

ROI-based or network-based analysis (ROI-functional connectivity, ICA, ROI-based graph…)

(Zang, Zuo, Milham, Hallett, 2015)

99

Coordinate-based meta-analysis (CB-meta)

Activation likelihood estimation (ALE)

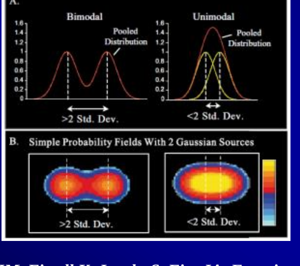
Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage. 2002 Jul;16(3 Pt 1):765-80.

Chein JM, Fissell K, Jacobs S, Fiez JA. Functional heterogeneity within Broca's area during verbal working memory. Physiol Behav. 2002 Dec;77(4-5):635-9.

(Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, Turkeltaub PE, Kochunov P, Fox PT. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp. 2005 May;25(1):155-64)

100

Coordinate-based meta-analysis (CB-meta)



Activation likelihood estimation (ALE)

Chein JM, Fissell K, Jacobs S, Fiez JA. Functional heterogeneity within Broca's area during verbal working memory. Physiol Behav. 2002 Dec;77(4-5):635-9.

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Seed-based d Mapping (SDM)
formerly "Signed Differential Mapping"
http://www.sdmproject.com/

Radua J and Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br J Psychiatry 2009; 195:393-402.

Radua J, van den Heuvel OA, Surguladze S and Mataix-Cols D. Meta-analytical comparison of voxel-based morphometry studies in obsessive compulsive disorder vs other anxiety disorders. Arch Gen Psychiatry 2010; 67:701-711.

Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N and Surguladze S. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. Eur Psychiatry 2012; 27:605–611.

Radua J, Rubia K, Canales-Rodriguez EJ, Pomarol-Clotet E, Fusar-Poli P and Mataix-Cols D. Anisotropic kernels for coordinate-based meta-analyses of neuroimaging studies. Front Psychiatry 2014; 5:13.

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Resting-state fMRI

Very similar design across studies!

resting-state fMRI:

> 2,000 papers in disorders

> 300 papers in depression

But, only 9 CB-meta papers for all disorders

103

12 CB-meta papers on RS-fMRI of brain disorders

[1] Xu Y, Zhuo C, Qin W, Zhu J, Yu C. Altered Spontaneous Brain Activity in Schizophrenia: A Meta-Analysis and a Large-Sample Study. Biomed Res Int. 2015; Article ID 204628, in press.

[2] Iwabuchi SJ, Krishnadas R, Li C, Auer DP, Radua J, Palaniyappan L. Localized connectivity in depression: A meta-analysis of resting state functional imaging studies. Neurosci Biobehav Rev. 2015 Apr;51:77-86.

[3] Graham J, Salimi-Khorshidi G, Hagan C, Walsh N, Goodyer I, Lennox B, Suckling J. Meta-analytic evidence for neuroimaging models of depression: state or trait? J Affect Disord. 2013 Nov;151(2):423-31.

[4] Sundermann B, Olde Lütke Beverborg M, Pfleiderer B. Toward literature-based feature selection for diagnostic classification: a meta-analysis of resting-state fMRI in depression. Front Hum Neurosci. 2014 Sep 10;8:692.

[5] Kühn S, Gallinat J. Resting-state brain activity in schizophrenia and major depression: a quantitative meta-analysis. Schizophr Bull. 2013 Mar;39(2):358-65.

[6] Palmer SM, Crewther SG, Carey LM; START Project Team. A meta-analysis of changes in brain activity in clinical depression. Front Hum Neurosci. 2015 Jan 14;8:1045.

[7] Chen ZQ, Du MY, Zhao YJ, Huang XQ, Li J, Lui S, Hu JM, Sun HQ, Liu J, Kemp GJ, Gong QY. Voxel-wise meta-analyses of brain blood flow and local synchrony abnormalities in medication-free patients with major depressive disorder. J Psychiatry Neurosci. 2015 Apr 8;40(2):140119.

[8] Hannawi Y, Lindquist MA, Caffo BS, Sair HI, Stevens RD. Resting brain activity in disorders of consciousness: A systematic review and meta-analysis. Neurology. 2015 Mar 24;84(12):1272-1280.

[9] Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry. 2015 Jun;72(6):603-11.

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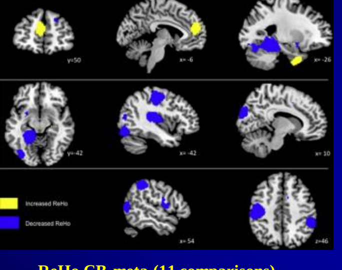
Depression, RS-fMRI, ReHo only, CB-meta

Iwabuchi SJ, Krishnadas R, Li C, Auer DP, Radua J, Palaniyappan L. Localized connectivity in depression: A meta-analysis of resting state functional imaging studies. Neurosci Biobehav Rev. 2015 Apr;51:77-86.



ReHo CB-meta (11 comparisons)

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[2] Depression, RS-fMRI, ReHo only, CB-meta

Iwabuchi SJ, Krishnadas R, Li C, Auer DP, Radua J, Palaniyappan L. Localized connectivity in depression: A meta-analysis of resting state functional imaging studies. Neurosci Biobehav Rev. 2015 Apr;51:77-86.

Table 1
Summary of the characteristic features of studies included in the meta-analysis.

Study	Clinical group	Patients n	Controls n	% Females	Mean age of patients (SD)	Duration of illness mean (SD) in months	Episodes	Medication status (subgroup)	Scanner	Statistical threshold	HAMD-24 equivalent mean score	Quality scores (out of 20)
Chen et al. (2013)	MDD	41	44	74	29.88 (1.49)	12.2 (NA)	First episode	Treatment-naïve (Unmedicated)	3T EC/GSR	Corrected	25.14	19
Chen et al. (2012)	MDD	15	15	40	24.07 (5.79)	3.33 (3.71)	First episode	Treatment-naïve (Unmedicated)	1.5T EC/GSNR	Corrected	31	20
Guo et al. (2011)	TSD	17	17	41	26.71 (NA)	2.59 (1.33)	First episode	Treatment-naïve (Unmedicated)	1.5T EC/GSNR	Corrected	34.5	19
Guo et al. (2011)	TRD	24	19	50	27.88 (8.35)	30(44.34)	Multiple	One week washout before scan (Medicated)	1.5T EC/GSNR	Corrected	33.5	20
Liu et al. (2010)	MDD	14	15	47	29.13 (13.55)	12.1 (3.6)	First episode	Treatment-naïve (Unmedicated)	3T EC/GSNR	Uncorrected	32.6	19
Liu et al. (2010)	MDD	16	16	75	30.38 (NA)	12.1 (NA)	First episode	14 patients treatment naïve; 2 patients on medication (Medicated)	1.5T EC/GSNR	Uncorrected	Na	16
Peng et al. (2011)	MDD	16	16	63	34.1 (9.2)	3.1 (0.7)	First episode	Treatment-naïve (Unmedicated)	3T EC/GSNR	Corrected	31.71	20
Wang et al. (2013)	MDD	14	14	36	32.93 (13.87)	6.12 (5.82)	First episode	Treatment-naïve (Unmedicated)	3T EC/GSNR	Corrected	35	20
Wu et al. (2011) (TRD)	TRD	22	26	32	35(13)	103(65)	Multiple	Treatment-naïve for 2 months prior to scan (Unmedicated)	3T EC/GSNR	Uncorrected	30	19
Wu et al. (2011) (TSD)	TSD	22	26	55	35(13)	32(64)	Multiple	Treatment-naïve for 2 months prior (Unmedicated)	3T EC/GSNR	Uncorrected	23.2	19
Yao et al. (2009)	MDD	22	22	55	38.2 (10.2)	60(54)	Multiple	5 patients treatment-naïve; 17 patients had 2 weeks washout before scan (Medicated)	1.5T EC/GSNR	Uncorrected	48.86	19

TRD, treatment resistant depression; TSD, treatment sensitive depression; MDD, major depressive disorder with both treatment resistant and treatment sensitive samples; NA, not available; EC, eyes closed resting state; GSR, global signal regressed; GSNR, global signal not regressed; SD, standard deviation; HAMD, Hamilton Depression Scale.

S.J. Iwabuchi et al. / Neuroscience and Biobehavioral Reviews 51 (2015) 77–86

"…it is worth noting that all primary studies have been so far conducted only in China, thus limiting the generalizability of the current findings to other populations."

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meta-analysis for voxel-based neuroimaging

Based on comparison between groups of resting-state fMRI

Voxel-wise whole-brain analysis (ALFF, ReHo, degree centrality…)

vs.

ROI-based or network-based analysis (ROI-functional connectivity, ICA, ROI-based graph…)

(Zang, Zuo, Milham, Hallett, 2015)

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Project: Call for participating Resting-state fMRI meta-analysis for PD (REST-meta-PD)

ZANG Yu-Feng, WU Tao, Mark HALLETT

- ❖ **Resting-state fMRI in PD: 82 research articles published, from 44 research groups**
- ❖ **25 research group participated**
- ❖ **ALFF, ReHo, Degree centrality (Whole-brain and voxel-wise analytic methods)**

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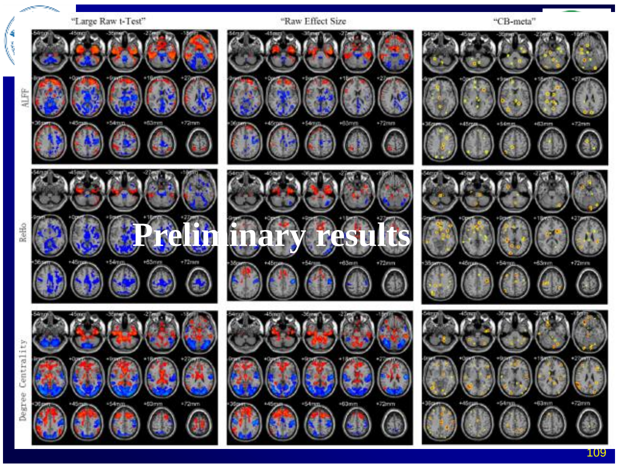

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PNAS

CrossMark

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)

more stringent correction
less false positive

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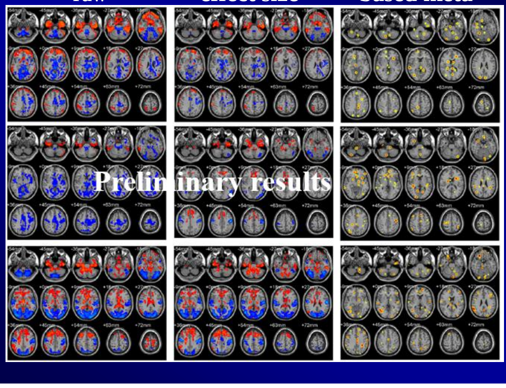
Fixed on raw	Random on effect size	Coordinate-based meta



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More stringent correction, less false positive

PNAS

CrossMark

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Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

PLoS Med. 2005 Aug;2(8):e124.

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Suggestions for application studies of resting-state fMRI

- Fewer analytic methods
- Whole-brain voxel-wise comparison
- Publish effect size image, in addition to a few clusters surviving correction

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Potential framework

Precise localization of abnormal brain activity with Bayesian model of PD

Abnormality probability map by meta-analysis of resting-state fMRI studies — P1

A new patient Resting-state fMRI vs Large sample healthy aged people as reference (fMRI + memory test) — P2

P1+P2: a most likely PD-related voxel in the subthalamic nucleus (effective target for DBS)

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Outline

- What is resting-state fMRI
- Analytic methods of resting-state fMRI
- Correlation of resting-state fMRI and FDG-PET
- Meta-analysis of resting-state fMRI in brain disorders
- Precise localization and brain stimulation

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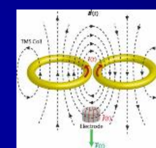
Transcranial Magnetic Stimulation (TMS)

TMS

Navigation system

Focus of "Figure-8" coil



(Figures from CCBD)

Focus size: 3 mm
Focus depth: 15 mm

(modified from google)

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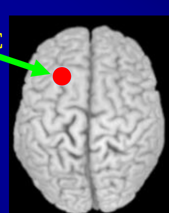
TMS for depression

TMS only for depression by FDA

DLPFC

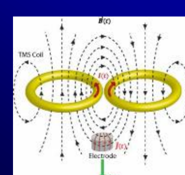


Meta-analysis:
left DLPFC, high frequency, 30% efficacy

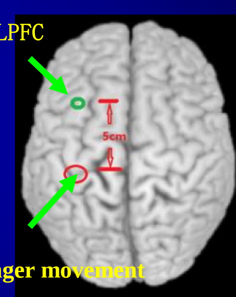
(Ren J et al., 2014)

TMS for depression: targeting

"5-cm" method



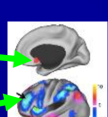
DLPFC

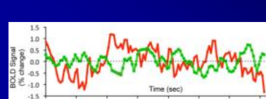


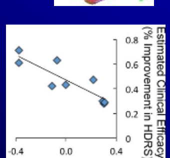
TMS for depression: deep target?

deep target

Cortical target







Left DLPFC - sgACC

more anti-correlation, better effects

(Fox M et al., 2012, Biol Psychiatry)

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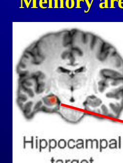
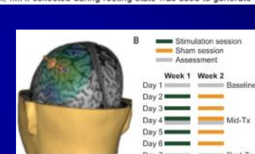
TMS, functional connectivity, hippocampus, enhance memory performance, healthy people

…individualized stimulation targeting…

Identification of stimulation locations and rTMS parameters
We identified a stimulation location for each subject using individual maps of hippocampal resting-state functional connectivity obtained at the baseline assessment at the beginning of the first study week. For each subject, fMRI collected during resting state was used to generate

Memory area





Resting-state fMRI functional connectivity

(Wang JX, …, Voss JL. Science. 2014)

Deep brain stimulation (DBS)
Transcranial magnetic stimulation (TMS)
Transcranial ultrasound stimulation (TUSS)

适应症:

- Epilepsy
- Movement disorders
- Chronic pain
- Depression
- Obsessive compulsive disorder
- ……

关键: 异常脑活动精准定位!

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感谢所有的合作者!
(几页名字)

Thanks for your attention!

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