Towards Better Treatment Guided by Neuroimaging for Major Depressive Disorder

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Global Health Crisis: MDD

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

Famous Physicist committed suicide after suffering MDD

Diagnose of MDD

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

Oquendo et al., 2014. Depress Anxiety

Biomarkers of MDD

- Proinflammatory cytokine?
- HPA axis?
- Cortisol?
- MDD
- BDNF?
- Functional MRI?
- Structural MRI?

A Case

A famous journalist: Jin Zhang

First visit: MDD

Medicine A: suicidal ideation

Switch to Medicine B: turn to mania

Diagnose and treatment guided by brain imaging?

Diagnosed as bipolar disorder

Switch to Medicine C: recovery

fMRI Studies on MDD

- 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!
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

Roadmap for Applying fMRI in MDD

Big data of MDD brain imaging + deep learning

Neural underpinnings of MDD

Computational sharing platform

Head Motion

Standarization

Validating fMRI methodology

Methodological Issues: Head Motion

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

Need an effective motion correction strategy!


Van Dijk et al, 2012. Neuroimage

Proposed an effective head motion correction strategy

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

Yan et al., 2013a. Neuroimage

Mean regression + SD division

The Impact of Standardization Procedures on Confound Variables: Site Effects

Yan et al., 2013b. Neuroimage

Proposed an effective standardization strategy

Mean regression + SD division

Yan et al., 2013b. Neuroimage
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

Traditional fMRI Preprocessing Toolbox

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

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

Peer Evaluation

- Cited by 1352 times, ESI Top 1%
- Top cited paper and hot paper

REST-meta-MDD

- Started a consortium for big data sharing on MDD. Connected by the preprocessing pipeline, DPARSF, cited for over 2000 times

Yan et al., 2016. Neuroinformatics

Corresponding author

Yan et al., 2016. Neuroinformatics

The R-fMRI Maps Project

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

Contradicting findings about DMN FC in MDD

Meta-Analysis

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

Yan et al., 2019. PNAS
Proposals

1. Using static functional MRI to study the small-world properties of depression
   - Affiliated First Hospital of Zhejiang University

2. Depression brain function connectivity lateralization study
   - Xiangya Hospital of Hunan

3. Major depressive disorder anterior cingulate cortex local brain activity and functional connectivity changes
   - Hangzhou Normal University; West China Hospital; Zhejiang University

4. Discussion on depression symptoms subtypes' brain functional abnormalities: based on HAMD's project division
   - Southwest University Department of Psychology

5. Prediction of depression based on resting-state imaging and deep learning methods
   - Southwest University Department of Psychology

6. Structural and functional network of depression patients with anxiety
   - Beijing Anubu Hospital

7. Depression dynamic functional network connectivity study
   - Central South University Xiangya Hospital

8. Depression based on brain network overall function's rest imaging study
   - Chongqing Medical University Affiliated First Hospital

9. Brain functional imaging study of depression patients with insomnia
   - Beijing Anubu Hospital

10. The structural and functional alterations of brain in MDD with gastrointestinal symptoms
    - Shanxi Medical University First Hospital

11. Evolution of brain network in depression: an age and disease duration-associated cross-sectional study
    - Sichuan University West China Hospital

12. Abnormal resting-state functional connectivity of nucleus accumbens in MDD patients
    - Xiangya Hospital of Hunan

13. Resting-state functional connectivity of the habenula in depressive disorder patients with and without suicide-related behaviors
    - Chongqing Medical University Affiliated First Hospital

14. Common and different patterns of altered functional activities in drug-naive and treated first-episode patients
    - Suzhou General Hospital

15. Dysregulated functional activity of MDD patients and associations with depression severity
    - Chongqing Medical University Affiliated First Hospital

16. Integrated graphic measures and deep learning technology to detect MDD at the individual level
    - Sichuan University West China Hospital MR Research Center

17. Disrupted intrinsic functional brain topology in MDD

18. Depression-induced changes in global connectivity and brain network properties

19. Disrupted Intrinsic Functional Brain Topology in MDD

20. The functional connectivity of depression brain was decreased, then how about the topological properties?
    - Hong Yang
Disrupted Intrinsic Functional Brain Topology in MDD

Supplementary

Craddock’s 200 functional clustering atlas

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REF-
meta-
MDD Progress

4/18/22

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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

Supplementary

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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

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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


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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

<table>
<thead>
<tr>
<th>ID</th>
<th>Dataset Name</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1  | Dataset1     | High-quality MDD data collection | 1
| 2  | Dataset2     | Comprehensive MDD patient profiles | 1
| 3  | Dataset3     | Large-scale MDD imaging datasets | 1

### International Collaboration

Cross-culture MDD data collection?

### Go to Surface

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

Timothy T. Coakley

International Conference on Brain Imaging of Depression

Coalson et al., 2018, PNAS

Why Surface-based Analysis

Coakson et al., 2018, PNAS
Why Surface-based Analysis

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

Coalson et al., 2018. PNAS

Go to Surface

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

Yan et al., 2021. Science Bulletin

Ongoing Studies

Vertex-wise surface based cross culture MDD study

Specificity? MDD, Bipolar Disorder, Schizophrenia?

Deep Learning?

Transfer Learning

Classify the sex of a participant from brain structural imaging from anybody and any scanner with about 95% accuracy

Sex Classifier: 80000 MRI Samples

Depression Classifier: 8000 MRI Samples

Data Application

34 Datasets, 50876 subjects, 85712 dMRI samples

Lu, …, Yan*, Under review
Cross Validation

Cross dataset 5-fold cross validation

<table>
<thead>
<tr>
<th>Fold 1</th>
<th>Fold 2</th>
<th>Fold 3</th>
<th>Fold 4</th>
<th>Fold 5</th>
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<tbody>
<tr>
<td>AD</td>
<td>UK Dataset</td>
<td>ADN</td>
<td>AD</td>
<td>AD</td>
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</tbody>
</table>

Random 5-fold cross validation

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<tr>
<th>Fold 1</th>
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<th>Fold 4</th>
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<td>AD</td>
<td>AD</td>
</tr>
</tbody>
</table>

Sex Classifier Performance

ROC curve

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.

Model Interpretation

CNN Classifier

Occlusion Accuracy:
- 95% 50% 82% 50% 82% 50% 87% 93%

Original Accuracy - Occlusion Accuracy:
- 8% - 3%

Sex Model Interpretation

Occlusion map

Transfer to AD

Less is more?
Cross Validation
Cross site 5-fold cross validation

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%

Independent Validation
AIBL (101 AD samples and 523 NC samples)
AUC: 97%  
Accuracy: 94.2%  
Sensitivity: 88.1%  
Specificity: 95.4%

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%

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

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^{-10})  
• All Sample (r = -0.5787, p<1×10^{-10})
More Severe, Classifier Output Score higher!
# Model Interpretation

Occlusion map

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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

Koster et al., 2011. Clinical Psychol Rev
Rumination and Subsystems of DMN

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

Depression and Rumination

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

Future Directions

Rumination paradigm
Peak during rumination
TMS treatment

To live a joyful life!
“Mind Flower Project”
Institute of Psychology, CAS

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

IPCAS
Hospitals

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

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

Wearable Device

Standard
- Size
  - Terminal: 48.5mm×18.5mm×13mm
  - Wristband: 25mm×260mm
- Weight: 25g
- Battery
  - Standby time: 144 h
  - Work time: 48 h
  - Recharge time: 2.5 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: 5Hz
- Acceleration
  - Frequency: 20Hz
- Temperature
  - Frequency: 1Hz
- Event marker
  - Subject can mark the events

Wearable Device

PPG

Heart Rate

MRV: SDRR, RMSSD, NSR, N50
Frequency Domain
 PSD_LF, PSD_HF, NSR

EDA

Time Domain
 SCL

Frequency Domain
 SCR

Acceleration

Time Domain

ACC

GYRO

Sleep Monitor

EEG based

References:

“Kong” Therapy

I. Static tasks
1. Relax
2. Determine target syndrome
3. Imagine symbol
4. Imagine carriers
5. Fill in sheet A

II. Dynamic tasks
6. Relax
7. Clean and put
8. Move to “Kong”
9. Move back and evaluate
10. Fill in sheet B

“Kong” Therapy

References:
**Therapists of Mind Flower Project**

**Supervisor therapist**
Tian-Jun Liu

**Level A therapist**
Xiao-Qiong Peng, 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 Ce, 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, Xin-Yuan Zhou

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**Recruitment and Screening**

**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 currently taking antidepressant medication
  3. Fluent and literate in Chinese
  4. Written informed consent

- **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 with therapy
### Questionnaires

<table>
<thead>
<tr>
<th>Serial Number</th>
<th>Scale</th>
<th>Number of items</th>
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<tbody>
<tr>
<td>1</td>
<td>Ruminative Response Scale</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Toronto Alexithymia Scale</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>Beck Depression Inventory</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>Subjective Social Class Test</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Insomnia Severity Index</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>General Self-Efficacy Scale</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>Mindful Attention Awareness Scale</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>Body Perception Questionnaire</td>
<td>46</td>
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<tr>
<td>9</td>
<td>Intolerance of Uncertainty Scale</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>Consummatory subscale of TEPS</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>Cognitive Failures Questionnaire</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>Behavioral Activation/Inhibition Scale</td>
<td>20</td>
</tr>
<tr>
<td>13</td>
<td>Psychological Flexibility Questionnaire</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>Childhood Trauma Questionnaire</td>
<td>28</td>
</tr>
<tr>
<td>15</td>
<td>Life Event Scale</td>
<td>50</td>
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<td>16</td>
<td>Big five personality scale</td>
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<tr>
<td>17</td>
<td>Self-Rating Scale of Systemic Family</td>
<td>43</td>
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<tr>
<td>18</td>
<td>Dialectical Thinking Scale</td>
<td>33</td>
</tr>
<tr>
<td>19</td>
<td>Analysis-Holism Scale</td>
<td>25</td>
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<tr>
<td>20</td>
<td>Analysis-Holism thinking style task</td>
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<tr>
<td>21</td>
<td>Sensitivity to Punishment and Reward Questionnaire</td>
<td>35</td>
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### Questionnaires (Follow-up)

<table>
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#### TMS (Phase II)

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

TMS guided by individualized target.

#### How to Participate

Welcome to join Mind Flower Project!

http://ibook.psych.ac.cn/MindFlower
Collaboration is Welcome

CCTV Documentary

BRTV Documentary

Further Help

The R-fMRI Course V3.0

Chuan-Xiong Gan, Ph.D.
http://rfmri.org/wiki

The R-fMRI Lab
International Big Data Center for Depression Research
Institute of Psychology, Chinese Academy of Sciences

http://rfmri.org/Course

Official Account: RFMRILab

Acknowledgments

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Thanks for your attention!