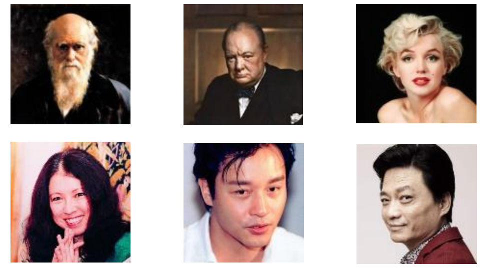
基于脑影像大数据的抑郁症神经机制与生物学指标

Chao-Gan YAN, Ph.D.
严超赣

yancg@psych.ac.cn
http://rfmri.org
International Big-Data Center for Depression Research
Institute of Psychology, Chinese Academy of Sciences

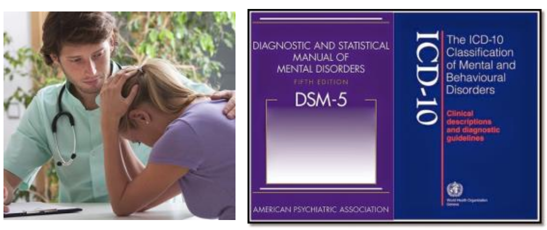
全球健康危机：抑郁症



- 全球有3亿抑郁症患者(WHO, 2020)
- 中国抑郁症患病率为3.4% (Huang et al., 2019, Lancet Psychiatry)
- 中国每年因抑郁症造成的经济损失高达494亿元（WHO, 2017）

2

抑郁症诊断



抑郁症主要诊断手段仍然依靠基于症状学的临床观察，亟需开发生物学客观标准

Oquendo et al., 2014. Depress Anxiety

3

抑郁症临床表现

- 情绪低落、心境抑郁
- 兴趣减退、愉悦感丧失
- 体重显著减少或增加
- 失眠或者睡眠过多
- 精神运动激越或迟滞
- 感到疲劳，缺乏精力
- 感到自己没有价值，或者自罪自贬
- 注意力和思考能力下降或犹豫不决
- 自杀念头、自杀计划或自杀行为

在连续两周的时间内，表现五项以上症状（前两项至少含一项）

4

抑郁症生物标记

典型案例

财新传媒副主编 张进

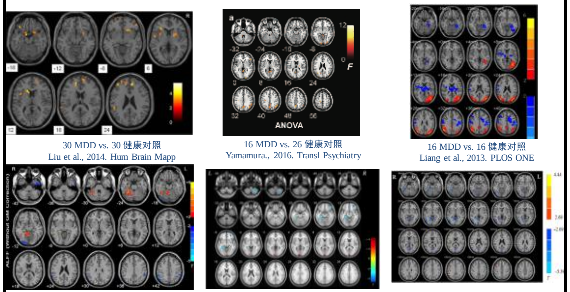
初诊为抑郁症 → 服用A药，抑郁想自杀 → 换用B药，转躁狂 → 确诊为双相障碍 → 换用C药，病情痊愈

脑影像学生物指标指导诊断和用药？

6

抑郁症脑影像研究现状

ALFF fALFF ReHo



30 MDD vs. 30 健康对照
Liu et al., 2014. Hum Brain Mapp

16 MDD vs. 26 健康对照
Yamamura., 2016. Transl Psychiatry

16 MDD vs. 16 健康对照
Liang et al., 2013. PLOS ONE

18 MDD vs. 18 健康对照
Wang et al., 2012. PLoS ONE

22 MDD vs. 19 健康对照
Liu et al., 2013. J Affect Dis

25 MDD vs. 25 健康对照
Liu et al., 2017. J Aff Dis

7

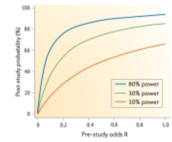
小样本研究遇到的问题

ANALYSIS

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

Katherine S. Button, John P. A. Ioannidis, Claire Mokrysz, Brian A. Nosek, Jonathan Flint, Emma S. J. Robinson and Marcus R. Munafò

Button et al., 2013. Nat Rev Neurosci



- 统计力不足时，发现的结果为真的可能性很小
- 神经科学领域统计力约为8%-31%

ANALYSIS

Scanning the horizon: towards transparent and reproducible neuroimaging research

Russell A. Poldrack, Chris I. Baker, Joke Durnez, Krzysztof J. Gorgolewski, ...

Poldrack et al., 2017. Nat Rev Neurosci

2015年，fMRI研究每组样本的中位数仅为19

8

小样本研究遇到的问题

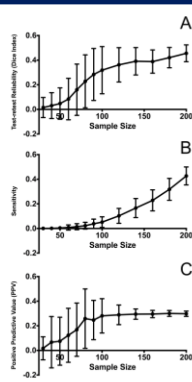
Xiao Chen

考察了样本量的影响

基对于被试间设计，样本量小于80的结论可靠性存疑

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

ESI Top 1% Highly Cited



9

抑郁症脑影像研究现状

ANALYSIS

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

Katherine S. Button, John P. A. Ioannidis, Claire Mokrysz, Brian A. Nosek, Jonathan Flint, Emma S. J. Robinson and Marcus R. Munafò

Button et al., 2013. Nat Rev Neurosci

ANALYSIS

Scanning the horizon: towards transparent and reproducible neuroimaging research

Russell A. Poldrack, Chris I. Baker, Joke Durnez, Krzysztof J. Gorgolewski, ...

Poldrack et al., 2017. Nat Rev Neurosci

- 样本量小，统计力不足
- 分析方法各异，研究发现相互抵触
- 分析方法不正确，假阳性高

暂时无法作为抑郁症诊断生物学指标！

10

抑郁症脑影像学应用于临床实践

抑郁症脑影像生物学指标

抑郁症脑影像大数据+深度学习

开展中工作

抑郁症脑机制研究

高效计算共享平台

头动

标准变换

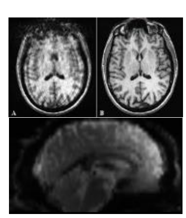
多重比较校正

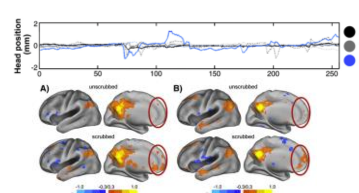
工作基础
2篇ESI Top 1‰
2篇ESI Top 1%

保证脑成像方法的有效可靠

11

解决脑影像方法学问题：头动





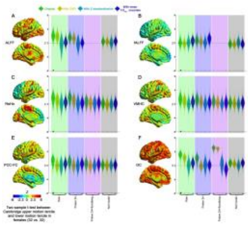
Power et al, 2012. Neuroimage
Van Dijk et al, 2012. Neuroimage

头动是静息态功能磁共振数据处理中重要的影响因素

头动伪迹控制亟需解决方案

12

解决脑影像方法学问题：头动



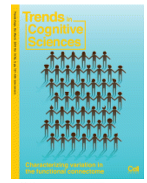
提出头动控制的解决方案

- 在个体水平上采用24头动参数回归模型进行校正
- 在组水平分析上进行头动协变量控制

- 被引1061次
- ESI Top 0.1%高被引论文

Yan et al., 2013a. Neuroimage

解决脑影像方法学问题：标准化



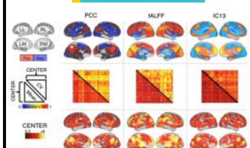


Table 1. Factors can introduce unintended variations in fMRI measurement.

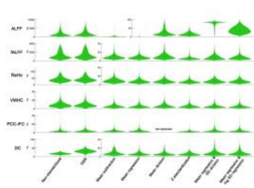
Category	Factor
1. Acquisition-related variations	Scanner make and model (Friedman and Glover, 2006b), sequence type (spiral vs. echo planar; single-echo vs. multi-echo) (Klarhofer et al., 2002), parallel vs. conventional acquisition (Feinberg et al., 2010; Lin et al., 2005), coil type (surface vs. volume,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

Yan et al., 2013b. Neuroimage

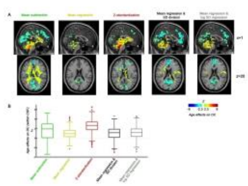
Biswal et al., 2010, PNAS

14

解决脑影像方法学问题：标准化



标准化对中心效应的影响



标准化对年龄效应的影响

提出了解决方案

- 均值回归 + 标准差商除

- 被引321次
- ESI Top 1%高被引论文

Yan et al., 2013b. Neuroimage

15

解决脑影像方法学问题：标准化

Yu-Wei Wang

更好地去除站点效应方法？

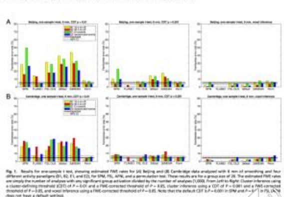
National Natural Science Foundation of China (81671774)

16

解决方法学问题：多重比较校正

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

Anders Eklund, Thomas E. Nichols, and Hans Knutsson



Eklund et al., 2016. PNAS

17

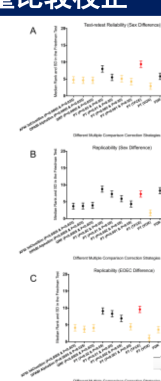
解决方法学问题：多重比较校正

Xiao Chen

以可重复性为指标，提出了多重比较校正的解决方案

基于无阈限团块增强的置换检验（permutation test with TFCE）这种多重比较校正方法，能够很好地将假阳性率控制在5%以下，并且具有最高的可重复性

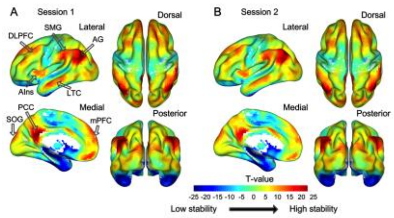
- 引用140次
- ESI Top 1%高被引论文



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

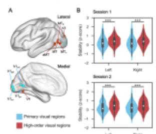
18

研发新方法：脑功能动态模式稳定性



内在功能稳定性的跨脑区分布模式

Le Li

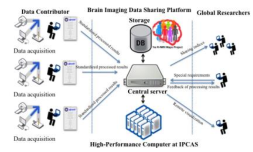


视觉高低级脑区的内在功能稳定性

Li, Lu, Yan*, 2019. Neuroimage

19

开发脑影像数据标准化分析软件平台



- 整合方法学解决方案
- 一键式脑影像处理软件DPARSF
- 多中心大数据协作平台DPABI

Neuroinformatics, 2016. 独立通讯作者，引用1173次，ESI前1‰高被引论文

Front Syst Neurosci, 2010. 第一作者兼共同通讯作者，引用2487次

20

同行评价及国际影响力

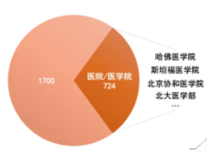
2015-2019年中国医学领域论文第十名

来自58个国家/地区的研究者使用DPARSF/DPABI合计发表3000余篇论文

软件使用者包括：

Seiji Ogawa
功能磁共振发明人

Bharat Biswal
静息态功能磁共振创始人



支持了724家医院/医学院的临床应用研究

21

抑郁症脑影像学应用于临床实践

抑郁症脑影像生物学指标

抑郁症脑影像大数据+深度学习

开展中工作

抑郁症机制研究

高效计算共享平台

头动

标准变换

多重比较校正

工作基础
2篇ESI Top 1‰
2篇ESI Top 1%

保证脑成像方法的有效可靠

22

建立全球最大抑郁症脑功能影像数据库

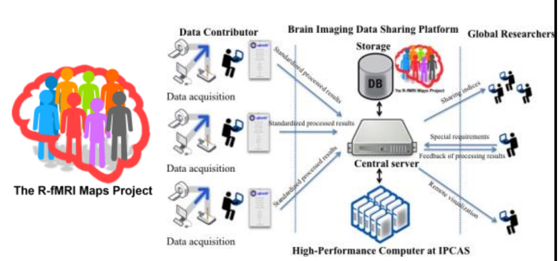
以他引共计2400余次的DPABI/DPARSF数据处理软件作为纽带，发起了抑郁症脑影像大数据联盟，展开多中心大数据研究

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

已成功累积1300例抑郁症患者与1128例正常对照数据，为全球最大的抑郁症脑功能影像数据库

23

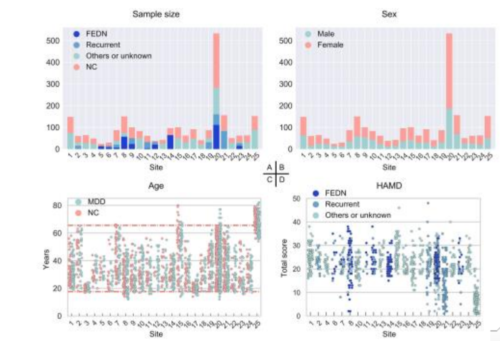
The R-fMRI Maps Project



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

24

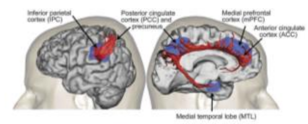
REST-meta-MDD



Yan et al., 2019, PNAS.

25

核心科学问题：抑郁症默认网络机制



大脑默认网络

抑郁反刍思维心理模式

- 默认网络是大脑中消耗能量最多的网络，与抑郁反刍思维紧密相关
- 反刍思维是对过去的悲伤事件本身及其原因和后果的反复咀嚼
- 研究瓶颈：抑郁症默认网络研究结果不一致，机制不清楚
- 突破点：
  - 1）改善脑影像方法，提高结果准确性
  - 2）开展大数据分析，提高结果可重复性
  - 3）揭示认知心理模式，明确抑郁症默认网络机制

Raichle et al., 2001. PNAS; Kaiser et al., 2015. JAMA Psychiatry; Scalabrini et al., 2020. Neuropsychopharmacology

26

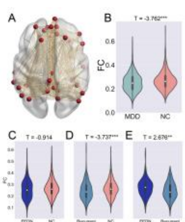
明确抑郁症患者默认网络功能连接降低

脑影像大数据

＋

- 高效去噪算法
- 有效的多中心标准化方法
- 可靠的高维统计方法

＝ 可重复性高的研究结果



PNAS

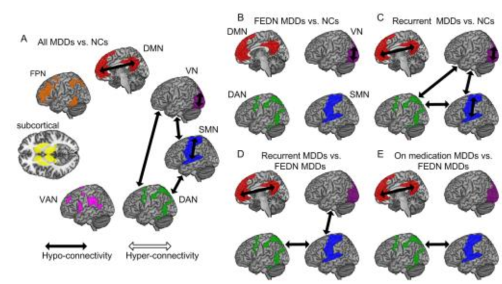
Reduced default mode network functional connectivity in patients with recurrent major depressive disorder

解决了关于默认网络功能连接在抑郁症中增加或减少的争论，为揭示抑郁症默认网络机制奠定了基础

PNAS, 2019. 独立第一作者兼共同通讯作者，ESI前1%高被引论文

27

抑郁症脑影像大数据研究



Yan, et al., 2019. PNAS

28

同行评价及影响

PNAS

- ➢ 被引103次
- ➢ ESI Top 1%高被引论文

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.

Lianne Schmaal
墨尔本大学教授
ENIGMA抑郁症工作组主席

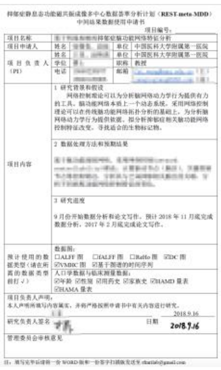
REST-meta-MDD联盟最近发表了首篇大规模的抑郁症静息态功能磁共振成像大数据分析…未来 ENIGMA-MDD 和 REST-meta-MDD 两个联盟的合作对于研究抑郁症大脑变化的文化特异性和共性至关重要。

29

REST-meta-MDD

30

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。

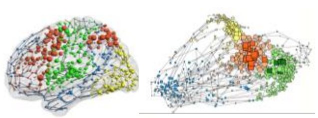
专家评分（平均分）: 8.55 分

31

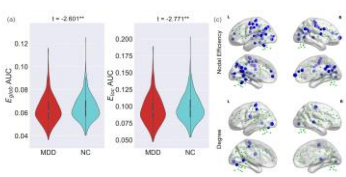
Proposals

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

发现抑郁症患者脑网络效率降低



抑郁症患者的节点间功能连接降低，那么所有节点组成的网络拓扑效率又如何呢？



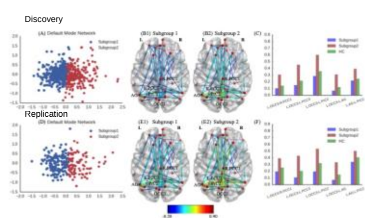
抑郁症患者的脑网络局部效率和全局效率均比正常对照显著降低

Hong Yang

Yang et al., 2021.
Molecular Psychiatry.
独立通讯作者

33

REST-meta-MDD Progress



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

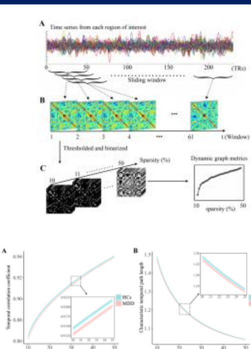
Su-Gai Liang

Tao Li

Liang et al., 2020.
Neuroimage:Clinical
共同通讯作者

34

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

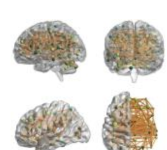
Zhe-Ning Liu

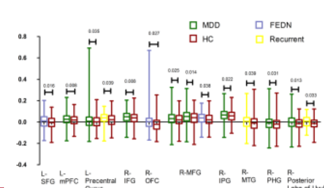
Long et al., 2020.
Neuroimage:Clinical

35

REST-meta-MDD Progress

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





Yu-Dan Ding

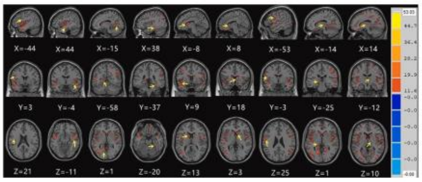
Wen-Bin Guo

Ding et al., 2021.
J Affect Disord.

36

REST-meta-MDD Progress

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

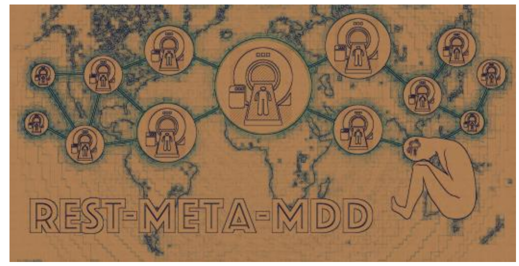



Peng-Hong Liu   Ke-Rang Zhang

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

37

International Collaboration



38

International Collaboration

39

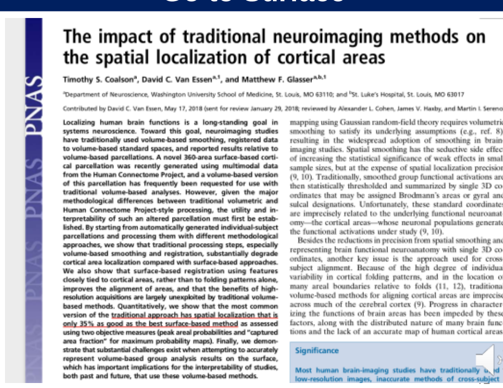
International Collaboration

International Conference on Brain Imaging of Depression


Cross-culture MDD data collection?

40

Go to Surface



PNAS

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

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

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

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

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

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

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

Significance

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

Why Surface-based Analysis

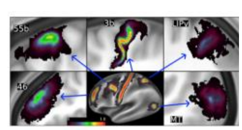
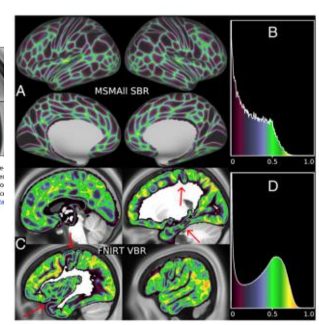


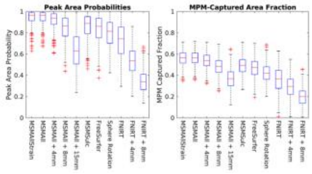
Fig. 1. Probabilistic maps for five areas using both MSMAll areal-feature-based surface registration and FNIRT volume alignment. The volume-based peak probabilities are all lower than the surface-based probabilities for these example areas. Each volume-based area is shown on a parasagittal slice through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



Coalson et al., 2018. PNAS

42

Why Surface-based Analysis

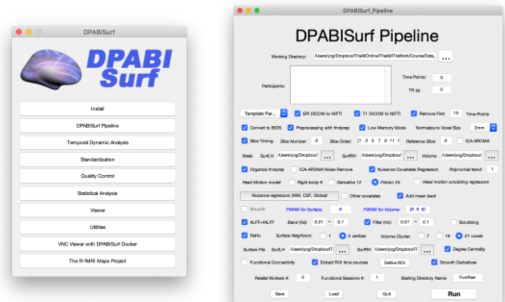


Widespread adoption of surface-based approaches has been slow: the desire to replicate or compare with existing studies that used the traditional volume-based approach; the relative lack of "turn-key" tools for running a surface-based analysis; the learning curve for adopting surface-based analysis methods;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

Coalson et al., 2018. PNAS

43

Go to Surface

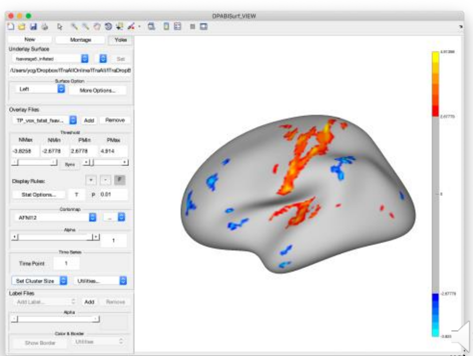


Based on fMRIPprep, FreeSurfer, ANTs, FSL, AFNI, PALM, GNU Parallel, MATLAB, Docker and DPABI.

Yan et al., 2021. Science Bulletin

44

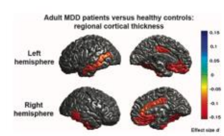
Go to Surface



Yan et al., 2021. Science Bulletin

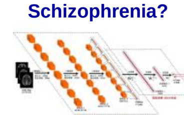
45

Ongoing Studies



Vertex-wise surface based cross culture MDD study

Specificity? MDD, Bipolar Disorder, Schizophrenia?



Deep Learning?

46

二维深度学习框架移植

性别分类任务：8万例脑成像数据

抑郁症分类任务：8千例脑成像数据

任何人在任何地方扫描的脑影像：
以 95% 的正确率判断男女
Lu, …, Yan*, Under review

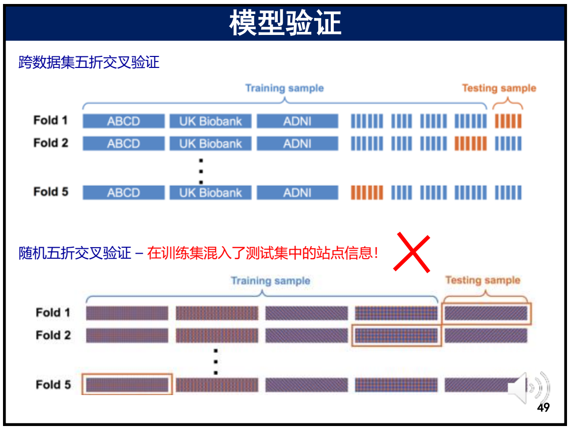
47

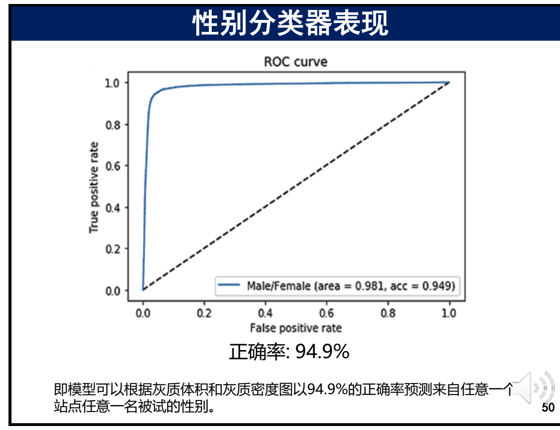
数据申请

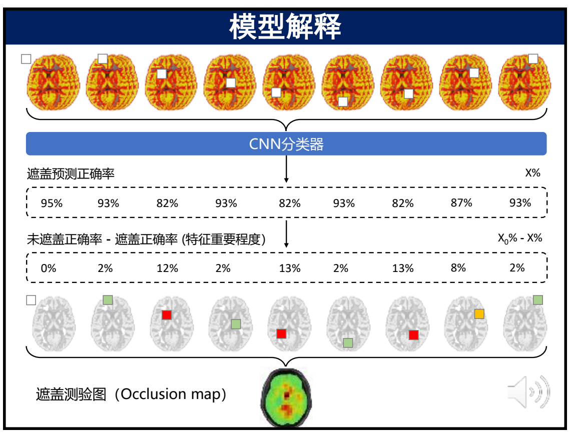
Full Name of Dataset	Abbreviation	Number of T1 Scans	Age (mean±std)	Number of Subjects	Number of Sites/Scanners
Adolescent Brain Cognition Development	ABCD	31176	13.76±10.08	11875	21
UK Biobank	UKB	20124	63.1±7.46	20124	4
Alzheimer's Disease Neuroimaging Initiative	ADNI	16596	74.97±7.4	2546	57
Open Access 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	Bjen	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	

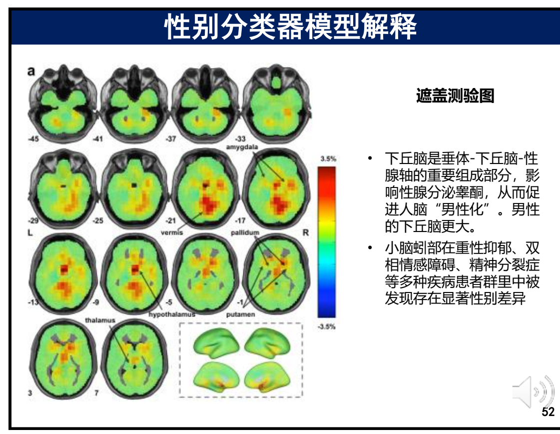
共计34个数据集，50876位被试，85712个结构像样本

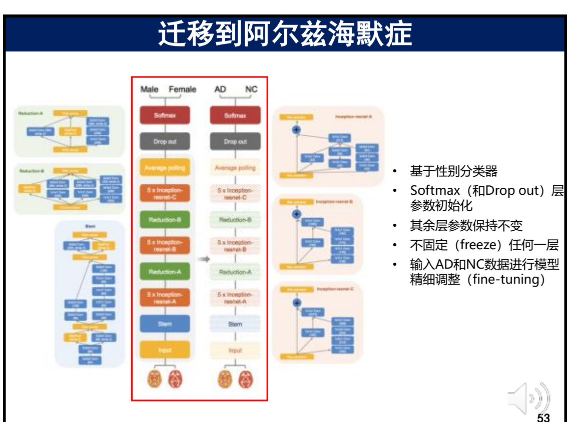
48

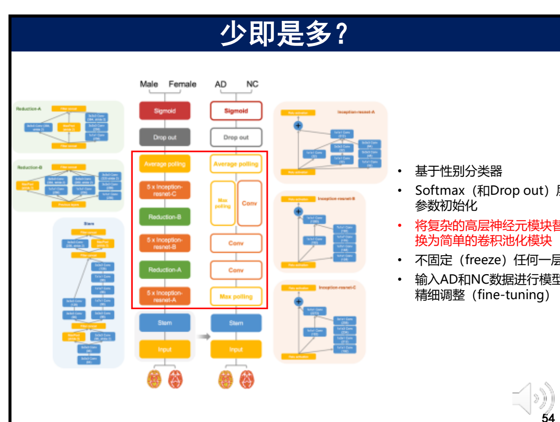

模型验证
跨数据集五折交叉验证
Training sample
Testing sample
Fold 1
Fold 2
Fold 5
ABCD
UK Biobank
ADNI
随机五折交叉验证 – 在训练集混入了测试集中的站点信息!
Fold 1
Fold 2
Fold 5
49


性别分类器表现
ROC curve
True positive rate
False positive rate
Male/Female (area = 0.981, acc = 0.949)
正确率: 94.9%
即模型可以根据灰质体积和灰质密度图以94.9%的正确率预测来自任意一个站点任意一名被试的性别。
50


模型解释
CNN分类器
遮盖预测正确率
X%
95% 93% 82% 93% 82% 93% 82% 87% 93%
未遮盖正确率 - 遮盖正确率 (特征重要程度)
X0% - X%
0% 2% 12% 2% 13% 2% 13% 8% 2%
遮盖测验图（Occlusion map）

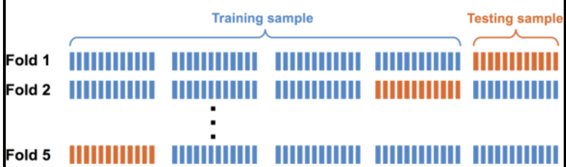

性别分类器模型解释
遮盖测验图
下丘脑是垂体-下丘脑-性腺轴的重要组成部分，影响性腺分泌睾酮，从而促进人脑"男性化"。男性的下丘脑更大。
小脑蚓部在重性抑郁、双相情感障碍、精神分裂症等多种疾病患者群里中被发现存在显著性别差异
amygdala
vermis
pallidum
thalamus
hypothalamus
putamen
52


迁移到阿尔兹海默症
Male Female
AD NC
基于性别分类器
Softmax（和Drop out）层参数初始化
其余层参数保持不变
不固定（freeze）任何一层
输入AD和NC数据进行模型精细调整（fine-tuning）
53


少即是多？
Male Female
AD NC
基于性别分类器
Softmax（和Drop out）层参数初始化
将复杂的高层神经元模块替换为简单的卷积池化模块
不固定（freeze）任何一层
输入AD和NC数据进行模型精细调整（fine-tuning）
54

模型验证

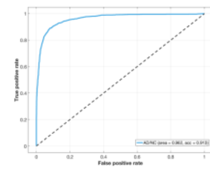
跨站点五折交叉验证



55

AD分类器表现

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

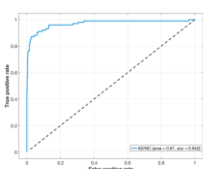


AUC: 96.2%
正确率: 91.3%
敏感度: 84.8%
特异性: 94.3%

56

独立样本验证

AIBL
(101 AD samples and 523 NC samples)

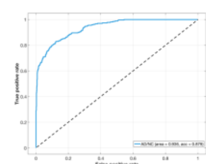


AUC: 97%
正确率: 94.2%
敏感度: 88.1%
特异性: 95.4%

57

独立样本验证

OASIS ½ (277 AD samples and 995 NC samples)
1) mini-mental state examination score between 20 and 26 (inclusive)
2) clinical dementia rating score = 0.5 or 1.0.



AUC: 93.6%
正确率: 87.9%
敏感度: 79.6%
特异性: 90.2%

58

AD分类器预测MCI预后

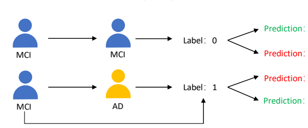
轻度认知障碍（Mild cognitive impairment, MCI）指一种不影响日常生活的认知能力下降的临床诊断。5年内会有一半MCI患者进展为AD患者。

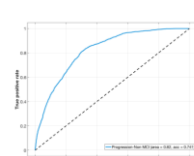
Serge et al., 2006. The lancet

59

AD分类器预测MCI预后

MCI预后预测示意图

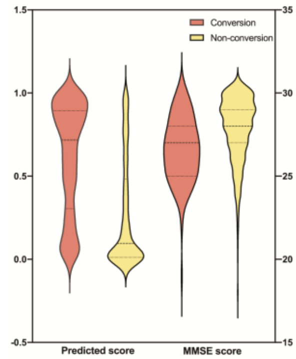




直接在MCI样本上测试AD分类器:
- （模型此前**并未**输入过MCI样本）
- 跟踪期内进展为AD的MCI被试中65.2%样本被预测为AD
- 跟踪期内未进展为AD的MCI被试中20.6%被预测为AD
- AD分类器有初步预测MCI预后的作用

60

AD分类器预测MCI预后



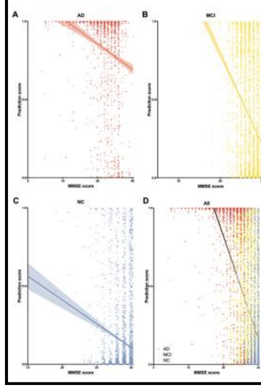
MMSE分数是衡量疾病严重程度的一个指标，分数越低越严重。

转化组MCI同未转化组MCI的双样本t检验：

- 分类器输出（Predicted score）：
  - 显著性：$p<1\times10^{-36}$
  - 效应量：Cohen's d=1.0298
- MMSE分数：
  - 显著性：$p<1\times10^{-14}$
  - 效应量：Cohen's d=0.6134

61

模型解释



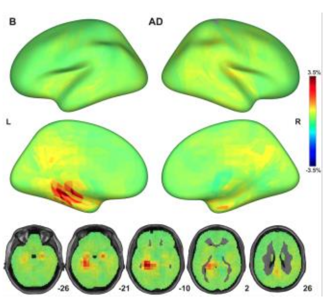
MMSE分数同AD分类器输出分数呈显著负相关

- AD样本（r=-0.3186, $p<1\times10^{-40}$）
- MCI样本（r=-0.1086, $p<1\times10^{-10}$）
- NC样本（r=-0.4079, $p<1\times10^{-188}$）
- 全部样本（r=-0.5787, $p<1\times10^{-188}$）

也即，疾病越严重，AD分类器输出分数越高！

62

AD分类器模型解释



遮盖测验图

- 海马和旁海马皮层是该模型用于分类最关键的脑区，也是AD患者脑萎缩最严重的区域，同AD病理学一致。
- 壳核和脑岛的萎缩在AD研究中也有报道。

63

其他模型

Table 2. Performance of the Alzheimer's disease classifier

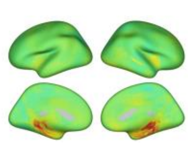
Base-model	Feature	Dataset	Accuracy	AUC	Sensitivity	Specificity
Sex classifier	GMV+GMD	ADNI	0.913	0.962	0.848	0.943
		AIBL	0.942	0.970	0.881	0.954
		OASIS	0.905	0.969	0.903	0.905
		MIRIAD	0.936	0.993	0.897	1.000
Sex classifier	GMD	ADNI	0.879	0.940	0.775	0.932
		AIBL	0.941	0.952	0.802	0.967
		OASIS	0.906	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

64

研究进展：云端阿尔茨海默病辅助诊断平台

http://brainimagenet.org/

- AD跨站点分类正确率：91.3%
- 独立大样本分类正确率：94.2%
- MCI转化：65.2% vs. 20.6%

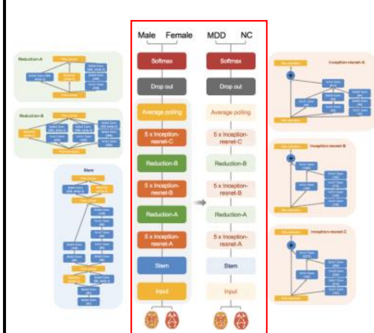


AD深度网络分类器的可解释性：遮挡（occlusion）测试

Lu, …, Yan*, Under review

65

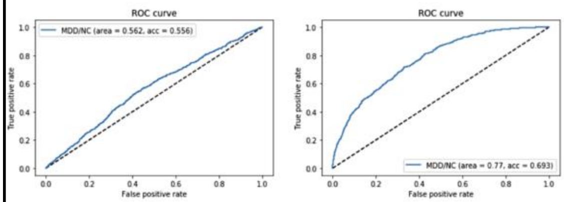
迁移到抑郁症



- 基于性别分类器
- Softmax（和Drop out）层参数初始化
- 其余层参数保持不变
- 不固定（freeze）任何一层
- 输入MDD和NC数据进行模型细调整（fine-tuning）

66

MDD分类器表现



跨站点交叉验证
正确率：**56.2%**

随机交叉验证
正确率：**69.3%**

总结：
1. MDD分类器表现不佳
2. 随机交叉验证结果优于跨站点交叉验证

49

大数据时代的小样本脑影像研究

Depression Model

抑郁症脑影像指标

影像大数据学习

Rumination

高效计算共享平台

头动

标准变换

Meditation

68

反刍思维研究

反刍思维

一种对负性情绪本身及其原因和可能后果的反复思考

例如：“这样的事情为什么偏偏发生在我的身上？”

“我究竟做了什么才导致这样的后果？”

反刍思维具有特别的形式特点：

- 自我强化
- 循环往复
- 往往持续时间很久

Susan Nolen-Hoeksema
(1959 – 2013)

Nolen-Hoeksema et al., 2008. Perspect Psychol Sci

69

反刍思维研究

反刍思维与MDD

具有反刍思维特质的个体在遭遇生活事件之后更容易陷入抑郁

反刍思维 ⇄ MDD

处于抑郁情绪影响下的个体反刍思维频率显著上升

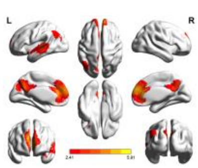
反刍思维不仅是伴随MDD的一种症状，可能也是导致抑郁发作的危险因素

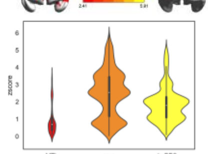
Koster et al., 2011. Clinical Psychol Rev

70

反刍思维研究

反刍思维任务态荟萃分析





Hui-Xia Zhou

Zhou et al., 2019. Neuroimage

71

反刍思维状态的脑网络机制

改进的“反刍思维状态”任务

方法学的改进

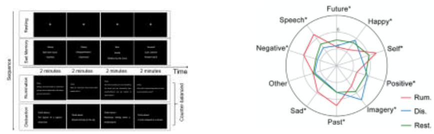
- 合理的样本量（每组N > 40）
- 被试内实验设计
- 多重比较矫正方法：尽量采用经过TFCE处理的置换检验

引导方式的改进：

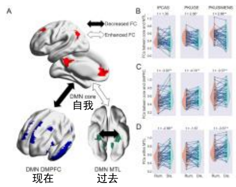
- 符合反刍思维定义的指导语：来自经典的反刍思维引导任务
- 加入预先的情绪引导：悲伤事件回忆
- 将整个心理状态拆分为时长合理（2 min）的小段

72

揭示抑郁反刍思维默认网络子系统机制



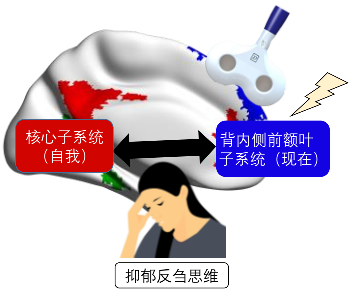
反刍思维任务态范式　　反刍思维认知心理过程



默认网络核心子系统与内侧颞叶子系统功能连接上升，与背内侧前额叶子系统功能连接减低

Neuroimage, 2020b. 独立通讯作者; 2020c. 独立通讯作者

提出抑郁症反刍思维默认网络新理论



Neuroimage, 2020b. 独立通讯作者; 2020c. 独立通讯作者

同行评价及国际影响力

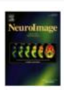
Rumination and the default mode network: Meta-analysis of brain imaging studies and implications for depression

By: Zhou, Hui-Xia; Chen, Xiao; Shen, Yang-Qian; et al.

NEUROIMAGE Volume: 206 Article Number: 116287 Published: FEB 1 2020

Times Cited: 31 (from All Databases)

Highly Cited Paper



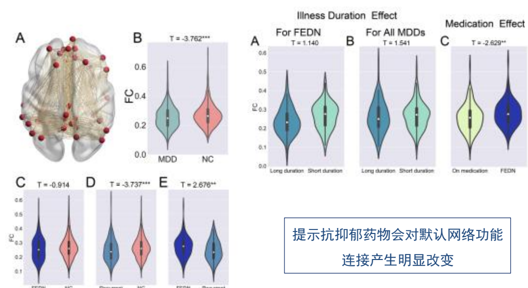
We are pleased to share a selection of recently published most downloaded articles from NeuroImage:

- The subsystem mechanism of default mode network underlying rumination: A reproducible neuroimaging study
  Xiao Chen, Ning-Xuan Chen, Yang-Qian Shen, Hui-Xian Li, Le Li, Bin Lu, Zhi-Chen Zhu, Zhen Fan, Chao-Gan Yan
- Obeying orders reduces vicarious brain activation towards victims' pain
  Emilie A. Caspar, Kalliopi Ioumpa, Christian Keysers, Valeria Gazzola

Neuroimage, 2020b. 独立通讯作者，2021年3月起入选ESI前1%高被引论文

Neuroimage, 2020c. 独立通讯作者，2020年第四季度Neuroimage下载量最高的文献

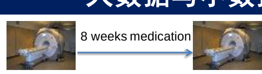
大数据与小数据研究的结合

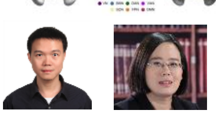


提示抗抑郁药物会对默认网络功能连接产生明显改变

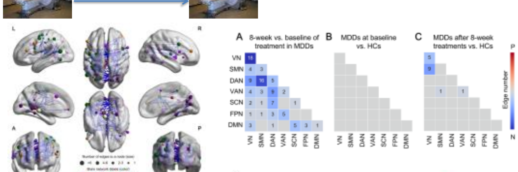
Yan, et al., 2019. PNAS

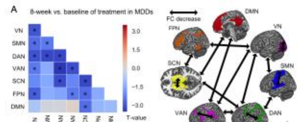
大数据与小数据研究的结合





Le Li　　Tian-Mei Si

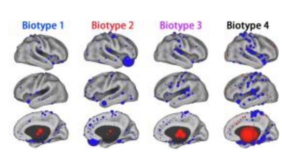




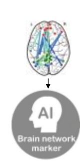
Li, et al., 2021. Human Brain Mapping

实现抑郁症生物亚型分类，提高治疗效果

Fehnel et al., 2013. CNS Spectr



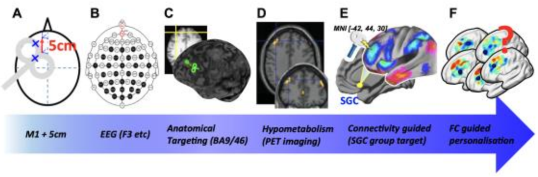
Drysdale et al., 2017. Nat Med



亚型1：SSRI单通道药物
亚型2：SNRI双通道药物
亚型3：TMS经颅磁刺激
亚型4：……

- 抑郁症异质性高，临床诊断分型存在挑战
- 基于脑网络的抑郁症生物亚型有助于改善治疗效果
- 难点1：脑影像与临床治疗效果大样本数据
- 难点2：生物亚型脑网络分类算法

亚型分类后的经颅磁刺激治疗优化

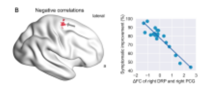


- 经颅磁刺激治疗技术面临响应率低(29%-46%)和疗程长(4-6周)等挑战
- 刺激抑郁症患者个体化靶点可以改善经颅磁刺激的治疗效果
- 难点3：如何通过功能影像技术定位个体化靶点

Cash et al., 2020. Biol Psychiatry

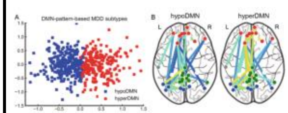
79

拟开展工作1 训练基于默认网络大数据的抑郁症亚型分类器

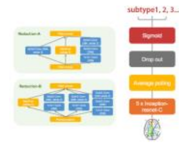


脑网络预测药物疗效
Hum Brain Mapp, 2021
（共同通讯，倒数第一）
Front Psychiatry, 2019.
（共同通讯，倒数第二）

抑郁症脑影像大数据联盟
第二轮数据征集（疗效信息）
已征集到1251例患者数据



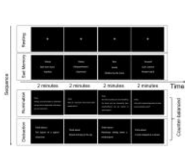
基于默认网络的抑郁症生物亚型
Neuroimage Clin, 2020
（共同通讯，倒数第二）
Mol Psychiatry, provisionally accepted
独立通讯作者



以疗效信息为优化函数，
训练深度学习亚型分类器

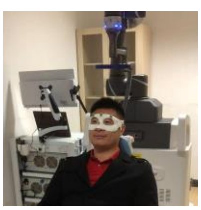
80

拟开展工作2 开发基于功能影像的个体化靶点定位技术



反刍思维任务范式

在背内侧前额叶区域中寻找与核
心子系统功能连接降低最大值点



个体化靶点精准
TMS刺激治疗

81

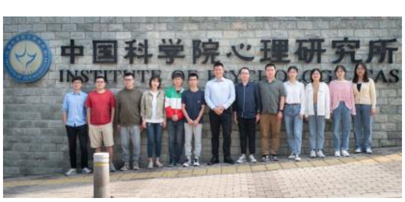
欢迎合作

CCTV-9《我们如何对抗抑郁》纪录片

北京卫视《为你喝彩》纪录片

82

Acknowledgments



Chinese Academy of Sciences
Xi-Nian Zuo
Wei-Wen Wang
Fei Luo
Hangzhou Normal University
Yu-Feng Zang
NYU Child Study Center
F. Xavier Castellanos
Peking University Sixth Hospital
Tian-Mei Si
Jing Liu

Funding
- National Natural Science Foundation of China
- National Key R&D Program of China
- Chinese Academy of Sciences

83

Thanks for your attention!

84