The Use of Neuroimaging and Computational Approaches to Inform Interventions for Mood Disorders

Faith M. Gunning, Ph.D.
Associate Professor of Psychology in Psychiatry
Vice Chair for Research
Vice Chair for Psychology
Department of Psychiatry
Weill Cornell Medicine

Disclosures
Supported by grants from NIMH.

256 Unique Ways to be Depressed

Choose 5 or more of 9 symptoms:
1. Depressed or irritable mood
2. Decreased interest in activities
3. Weight loss (or weight gain)
4. Insomnia (or sleeping too much)
5. Psychomotor agitation (or slowing)
6. Fatigue or loss of energy
7. Feelings of guilt or worthlessness
8. Impaired concentration
9. Suicidal thoughts
Resting-state connectivity biomarkers define neurophysiological subtypes of depression

Discovering Subtypes of Depression

Neurophysiological Subtype 1
Clinical Correlates

Neurophysiological Subtype 2
Clinical Correlates

Neurophysiological Subtype 3
Clinical Correlates

Depression Subtypes Based on Resting State fMRI
Four New Subtypes of Depression

<table>
<thead>
<tr>
<th>Subtype 1</th>
<th>Subtype 2</th>
<th>Subtype 3</th>
<th>Subtype 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low anxiety</td>
<td>Fatigue</td>
<td>High anxiety</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Agitation</td>
<td>Anhedonia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rescuing Dysfunctional Brain Circuits: Precision Medicine for Psychiatry

Repetitive Transcranial Magnetic Stimulation

Summary

- One role of neurobiological measures and computational approaches is to identify reliable/stable markers of specific expressions of depression or other mood disorders that respond best to specific treatments.
- To be useful these approaches must be able to match patients to treatments at the level of the individual.
- The computational approach reported in the Drysdale paper (2017) is one example of a promising computational approach that may help drive treatment selection.
Treatment Development Goal:
Use neurobiological models to identify distinct targets for interventions.

Etiological Factors
- Vascular Changes
- Inflammation
- Allostasis, etc.

Predisposing Factors
- Cognitive Control Abnormalities

Responses to Stress
- Inflammation
- Reactive Oxygen Species
- Dendritic Remodeling
- Neurogenesis
- Altered Network Connectivity

Mechanisms Mediating Depression in Aging
- Cognitive Control Network
- Default Mode Network
- Reward Systems

Why Target the Cognitive Control Network

A network that modulates the operation of other cognitive and emotional systems in the service of goal-directed behavior when prepotent modes of responding are not adequate to meet the demands of the current context.

Cognitive control deficits and network dysfunction are found across a host of psychiatric and neurologic illnesses.

In individuals suffering from depression, cognitive control dysfunction may contribute to difficulty engaging in goal-directed behavior, susceptibility to interference from irrelevant information, and trouble modulating affective responses.

The Cognitive Control Network is most susceptible to “normal” aging processes.

Executive dysfunction, a clinical expression of cognitive control dysfunction, occurs in approximately 40% of older, depressed adults and 20% of young and middle-aged adults with depression.
Executive Dysfunction and Poor Antidepressant Response in Geriatric Depression.

1. Cornell Study (Kalayam & Alexopoulos: Arch Gen Psychiatry 56: 713, 1999)
5. Old-Old Study (Sned et al 15:553, 2007)
9. Cornell Study (Morimoto, Gunning et al., 2011; IJP: Morimoto, Gunning et al 2012; AJGP)
10. IRL-GRAY Study (Kanevita et al., JAMA Psychiatry, 2014)

A Double Dissociation: Depressed elders have lower functional connectivity in the CCN and greater in the DMN than controls.

Functional Connectivity of the Cognitive Control Network at Rest and Self-Reported Dysexecutive Behavior
Two Behavioral Approaches to Targeting Dysfunctional Cognitive Control Networks.

- Psychotherapy that is designed to help individuals with depression with executive dysfunction to compensate – Problem Solving Therapy
- Cognitive remediation intervention designed to improve functioning of the cognitive control network.

Problem-Solving Therapy versus Supportive Therapy for Depression with Executive Dysfunction in 221 Older Adults

Carefully-designed interventions using game mechanics can be powerful agents for change

Anguera et al., 2013 Nature
Basis of a Therapeutic Video Game Intervention (Project EVO)

- Informed by understanding of aging of cognitive control functions.
- Delivered via iPads over the course of 4 weeks – at least 20 minutes per day for 6 days per week.
- Weekly meeting with Master’s level therapist/“coach”.
- Intervention is based on a dual-task that includes a motor component and the detection of “targets”.
- Difficulty is based on algorithms to individualize the intervention.
- In older adults, early version of the game trained cognitive control abilities to be comparable to that of untrained young adults (Anguera et al., 2013, *Nature*)

Change in Depressive Symptoms with a Therapeutic Video Game Intervention (EVO)
Cognitive Control Transfer Effects with EVO

Change in Activation of the Cognitive Control from Pre to Post EVO During a Cognitive Control Task

Right Arcuate Fractional Anisotropy and Improvement in HAM-D Score After Training
Overview of Study Design
Anguera, Arean, Gunning (MH R61 110509)

Subjects
- Participants between the ages of 45 and 75
- Suffering from MDD (pre-treatment Hamilton > 19)
- Selected for presence of cognitive control deficit
- Can be on a stable dose of antidepressant medication

Design
- R61 is single arm with all patients performing EVO
- Patients play game for 4 weeks/5 days per week/20 min per day.
- Brief weekly meeting with "coach" to assess mood and compliance with study procedures.
- Measurement of engagement of CCN pre- and post- EVO using
  • Resting state and task-based fMRI
  • Performance-based measures of CCN functions
  • Self-report of CCN functions.

Neuroimaging

Resting-State fMRI
Change in functional connectivity of the CCN.

Task-Based fMRI
Change in CCN activation during Stroop/Flanker task.

Cognitive and Self-Report

AID
(Working Memory)

TOVA
(Sustained Attention)

FrSBe
Self-report measure of executive dysfunction.
Change in Depressive Symptoms in Middle Aged and Older Adults

Depression significantly improved from baseline to week 4 of EVO. 
\[ t(31) = 7.64, \ p < 0.001 \]

Change in Resting State Connectivity from Baseline to Post EVO

Resting-State fMRI

Increased CCN functional connectivity following EVO.
Resting-State fMRI

- Post-EVO AID Accuracy
  - $r(23) = 0.44, p < 0.01$

- Post-EVO FrSBe Apathy Score
  - $r(23) = -0.47, p < 0.02$

Change in Task-Based fMRI Activation from Pre to Post Evo

Task-Based fMRI Activation Change Correlates with Executive Functions

- Post-EVO AID Accuracy
  - $r(28) = 0.47, p < 0.01$

- Post-EVO FrSBe Apathy Score
  - $r(28) = -0.43, p < 0.02$
Summary
- Based on a “deficit model” approach we can use cognitive data to identify individuals who are likely to respond best to a specific neurobiologically-informed intervention.
- Cognitive Control dysfunction is present in 20 to 40% of depressed patients.
- Other subtypes.Expressions of depression may be more responsive to interventions targeting either the reward system or the default mode network.

The Focus on Negative Self-Referential Processing
- Self-referential processing refers to one’s view of oneself in the world.
- Negative self-referential processing often is a core feature of depression that relates to a constellation of systems common in depression including guilt, rumination, worry, and pessimism.
- In resting state and task-based fMRI, self-referential processing has been tied to anterior aspects of the default mode network with a key node in the medial prefrontal cortex (ventral BA10).
- In a sample from Cornell of depressed individuals who were treatment resistant at least 85% had at least moderately severe symptoms of negative self-referential processing.
- Negative self-referential processing predicts recurrence of depression and poor antidepressant response.
Baseline Sample Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (N = 45)</th>
<th>Depressed (N = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.3 (6.9)</td>
<td>70.6 (6.0)</td>
</tr>
<tr>
<td>DRS</td>
<td>138.4 (6.9)</td>
<td>138.8 (4.4)</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.8 (1.1)</td>
<td>28.4 (1.9)</td>
</tr>
<tr>
<td>Education</td>
<td>17.0 (2.0)</td>
<td>14.7 (2.2)</td>
</tr>
<tr>
<td>MADRS</td>
<td>1.2 (1.5)</td>
<td>26.0 (5.1)</td>
</tr>
</tbody>
</table>

Trait Adjective Task

"Does this word describe you?"

- Witty
- Grumpy

Calculation of White Matter Integrity in Affective and Default Mode Networks

- Structural MRI sequence: 37-direction Diffusion Tensor Imaging (DTI)
- Measure of white matter microstructure: Fractional Anisotropy (FA)
- FA values extracted with FSL's Tract-Based Spatial Statistics (TBSS) approach
- FA skeletons restricted to regions of interest with binary masking procedure
Baseline FA and Number of Endorsed Negative Traits Following Antidepressant Treatment

\[
R^2 = 0.39824
\]

\[
R^2 = 0.59517
\]
Summary

- Negative self-referential processing is a common symptom in depression that is associated with recurrence of depression.
- In late-life depression, negative self-referential processing is tied to functional connectivity of anterior aspects of the default mode network.
- Structural connectivity of the default mode network predicts persistence of negative self-referential processing following 12 weeks of an SSRI.
- Psychotherapies targeting negative self-referential processing (e.g., Emotion Regulation Therapy) and/or novel neurostimulation targeting may better treat negative self-referential processing.

Conclusions and Current/Future Directions

- Neuroimaging can be used to inform alternative interventions for those patients who don’t respond to antidepressant medication.
- One role of computational approaches is to identify reliable/stable markers of specific expressions of depression or other mood disorders that respond best to specific treatments.
- Novel neurostimulation (e.g., individualized targeting) or behavioral approaches and/or combining neurostimulation with behavioral interventions may enhance treatment response.
The brain is organized into functional networks.

"Average Face"
Brain Network “Fingerprints” for Directing Treatment

“Average brain”

Accounting for individual differences improves treatment outcomes

Individualized network engagement

Weill Cornell Medicine