The REST-meta-MDD Project: towards a Neuroimaging Biomarker of Major Depressive Disorder

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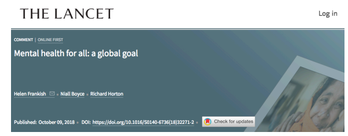
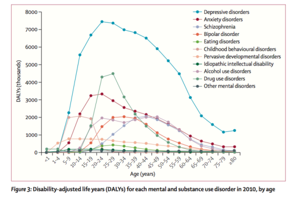
Institute of Psychology, Chinese Academy of Sciences

Global Health Crisis: MDD

Famous Physicist committed suicide after suffering MDD





- 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

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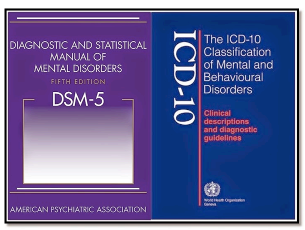
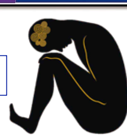
Diagnose of MDD



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



Oquendo et al., 2014. Depress Anxiety

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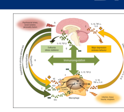
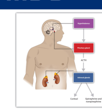
Biomarkers of MDD

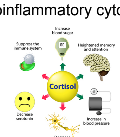


Proinflammatory cytokine?

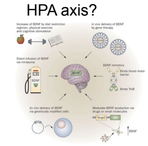


HPA axis?

MDD

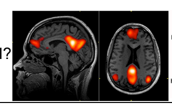


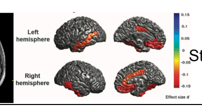
Cortisol?



BDNF?

Functional MRI?





Structural MRI?

A Case

A famous journalist: Jin Zhang

First visit: MDD → Medicine A: suicidal ideation → Switch to Medicine B: turn to mania → Diagnosed as bipolar disorder → Switch to Medicine C: recovery

Diagnose and treatment guided by brain imaing?

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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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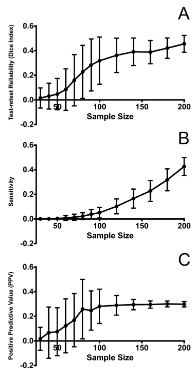
Sample Size

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

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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

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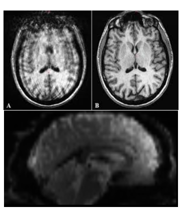
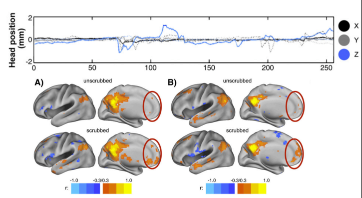
Methodological Issues: Head Motion





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

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

Need an effective motion correction strategy!

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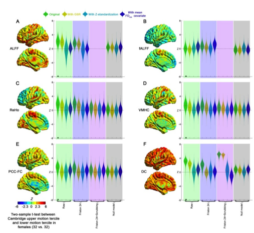
Methodological Issues: Head Motion



Proposed an effective head motion correction strategy

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

- Cited: 755 times
- ESI Top 0.1% highly cited paper

Yan et al., 2013a. Neuroimage

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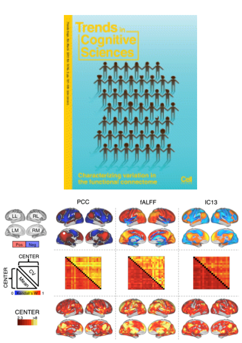
Methodological Issues: Standardization



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

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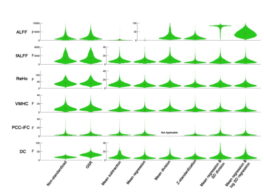
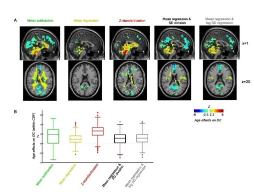
Methodological Issues: Standardization



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: 222 times
- ESI Top 1% highly cited paper

Yan et al., 2013b. Neuroimage

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Reproducibility and Multiple Comparison Correction

PNAS

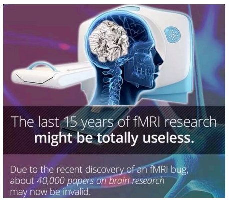
CrossMark

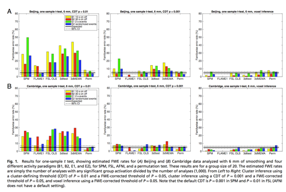
Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

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)





Eklund et al., 2016. PNAS

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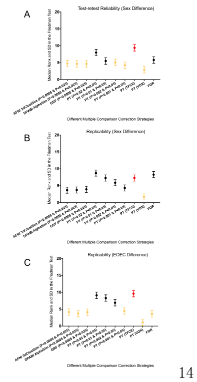
Reproducibility and Multiple Comparison Correction

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

Ranked ESI Top 1% of highly cited papers



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

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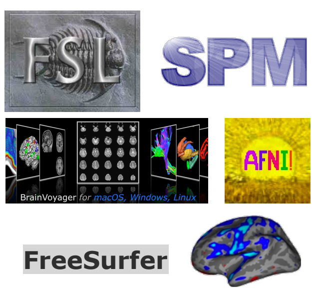
Traditional fMRI Preprocessing Toolbox



- 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 for 1803 times

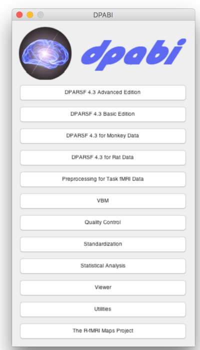
- Adapting methodological updates

Head motion (cited for 755 times)

Standardization (cited for 222 times)

Multiple comparison correction

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



Yan et al., 2016. Neuroinformatics

Corresponding author

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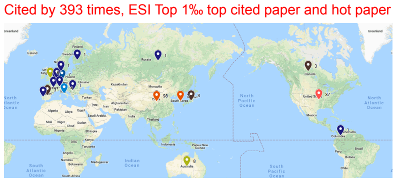
Peer Evaluation

Cited by 393 times, ESI Top 1‰ top cited paper and hot paper



Received: 11 September 2017 | Revised: 27 March 2018 | Accepted: 18 April 2018

DOI: 10.1002/hbm.24200

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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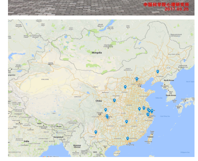
REST-meta-MDD

Started a consortium for big data sharing on MDD. Connected by the preprocessing pipeline, DPARSF, cited for over 1800 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

表 1. REST-meta-MDD 计划参与研究组以及数据构成情况

编号	参与研究单位	研究组负责人	样本量	
			MDD	NC
1	北京大学第六医院	司天梅	74	74
2	苏州市广济医院	柳艳松	30	30
3	中南大学湘雅二医院	姚树桥	27	37
4	中南大学湘雅二医院	郭文斌	24	24
5	上海交通大学医学院附属精神卫生中心	方贻儒/彭代辉	13	11
6	上海交通大学医学院附属精神卫生中心	方贻儒/朱俊娟	15	15
7	浙江大学医学院附属邵逸夫医院	陈炜	38	49
8	中国医科大学第一临床医院精神医学科	王菲	75	75
9	暨南大学第一临床医学院	王颖	50	50
10	山西医科大学第一医院	张克让	50	33
11	重庆医科大学附属第一医院精神科	蒙华庆/罗庆华	32	29
12	重庆医科大学附属第一医院精神科	罗庆华/蒙华庆	32	6
13	西安市中心医院	杨健	25	17
14	中南大学湘雅二医院	谢光荣	64	32
15	东南大学医学院	袁勇贵	50	50
16	四川大学华西医院华西磁共振研究中心	龚启勇	31	31
17	重庆医科大学附属第一医院精神科	况利	47	44
18	浙江大学医学院附属第一医院	杨虹	21	20
19	安徽医科大学	汪凯	51	36
20	西南大学心理学部	邱江	282	251
21	首都医科大学附属北京安定医院	王传跃	86	70
22	中南大学湘雅二医院精神卫生研究所	刘哲宁	30	20
23	四川大学华西医院心理卫生中心	李涛	32	30
24	昆明医学院第一附属医院	许秀峰	32	31
25	东南大学附属中大医院神经内科	柏峰	89	63

注：MDD：重性抑郁障碍；NC：健康对照

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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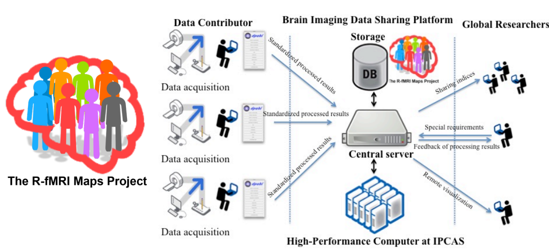
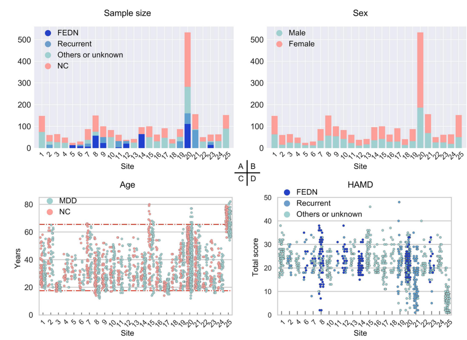
The R-fMRI Maps Project



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

REST-meta-MDD



Yan et al., 2019, PNAS.

Contradicting findings about DMN FC in MDD

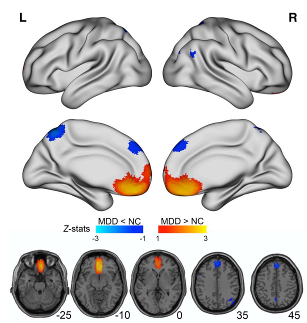
SUPPLEMENTARY TABLES

Supplementary Table S1. A summary of fMRI studies revealing altered default mode network (DMN) functional connectivity (FC) in individuals with MDD.

Study	Sample Size: MDD	Sample Size: Healthy Control	MDD Group's Age, Mean (SD)	Methodology	Principle Findings on FC within DMN: Increased FC	Principle Findings on FC within DMN: Decreased FC	Multiple Comparison Correction Strategy	Episodes†
Greicius et al., 2007*	28	20	38.5 (N/A)	ICA	sgACC		Joint expected probability distribution with height and extent thresholds of p < 0.01, masked within the DMN	N/A
Bluhm et al., 2009*	14	15	21.9 (5.1)	Seed-based Analysis: PCC	no results	no results	FDR	N/A
Cullen et al., 2009	12	14	16.5 (0.95)	Seed-based Analysis: sgACC		sgACC, right medial frontal cortex	GRF theory base correction (min $z > 2.3$, cluster significance: $p < 0.05$)	N/A
Sheline et al., 2010	18	17	35.9 (1.3)	Seed-based Analysis: PCC	dmPFC		Thresholded using $p < 0.01$ (z = 2.58)	Eight first-episode drug naïve
Zhou et al., 2010*	20	18	40.6 (10.7)	Seed-based Analysis: PCC	sgACC		Within combined FC mask, $p < 0.01$ for each voxel and a cluster size of at least 675 mm^3, equal to the corrected threshold of $p < 0.001$, determined by a Monte Carlo simulation (AFNI AlphaSim)	All first-episode drug naïve

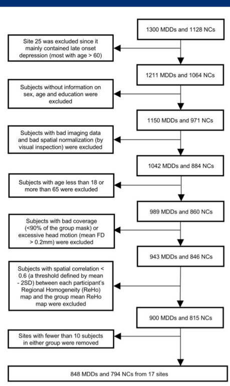
Yan et al., 2019, PNAS.

Meta-Analysis



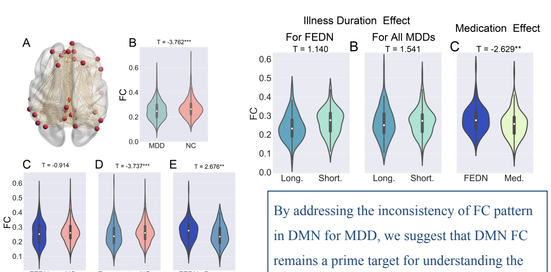
Yan et al., 2019, PNAS.

REST-meta-MDD



Linear Mixed Model:
y ~ 1 + Diagnosis + Age + Sex + Education + Motion + (1 | Site) + (Diagnosis | Site)

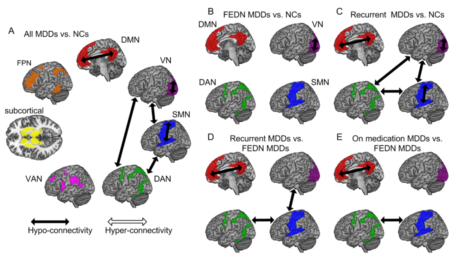
REST-meta-MDD



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

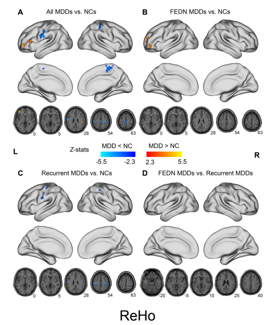
Yan et al., 2019, PNAS.

REST-meta-MDD



Yan et al., 2019, PNAS. 25

REST-meta-MDD



Yan et al., 2019, PNAS. 26

REST-meta-MDD

PNAS

Check for updates

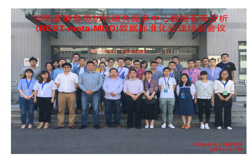
Reduced default mode network functional connectivity in patients with recurrent major depressive disorder

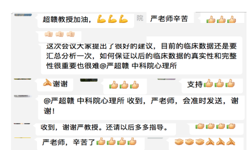
Chao-Gan Yan[a,b,c,d,1], Xiao Chen[a,b,2], Le Li[a,b,2], Francisco Xavier Castellanos[d,e], Tong-Jian Bai[f], Qi-Jing Bo[g], Jun Cao[h], Guan-Mao Chen[i], Ning-Xuan Chen[a,b], Wei Chen[j], Chang Cheng[k], Yu-Qi Cheng[l], Xi-Long Cui[k], Jia Duan[m], Yi-Ru Fang[n], Qi-Yong Gong[o,p], Wen-Bin Guo[k], Zheng-Hua Hou[q], Lan Hu[h], Li Kuang[h], Feng Li[g], Kai-Ming Li[o], Tao Li[r], Yan-Song Liu[s], Zhe-Ning Liu[k], Yi-Cheng Long[k], Qing-Hua Luo[h], Hua-Qing Meng[h], Dai-Hui Peng[n], Hai-Tang Qiu[h], Jiang Qiu[t], Yue-Di Shen[u], Yu-Shu Shi[v], Chuan-Yue Wang[g], Fei Wang[m], Kai Wang[f], Li Wang[w,x], Xiang Wang[k], Ying Wang[i], Xiao-Ping Wu[y], Xin-Ran Wu[t], Chun-Ming Xie[z], Guang-Rong Xie[k], Hai-Yan Xie[aa], Peng Xie[bb,cc,dd], Xiu-Feng Xu[l], Hong Yang[v], Jian Yang[ee], Jia-Shu Yao[j], Shu-Qiao Yao[k], Ying-Ying Yin[q], Yong-Gui Yuan[q], Ai-Xia Zhang[ee], Hong Zhang[y], Ke-Rang Zhang[ff], Lei Zhang[a,b], Zhi-Jun Zhang[z], Ru-Bai Zhou[n], Yi-Ting Zhou[r], Jun-Juan Zhu[n], Chao-Jie Zou[l], Tian-Mei Si[w,x], Xi-Nian Zuo[a,b,c], Jing-Ping Zhao[k,1], and Yu-Feng Zang[gg,hh,1]

[a]Key Laboratory of Behavioral Science, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China; [b]Department of Psychology, University

Yan, et al., 2019. PNAS 27

REST-meta-MDD





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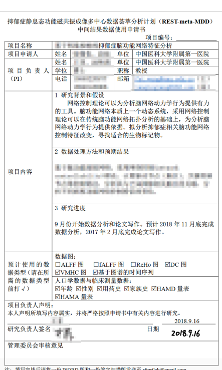
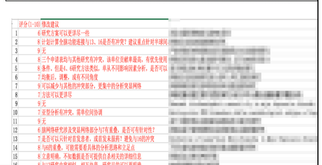
REST-meta-MDD




申请书 20: 抑郁症脑功能网络特征分析

PI	贡献 MDD 数量	贡献对照数量

备注：

评审专家意见：

专家 4: 研究进度中“2017 年 2 月底完成论文写作”有误。

专家 7: 网络分析的重叠。

专家 12: 采用网络控制理论的分析方法，与本项目的其它研究未发现重叠。

专家评分（平均分）：8.55 分

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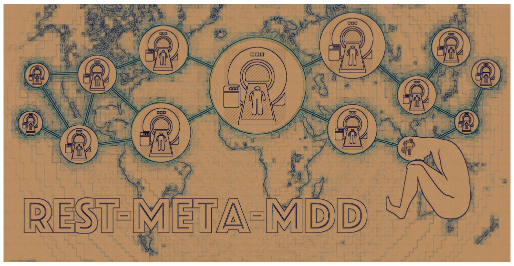
Proposals

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

International Collaboration



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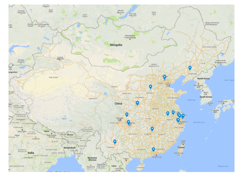
International Collaboration

International Conference on Brain Imaging of Depression



Cross-culture MDD data collection?

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Prospective Studies

- RDoC and task-based fMRI?
- Imaging genetics?
- Treatment: medication and brain stimulation?
- Longitudinal study?

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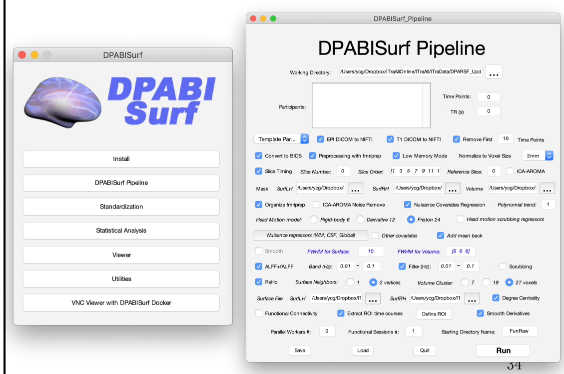
Go to Surface



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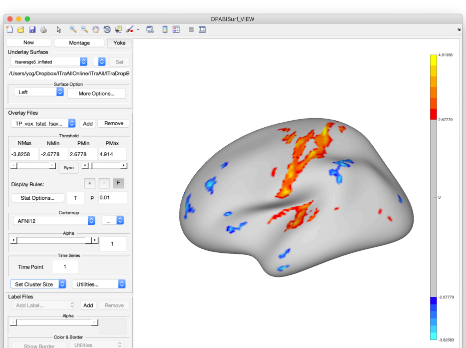
Go to Surface



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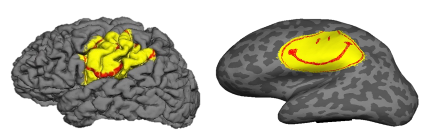
Why Surface-based Analysis

- Function has surface-based organization
- Inter-subject registration: anatomy, not intensity
- Smoothing
- Clustering
- 2D ReHo other than 3D ReHo



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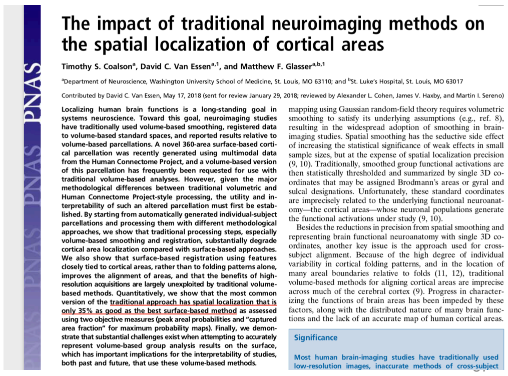
Based on Freesurfer Course

Why Surface-based Analysis



PNAS

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

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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

Why Surface-based Analysis

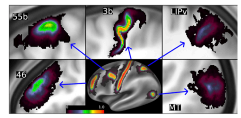
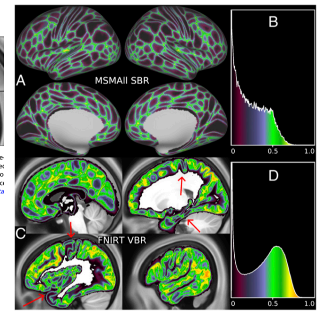
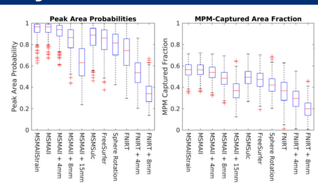


Fig. 1. Probabilistic maps for five areas using both MSMAll areal-feature-based surface registration and FNIRT volume alignment. The volume-basec peak probabilities are all lower than the surface-based probabilities fo these example areas. Each volume-based area is shown on a parasagittal slice through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



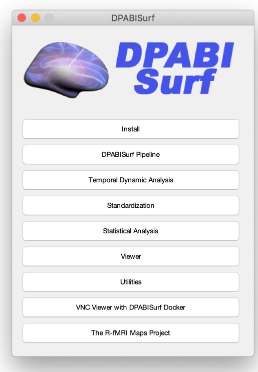
Coalson et al., 2018. PNAS

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



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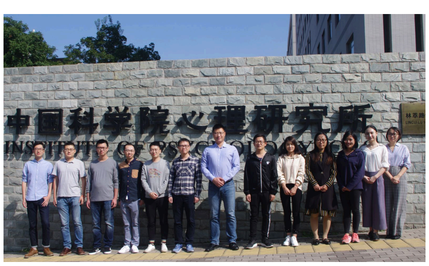

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Thanks for your attention!