Towards Better Treatment Guided by Neuroimaging for Major Depressive Disorder

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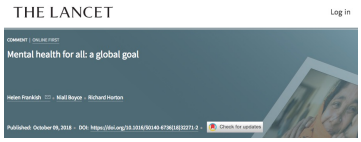
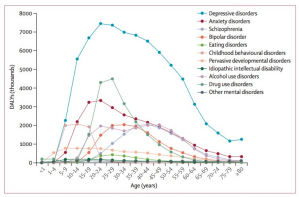
Global Health Crisis: MDD

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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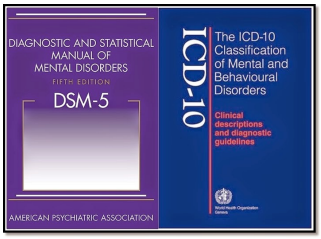
Diagnose of MDD



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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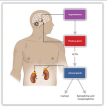
Biomarkers of MDD

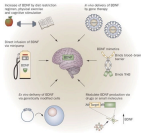
Proinflammatory cytokine?



HPA axis?

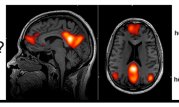
Cortisol?

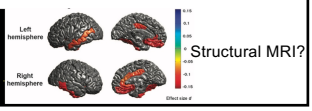
MDD



BDNF?

Functional MRI?





Structural MRI?

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A Case

A famous journalist: Jin Zhang

First visit: MDD → **Medicine A: suicidal ideation** → **Switch to Medicine B: turn to mania** → **Switch to Medicine C: recovery**

Diagnosed as bipolar disorder

Diagnose and treatment guided by brain imaging?

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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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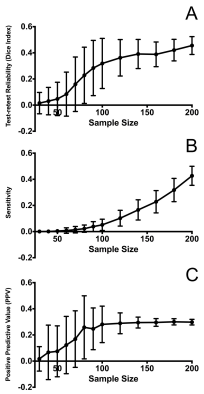
Sample Size

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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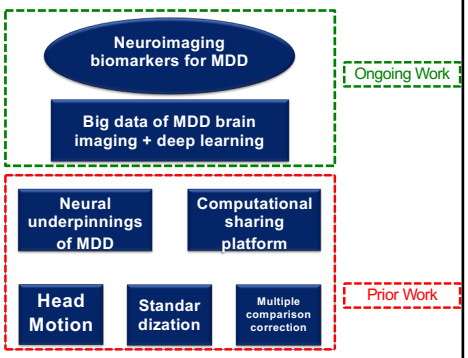
Roadmap for Applying fMRI in MDD



Validating fMRI methodology

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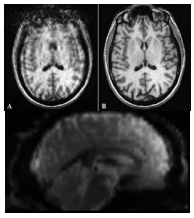
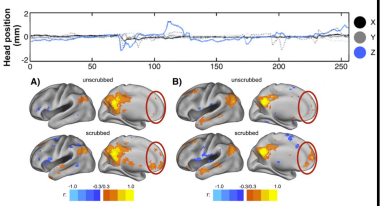
Methodological Issues: Head Motion





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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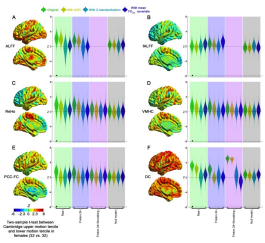
Methodological Issues: Head Motion



Proposed an effective head motion correction strategy

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

- Cited: 1095 times
- ESI Top 0.1% highly cited paper

Yan et al., 2013a. Neuroimage

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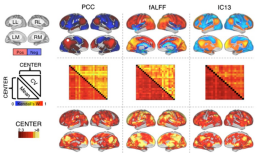
Methodological Issues: Standardization



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) (Kasthofer 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 (Harbstra 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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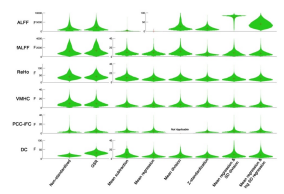
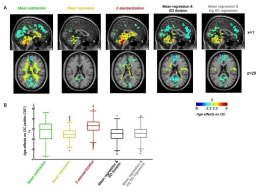
Methodological Issues: Standardization



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: 328 times
- ESI Top 1% highly cited paper

Yan et al., 2013b. Neuroimage

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Reproducibility and Multiple Comparison Correction

PNAS

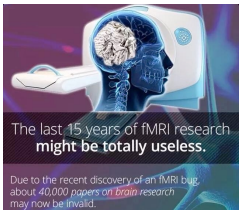
CrossMark

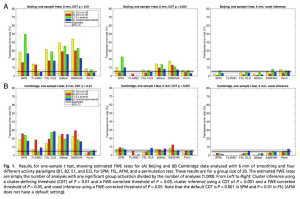
Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

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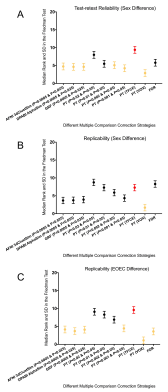
Reproducibility and Multiple Comparison Correction

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

Cite: 156 times
Ranked ESI Top 1% of highly cited papers



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

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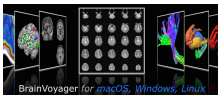
Traditional fMRI Preprocessing Toolbox

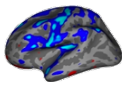
FSL

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 2704 times

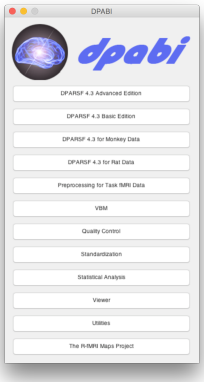
- Adapting methodological updates

Head motion (cited 1159 times)

Standardization (cited 340 times)

Multiple comparison correction (cited 176 times)

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



Yan et al., 2016. Neuroinformatics
Corresponding author

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Peer Evaluation

Cited by 1532 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.24260

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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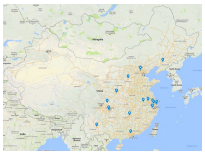
REST-meta-MDD

Started a consortium for big data sharing on MDD. Connected by the preprocessing pipeline, DPARSF, cited for over 2000 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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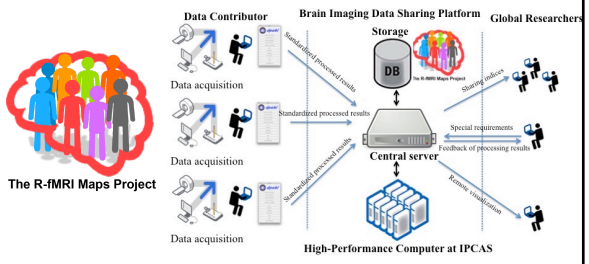
The R-fMRI Maps Project



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

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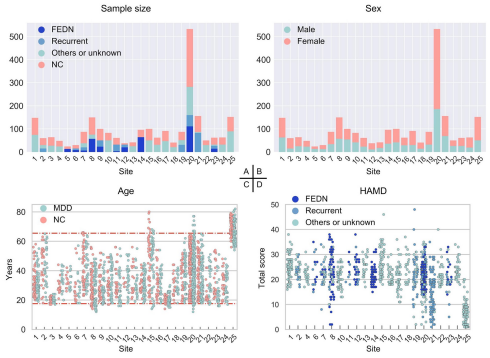
REST-meta-MDD



Yan et al., 2019, PNAS.

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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 na ïve
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 na ïve

Yan et al., 2019, PNAS.

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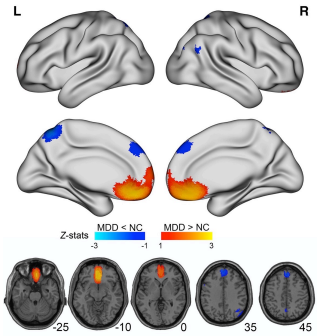
Meta-Analysis



Yan et al., 2019, PNAS.

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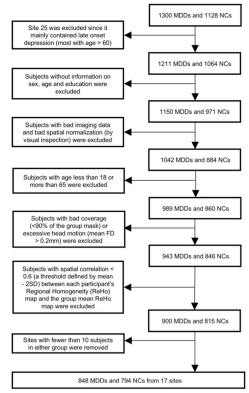
REST-meta-MDD



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

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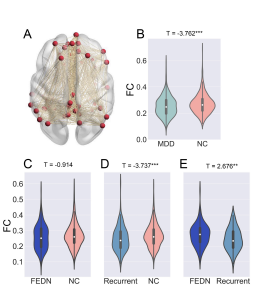
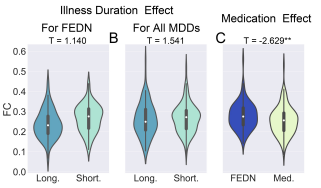
REST-meta-MDD





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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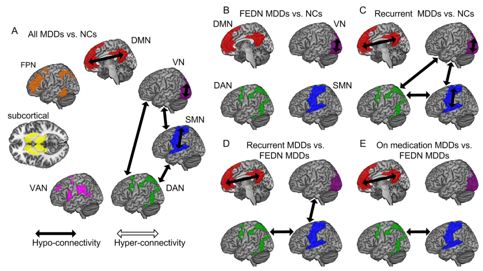
REST-meta-MDD



Yan et al., 2019, PNAS. 25

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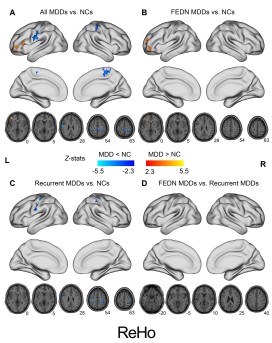
REST-meta-MDD



Yan et al., 2019, PNAS. 26

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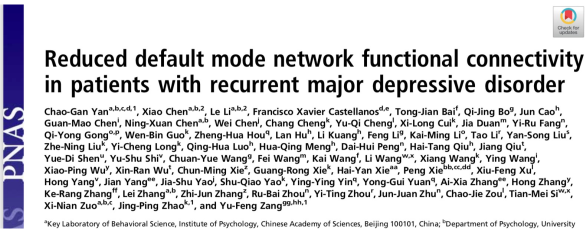
REST-meta-MDD



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

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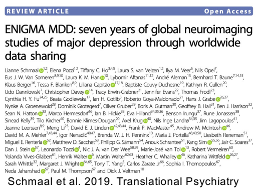
REST-meta-MDD

PNAS

- Cited 144 times
- ESI Top 1% Highly Cited

Lianne Schmaal
Chair of ENIGMA-MDD



REVIEW ARTICLE Open Access

ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing

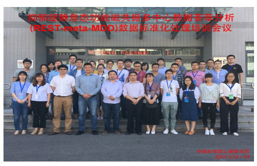
Schmaal et al. 2019. Translational Psychiatry

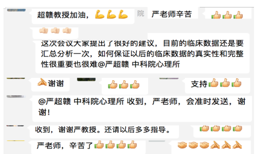
ENIGMA MDD. Many research institutions in China have shared neuroimaging data from individuals with depression with the REST-meta-MDD consortium, which has recently published the first large-scale mega-analysis on resting state functional MRI data of 1300 depressed patients and 1128 healthy controls from 25 research groups in China[129]. Future collaborations between the ENIGMA MDD and REST-meta-MDD consortia will be important for identifying potential cultural differences in brain alterations associated with MDD.

Yan, et al., 2019. PNAS 28

28

REST-meta-MDD





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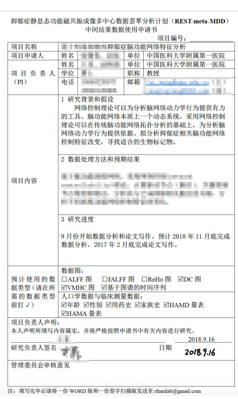
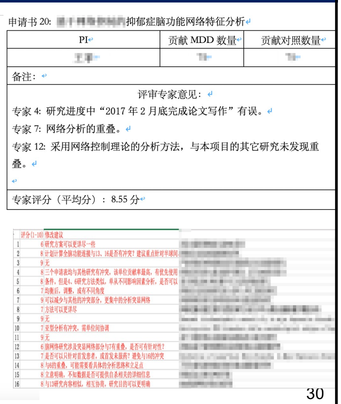
REST-meta-MDD





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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图化研究	湘雅二医院
3	严重抑郁症内侧前脑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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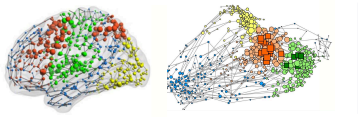
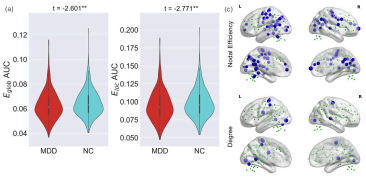
Disrupted Intrinsic Functional Brain Topology in MDD



The functional connectivity of depression brain was decreased，then how about the topological properties?



Hong Yang

Yang et al., 2021. Molecular Psychiatry.

Degreased global efficiency and local efficiency

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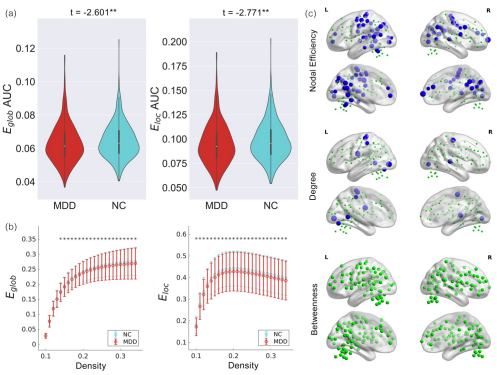
Disrupted Intrinsic Functional Brain Topology in MDD



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Dis tional Brain Topology in MDD

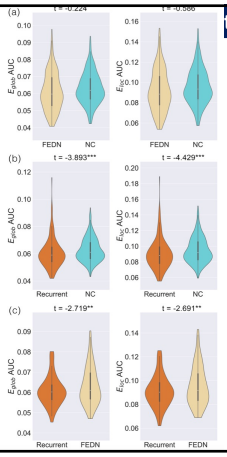

Figure 2. Subgroup differences in network topological properties (efficiency, E_{glob}, and local efficiency, E_{loc}). Distributions of areas under the curve (AUCs) are depicted. (a) First episode drug naïve (FEDN) major depressive disorder (MDD) patients vs. normal controls (NCs). (b) Patients with recurrent MDD vs. NCs. (c) FEDN patients vs. recurrent patients with MDD. **: p < 0.01, ***: p < 0.001.

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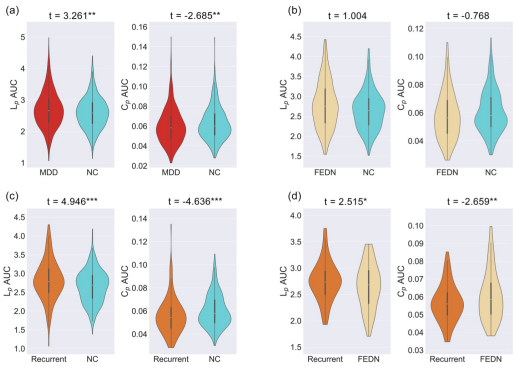
Disrupted Intrinsic Functional Brain Topology in MDD



Confirmatory metrics (path length and clustering coefficient)

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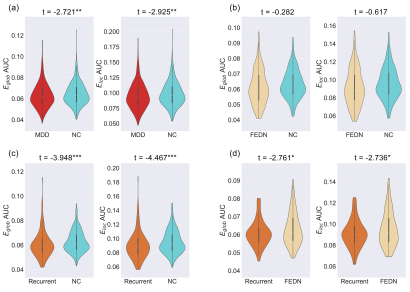
Disrupted Intrinsic Functional Brain Topology in MDD



Scrubbing

Supplementary

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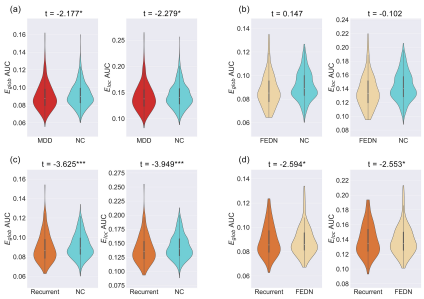
Disrupted Intrinsic Functional Brain Topology in MDD



Craddock's 200 functional clustering atlas

Supplementary

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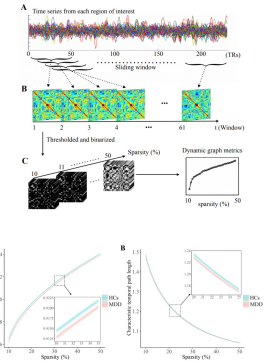
REST-meta-MDD Progress



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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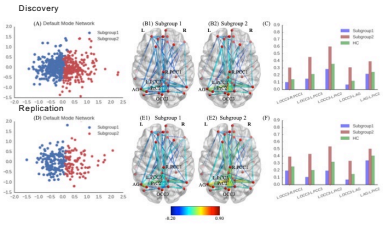
REST-meta-MDD Progress



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

39

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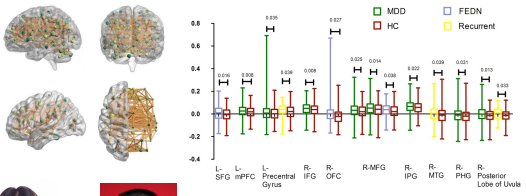
REST-meta-MDD Progress

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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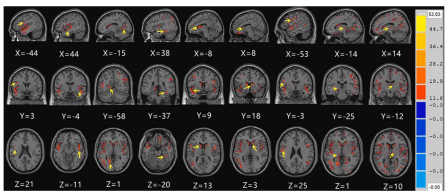
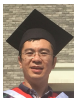
REST-meta-MDD Progress

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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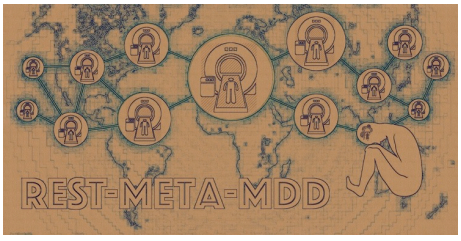
Open Access of REST-meta-MDD Data



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

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Open Access of REST-meta-MDD Data

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58	杨丽珠	yanglizhu@public.bta.net.cn	杨丽珠	yanglizhu@public.bta.net.cn	河北师范大学	2020.05.28

REST-META-MDD

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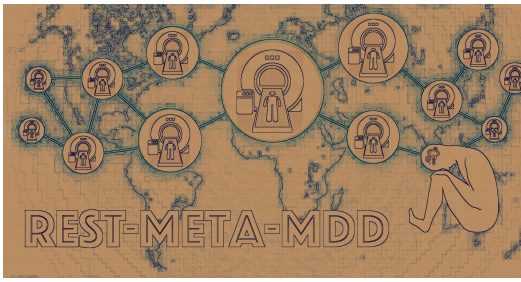
International Collaboration



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International Collaboration

第一届抑郁症脑成像国际会议暨抑郁症大数据国际研究中心成立仪式
The 1st International Conference on Brain Imaging of Depression & founding ceremony of the International Big-Data Center for Depression Research (IBCDR)
2019.07.28 · Beijing

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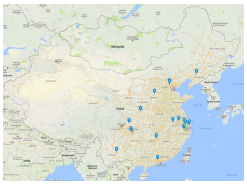
International Collaboration

International Conference on Brain Imaging of Depression



Cross-culture MDD data collection?

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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 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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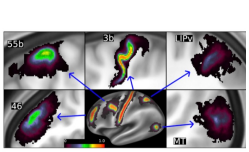
Why Surface-based Analysis



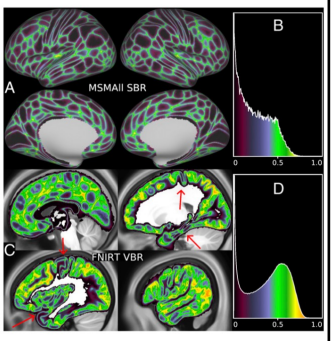


Fig. 1. Probabilistic maps for five areas using both MSMAll areal-feature-based surface registration and FNIRT volume alignment. The volume-based peak probabilities are all lower than the surface-based probabilities for these example areas. Each volume-based area is shown on a paraxagittal slice through the peak volumetric probability. See *SI Appendix, Supplemental Methods M2 and M3*. Data are available at https://balsa.wustl.edu/kK0Z.

Coalson et al., 2018. PNAS

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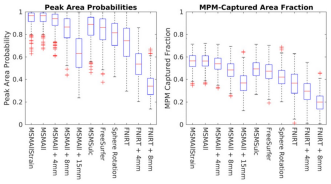
Why Surface-based Analysis



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

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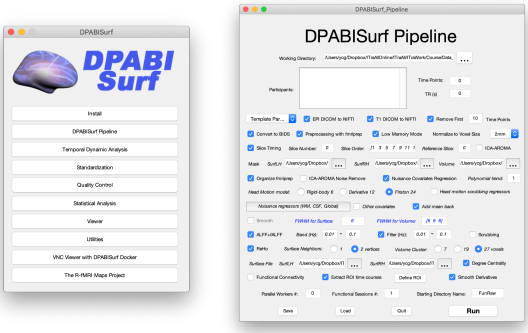
Go to Surface



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

Yan et al., 2021. Science Bulletin

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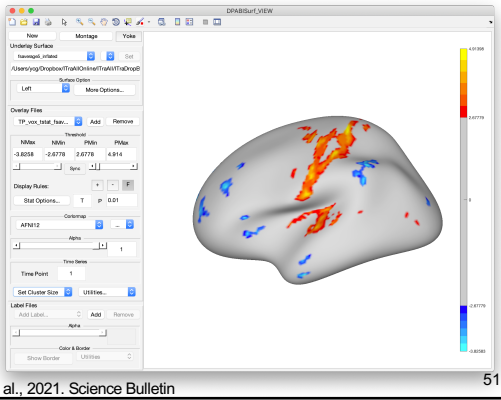
Go to Surface



Yan et al., 2021. Science Bulletin

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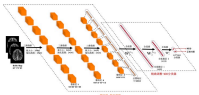
Ongoing Studies

Specificity? MDD, Bipolar Disorder, Schizophrenia?

Vertex-wise surface based cross culture MDD study



Deep Learning?

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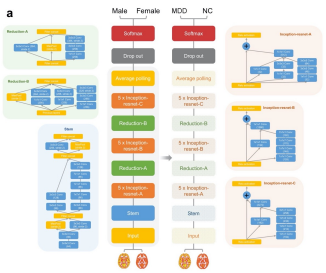
Transfer Learning



Sex Classifier: 80000 MRI Samples

Depression Classifier: 8000 MRI Samples

Classify the sex of a participant from brain structural imaging from anybody and any scanner with about 95% accuracy
Lu, …, Yan*, Under review

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Data Application

Full Name of Dataset	Abbreviation	Number of T1 Scans	Age (mean±std)	Number of Subjects	Number of Sites/Scanners
Adolescent Brain Cognition Development	ABCD	31176	13.76±10.08	11875	21
UK Biobank	UKB	20124	63.1±7.46	20124	4
Alzheimer's Disease Neuroimaging Initiative	ADNI	16596	74.97±7.4	2546	57
Open Access Series of Imaging Studies	OASIS	3150	67.54±20.64	1664	(5 Scanners)
REST-meta-MDD sample	MDD	2380	36.2±15.11	2380	17
Brain Genomics Superstruct Project	GSP	1570	21.54±2.89	1570	2
Human Connectome Project	HCP	1267	/	1267	1
Autism Brain Imaging Data Exchange	ABIDE	1102	17.09±8.06	1102	17
Autism Brain Imaging Data Exchange II	ABID2	1043	15.16±9.39	1043	19
1000 Functional Connectomes Project	FCP	897	25.8±10.76	897	33
ADHD-200 Sample	ADHD	876	12.35±3.28	876	8
Consortium for Reliability and Reproducibility	CORR	714	23.45±12.31	715	2
Cambridge Centre for Ageing Neuroscience (Cam-CAN)	CamC	652	54.36±18.55	652	1
Enhanced Nathan Kline Institute – Rockland Sample	NKIen	646	38.63±21.21	646	1
Southwest University Longitudinal Imaging Multimodal	SLIM	586	20.1±1.3	586	1
Child Mind Institute Healthy Brain Network	CMI	572	10.74±3.65	572	3
Establishing Moderators and Biosignatures of Antidepressant R	EBAC	540	/	540	4
Southwest University Adult Lifespan Dataset	SALD	493	45.16±17.45	493	1
Max Planck Institute Leipzig Mind-Brain-Body Dataset	MPI	316	/	316	1
Beijing Enhanced Sample	Beln	180	21.22±1.94	180	1
Enhanced Nathan Kline Institute – Rockland Sample	NKI	167	35.59±20.71	167	1
The Center for Biomedical Research Excellence	COBRE	147	/	147	1
The Age-ility Project	AGE	110	21.87±5.39	110	1
Parkinson's Disease Datasets	PDD	68	66.18±7.58	68	2
Power et al., 2012 Neuroimage Sample	POWER	63	14.25±6.05	63	1 (2 scanners)
NYU Institute for Pediatric Neuroscience	NYUpe	47	30.4±8.98	47	1
Beijing Eyes Open Eyes Closed Sample	EOEC	46	22.54±2.18	46	1
Multi-Modal MRI Reproducibility Resource	KARBY	42	31.76±9.35	42	1
Adelstein et al., 2011, PLoS ONE Sample	ADEL	39	29.59±8.38	39	1
Cleveland CCF	CCF	31	43.55±11.14	31	1
Virginia Tech Carilion Research Institute	VTC	25	26.84±8.17	25	1 (3 scanners)
Beijing Short TR Sample	BJTR	24	23.71±6.74	24	1
FIND Lab sample	FIND	13	24.08±3.73	13	1
The Midnight Scan Club dataset	MSC	10	29.1±3.35	10	1
		85712		50876	

34 Datasets, 50876 subjects, 85712 sMRI samples

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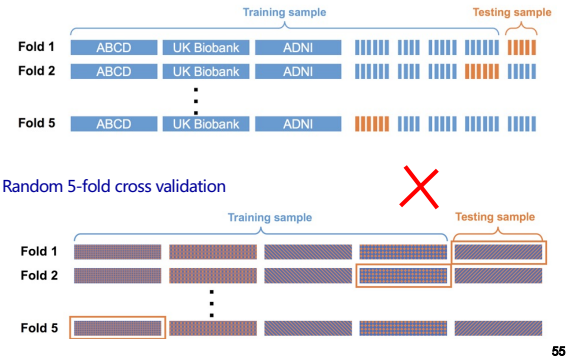
Cross Validation

Cross dataset 5-fold cross validation



Random 5-fold cross validation

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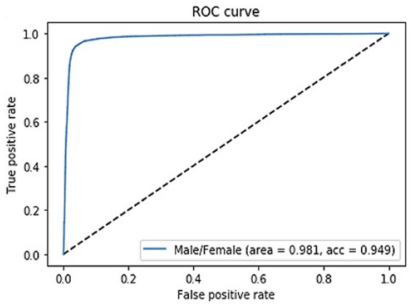
Sex Classifier Performance



Accuracy: 94.9%

The model can classify the sex of a participant with brain structural imaging data from anybody and any scanner with about 95% accuracy

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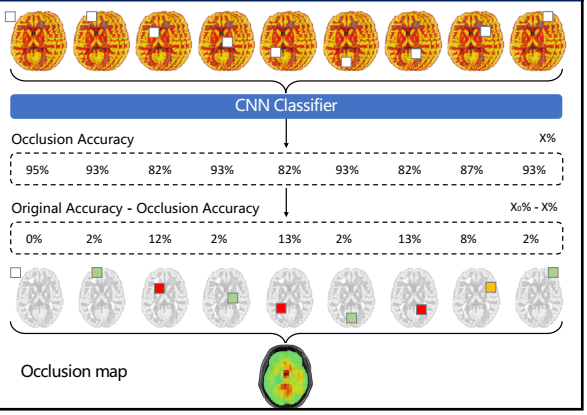
Model Interpretation



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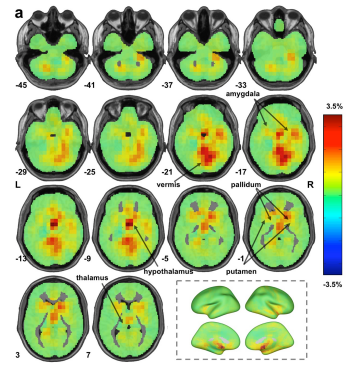
Sex Model Interpretation



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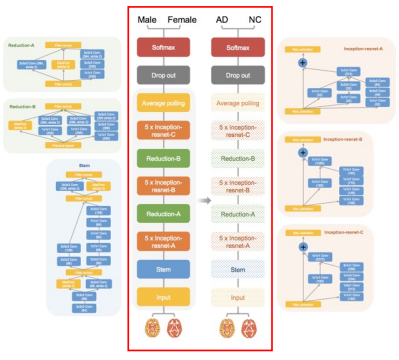
Transfer to AD



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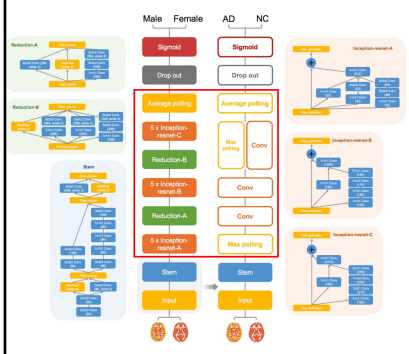
Less is more?



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Cross Validation

Cross site 5-fold cross validation

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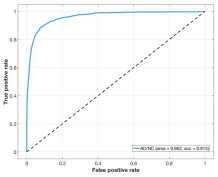
AD Classifier Performance

ADNI
(2,186 AD samples and 4,671 NC samples)



AUC: 96.2%
Accuracy: 91.3%
Sensitivity: 84.8%
Specificity: 94.3%

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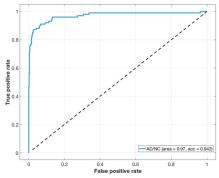
Independent Validation

AIBL
(101 AD samples and 523 NC samples)



AUC: 97%
Accuracy: 94.2%
Sensitivity: 88.1%
Specificity: 95.4%

63

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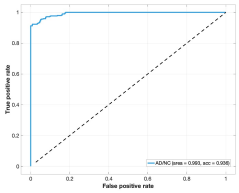
Independent Validation

MIRIAD
408 samples from 45 AD patients and 235 samples from 44 NCs



AUC: 99.3%
Accuracy: 93.6%
Sensitivity: 89.7%
Specificity: 100.0%

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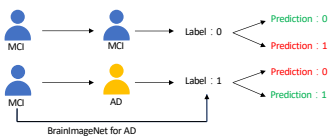
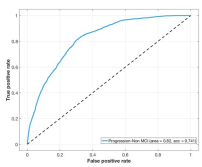
MCI prognosis





Direct Test AD classifier on MCI data

- 65.2% who finally converted into AD were predicted as AD
- 20.6% who did not convert into AD were predicted as AD

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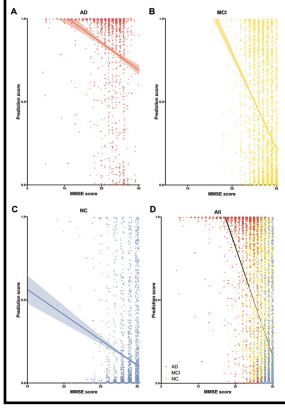
Model Interpretation



MMSE vs. Classifier Output Score

- AD (r=-0.3186, p<1×10^{-40})
- MCI (r=-0.1086, p<1×10^{-10})
- NC (r=-0.4079, p<1×10^{-188})
- All Sample (r=-0.5787, p<1×10^{-188})

More Severe, Classifier Output Score higher !

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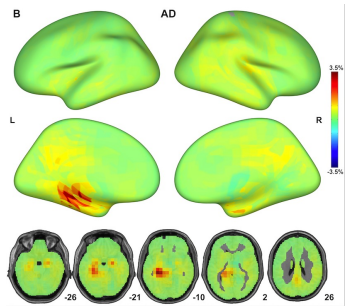
Model Interpretation



Occlusion map

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Other Models

Table 2. Performance of the Alzheimer's disease classifier

Base-model	Feature	Dataset	Accuracy	AUC	Sensitivity	Specificity
Sex classifier	GMV+GMD	ADNI	0.913	0.962	0.848	0.943
		AIBL	0.942	0.970	0.881	0.954
		OASIS	0.905	0.969	0.903	0.905
		MIRIAD	0.936	0.993	0.897	1.000
Sex classifier	GMD	ADNI	0.879	0.940	0.775	0.932
		AIBL	0.941	0.952	0.802	0.967
		OASIS	0.906	0.945	0.791	0.922
		MIRIAD	0.944	0.990	0.959	0.919
Sex classifier	GMV	ADNI	0.903	0.960	0.830	0.936
		AIBL	0.944	0.965	0.861	0.960
		OASIS	0.861	0.949	0.866	0.860
		MIRIAD	0.917	0.991	0.895	0.953
Sex classifier	T1-weighted	ADNI	0.886	0.928	0.766	0.910
		AIBL	0.947	0.961	0.822	0.971
		OASIS	0.730	0.940	0.918	0.704
		MIRIAD	0.938	0.991	0.936	0.940
Age prediction	GMV+GMD	ADNI	0.901	0.957	0.814	0.942
		AIBL	0.950	0.965	0.881	0.964
		OASIS	0.892	0.965	0.866	0.896
		MIRIAD	0.942	0.995	0.907	1.000

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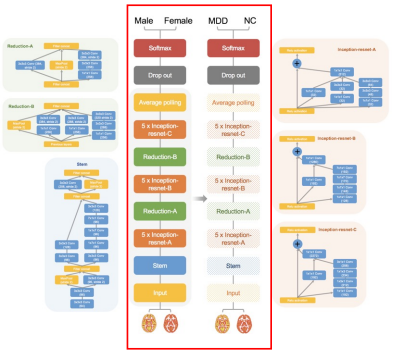
Transfer to Depression



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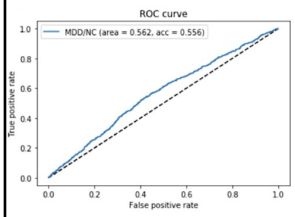
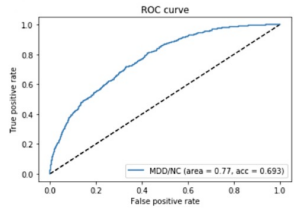
MDD Classifier Performance



Cross site 5-fold cross validation
Accuracy**56.2%**



Random 5-fold cross validation
Accuracy : **69.3%**

Not Good Yet!

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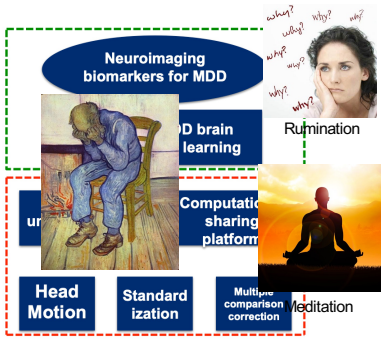
Roadmap for Applying fMRI in MDD



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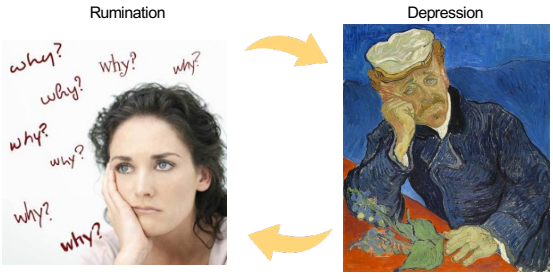
Rumination



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

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Koster et al., 2011. Clinical Psychol Rev

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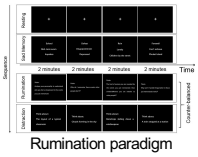
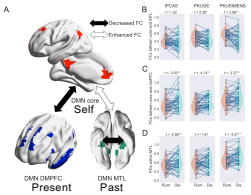
Rumination and Subsystems of DMN



Rumination paradigm

Psychological Process



Zhou et al., 2020. Neuroimage. (ESI Top 1% Highly Cited)

Chen et al., 2020. Neuroimage

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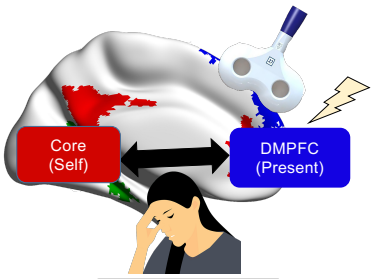
Depression and Rumination



Depressive Rumination

Zhou et al., 2020. Neuroimage. (ESI Top 1% Highly Cited)
Chen et al., 2020. Neuroimage

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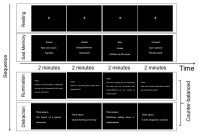
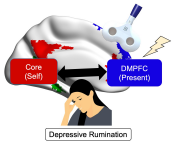
Future Directions



Rumination paradigm



Peak during rumination

TMS treatment

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心花计划
2021-2030

To live a joyful life!

"Mind Flower Project"
Institute of Psychology, CAS

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Mind Flower Project

- **Develop biomarkers based on neuroimaging and other research modalities for diagnosis and subtyping**
- **Explore next-generation psychotherapy based on traditional Chinese culture**
- **Develop novel neuromodulation therapies beyond antidepressant medication**

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心花计划
2021-2030

IPCAS

Moderate depression
Genetic, immune, neuroimaging
Behavior test, questionnaires
Psychotherapy, neuromodulation
Referred to hospitals
10 year follow-up

Hospitals

Severe depression
Genetic, immune, neuroimaging
Structured clinical interview
Antidepressant medication
Neuromodulation
Referred to therapists
Continuous follow-up

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Mind Flower Project: Protocol


Community


Screen through questionnaire/phone call


N = 120


Baseline:
MRI Scan
Questionnaires


Psychotherapy (Phase I)
("Kong" therapy)
Neuromodulation (Phase II)


Follow-up:
MRI Scan
Questionnaires

All participants will enter long-term follow-up

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Wearable Device

Standard

- **Size**
  - Terminal: 48.5mm×36.5mm×14mm
  - Wristband: 25mm×260mm
  - Weight: 20g
- **battery**
  - Standby time：168 h
  - Work time：48 h
  - Recharge time：2-3 h
- **Data transmission**
  - Bluetooth 4.0
  - USB
- **Memory size**
  - 256M
  - Can collect data for 120 h

Sensor

- **Pulse: PPG**
  - Frequency: 100Hz
- **Electrical resistance of the skin: EDA**
  - Frequency: 4Hz
- **Acceleration**
  - Frequency: 20Hz
- **Temperature**
  - Frequency: 1Hz
- **Event marker**
  - Subject can mark the events

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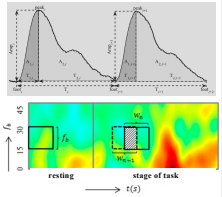
Wearable Device

PPG	Time Domain	Heart Rate
		HRV: SDNN, RMSSD, N20, N50
	Frequency Domain	PSD_LF, PSD_HF, LHR
EDA	Time Domain	SCL
		SCR
Acceleration	Time Domain	ACC
		GYRO



References:

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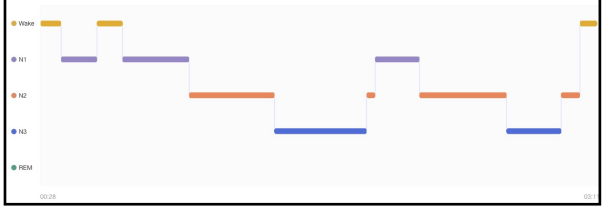
Sleep Monitor

EEG based



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"Kong" Therapy

I. Static tasks	II. Dynamic tasks
1. Relax	6. Relax
2. Determine target syndrome	7. Clean and put
3. Imagine symbol	8. Move to "Kong"
4. Imagine carriers	9. Move back and evaluate
5. Fill in sheet A	10. Fill in sheet B

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"Kong" Therapy

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Therapists of Mind Flower Project

Supervisor therapist

Tian-Jun Liu

Level A therapist

Xiao-Dong Feng, Fei Gao, Yi-Han He, Chong Liang, Ya-Qi Liang, Di Long, Min Shang, Xiao-Jun Sun, Xuan Wang, Wei Xu, Ya-Qing Yang, Xin-Yuan Zhou

Level B therapist

Qiao-Wei Cui, Su-Lan Dong, Lin-Xuan Gong, Shuang Han, Li Mao, Man Mao, Ya-Nan Niu, Ying-Peng Song, Jing Tian, Zhe Yang, Fu-Zhen Zhang, Ying-Bo Zhang

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Recruitment and Screening

Screen through questionnaire/ phone call

Clinical Sample

- Inclusion criteria
1. Age: 18-35 years
2. Meeting DSM-5 criteria for a major depressive episode with a diagnosis of major depressive disorder and are current taking antidepressant medication
3. Fluent and literate in Chinese
4. Written, informed consent
5. fMRI scanning eligibility

- Exclusion criteria
1. Meeting DSM-5 criteria for any other psychiatric disorders other than MDD
2. Severe impediment to vision, hearing and/or hand movement that is likely to interfere with ability to complete the assessments, or with comprehension of instructions or study requirements
3. Pregnant or breastfeeding
4. Any contraindication to being scanned in the 3.0T scanner (i.e., pacemaker or implanted device that has not been cleared for scanning)
5. Lifetime history of psychosis or psychotic ideation
6. Substance or alcohol abuse within the past 12 months
7. Presence of suicidal ideations representing imminent risk
8. Undergoing psychotherapy
9. A failure to respond to at least two previous antidepressant trials at adequate doses for 8 weeks
10. Unable to comply psychotherapy

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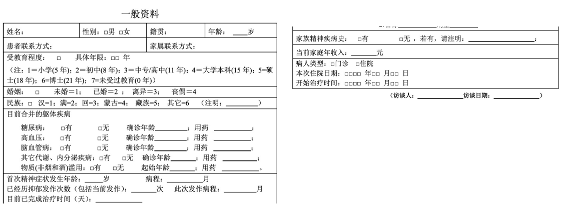
Structured Clinical Interview

Structured clinical interview: Informed consent and phenotypic information



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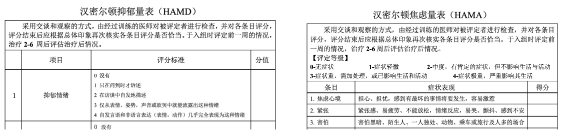
Structured Clinical Interview

Structured clinical interview: HAMD and HAMA



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MRI Acquisition Details

Scan: Baseline

T1-weighted 5m → Resting-state fMRI 10m → Think-aloud fMRI 10m → Gap → T2-weighted 5m → Rumination state fMRI 24m → DTI 11m

Scan: After therapy starts working

Resting-state fMRI 10m → Think-aloud fMRI 10m → Rumination state fMRI 24m

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MRI Acquisition Details

Scan: Follow-up

T1-weighted 5m → Resting-state fMRI 10m → Think-aloud fMRI 10m → Gap → T2-weighted 5m → Rumination state fMRI 24m → DTI 11m

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Questionnaires

Serial Number	Scale	Number of items
1	Ruminative Response Scale	22
2	Toronto Alexithymia Scale	38
3	Beck Depression Inventory	21
4	Subjective Social Class Test	1

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Questionnaires

Serial Number	Scale	Number of items
1	Insomnia Severity Index	7
2	Profile of Mood States	40
3	Subjective Units of Distress Scale	1
4	General Self-Efficacy Scale	10
5	Mindful Attention Awareness Scale	15
6	Body Perception Questionnaire	46
7	Intolerance of Uncertainty Scale	12
8	Consummatory subscale of TEPS	18
9	Cognitive Failures Questionnaire	25
10	Behavioral Activation/Inhibition Scale	20
11	Psychological Flexibility Questionnaire	15
12	Childhood Trauma Questionnaire	28

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Questionnaires

Serial Number	Scale	Number of items
1	Life Event Scale	50
2	big five personality scale	40
3	Self-Rating Scale of Systemic Family Dynamics	23
4	Dialectical Thinking Scale	33
5	Analysis-Holism Scale	25
6	Analysis-Holism thinking style task	14
7	Sensitivity to Punishment and Reward Questionnaire	35

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Questionnaires (Follow-up)

Serial Number	Scale	Number of items
1	Ruminative Response Scale	22
2	Insomnia Severity Index	7
3	Subjective Units of Distress Scale	1
4	General Self-Efficacy Scale	10
5	Mindful Attention Awareness Scale	15
6	Body Perception Questionnaire	46
7	Beck Depression Inventory	21

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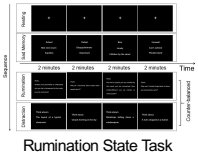
TMS (Phase II)



Rumination State Task

Looking for DMPFC region showing the largest reduction in FC during rumination

TMS guided by individualized target

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How to Participate

Welcome to join Mind Flower Project!

心花计划

http://ibcdr.psych.ac.cn/MindFlower

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Collaboration is Welcome

CCTV Documentary

BRTV Documentary

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Further Help

The R-fMRI Course V3.0

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http://rfmri.org/wiki

The R-fMRI Journal Club

Official Account: RFMRILab

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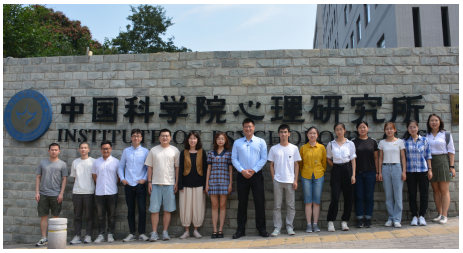
Acknowledgments



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Thanks for your attention!

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