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

- Whiteford et al., 2013. Lancet.
- WHO

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 ➔ Diagnosed as bipolar disorder ➔ Switch to Medicine C: recovery

Diagnose and treatment guided by brain imaging?

fMRI Studies on MDD

- Power failure: why small sample size undermines the reliability of neuroscience
  - Button et al., 2013. Nat Rev Neurosci
- Scanning the horizon: towards transparent and reproducible neuroimaging research
  - Pollock 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!
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

- Neuroimaging biomarkers for MDD
- Big data of MDD brain imaging + deep learning
- Neural underpinnings of MDD
- Computational sharing platform
- Head Motion Standardization
- Multiple comparison correction

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

Yan et al., 2013a. Neuroimage

Proposed an effective head motion correction strategy
- Individual-level correction with the Friston-24 model
- Group-level correction with head motion covariate

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

Methodological Issues: Standardization

- Proposed an effective standardization strategy
- Mean regression + SD division

Yan et al., 2013b. Neuroimage

Biswal et al., 2010, PNAS

Proposed an effective standardization strategy
- Cited: 222 times
- ESI Top 1% highly cited paper

Yan et al., 2013b. Neuroimage

The Impact of Standardization Procedures on Variables of Interest: Age Effects

The Impact of Standardization Procedures on Confound Variables: Site Effects
Reproducibility and Multiple Comparison Correction

Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates
Antoni Gollopp*, Thomas L. Noll**, and Mare Knebelov*

The last 45 years of fMRI research might be totally useless.

Eklund et al., 2016. PNAS

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

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

Traditional fMRI Preprocessing Toolbox

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

FreeSurfer

Traditional fMRI Preprocessing Toolbox

Computational sharing platform for fMRI

- Incorporating DPARSF
- Prior work, cited for 1803 times
- Adapting methodological updates
- Head motion (cited for 755 times)
- Standardization (cited for 222 times)
- Multiple comparison correction
- Standardized preprocessing pipeline
- Statistical toolbox
- Platform for data sharing

Yan et al., 2016. Neuroinformatics

Corresponding author

Peer Evaluation

Cited by 399 times, ESI Top 1‰ top cited paper and hot paper

Peer Evaluation

REST-meta-MDD

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

REST-meta-MDD consortium contains neuroimaging data of 1350 depressed patients and 1,128 normal controls from 25 research groups in China, forming the world's largest MDD R-fMRI dataset
The R-fMRI Maps Project

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

Contradicting findings about DMN FC in MDD

REST-meta-MDD

Meta-Analysis

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.
Proposals

1. "Abnormal interhemispheric connectivity in major depressive disorder: an voxel mirrored homotopic connectivity analysis of 2428 individuals from REST-meta-MDD working group" - Yan et al., 2019, PNAS

2. "Reduced default mode network functional connectivity in patients with recurrent major depressive disorder" - Yan et al., 2019, PNAS

3. "Different local brain activity and functional connectivity in major depression disorder patient with different sex and age" - Yan et al., 2019, PNAS

4. "The structural and functional deviation of major depressive disorder with different symptom severity" - Yan et al., 2019, PNAS

5. "The relationship of brain structure and functional connectivity in different major depressive disorder patients" - Yan et al., 2019, PNAS

6. "The relationship of brain structure and functional connectivity in different major depressive disorder patients" - Yan et al., 2019, PNAS
International Collaboration

International Conference on Brain Imaging of Depression

Cross-culture MDD data collection?

Prospective Studies

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

Go to Surface

Why Surface-based Analysis

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