PERSONALIZED INTERVENTION FOR PSYCHOLOGICAL PROBLEMS

Bonnie Klimes-Dougan, Ph.D., LP
Program of Research

- The overarching goal of my research is to understand and alleviate the suffering of those who struggle with distress, depression, and despair (self-injury and suicide).

- Identify risk and protective factors
- Identify optimal methods of intervening
  - Personalization
Premis

- Clinical practice in many areas of medicine is shifting toward personalized treatment. In other words, clinicians aim to treat patients based on their individual characteristics, including clinical presentation and/or biological markers.

- Biomarkers can help clinicians select the most effective treatments or reduce the risk of side effects by avoiding certain treatments in susceptible patients.
Outline

• I. Depression, adolescent development and disruption of the threat system.

• II. EBTs are Available to Treat Adolescent Depression

• III. The Solution of Personalization

• IV. Biological Markers Predicting Treatment Response for Adolescents with Depression
I. Depression, adolescent development, and functioning of the threat system
Depression

Affective  Cognitive  Vegetative
Depression

• Common Problem
  • 16% of the population

• Morbidity and Mortality
  • 60-70% of suicides are associated with a mood disorder

• Significant Impairment
  • Leading cause of economic global impairment worldwide

• Recurrent / Progressive
  • Early onset is associated with a poor prognosis
  • Brain plasticity may be critical

Brent & Kolko, 1990; www.sdchip.org/work_teams/wt_na/wt_na_pdfs/F-depression%
Functions of the Threat System

- SHORT TERM PROJECTS
  - Mobilizes energy – glucose
  - Raises HR/BP
  - Blunts pain

- LONG TERM PROJECTS
  - Slows digestion
  - Slows growth
  - Slows reproduction
  - Suppresses immune functioning
  - Speeds up aging
Adolescent Development

A. PFC
B. Subcortical/Limbic
Amygdala - Threat
Striatal - Reward

Somerville, Jones, & Casey, 2009
Threat System and Depression

I. CIRCUITS

- Desensitisation of cortisol receptors leads to distorted feedback and adrenaline and cortisol production.

II. PHYSIOLOGY

- Hypersecretion of CRF
- Adrenal hypertrophy
- Excess cortisol released
- Cortisol in circulation
- Impaired negative feedback by cortisol
- Immune system
- Neurotransmitters
- Neuropeptides
- Desensitisation of cortisol receptors, increased activity of macrophages, and increased release of pro-inflammatory cytokines

Brain circuits:
- Cortex
- Hypothalamus
- Hippocampus + amygdala
- Pituitary
- CRF
- ACTH
- adrenal cortex
- immune system
Cortical and Limbic Structures

Differentially influence these key brain regions

- Cortical (PFC)
- Limbic (Amygdala)
- Limbic (Hippocampus)

HPA Axis Stress Model

- Hypothalamus
  - CRH
  - Corticotropin Releasing Hormone

- Anterior Pituitary
  - ACTH
  - Adrenocorticotropic Hormone

- Adrenal Cortex
  - CORT

Negative Feedback
Impacts on the Brain

- Key Receptors
  - GR - glucocorticoid
  - MR - mineralcorticoid

- Receptor Regions of Concentration
  - Amygdala
  - Hippocampus
  - Hypothalamus
  - VMPFC
II. EBTs are Available to Treat Adolescent Depression
The Mental Health Intervention Spectrum for Mental Disorders

Evidence Based Treatments

Efficacy
Does it work in clinical trials?

Effectiveness
Does it work in clinical practice?

Efficiency
Does it contribute to more efficient use of resources?

Type of evidence for the treatment intervention

Adolescent Depression

EVIDENCE BASED TREATMENTS

Psychopharmacology:
- fluoxetine
- escitalopram

Psychotherapy:
- Cognitive Behavioral Therapy (CBT)
- Interpersonal Psychotherapy (IPT-A)
## Guidelines Based on Depression Severity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Mild to moderate</th>
<th>Moderate to Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Psycho-education</td>
<td>• Cognitive Behavioral Therapy (CBT)</td>
<td>• Medication</td>
</tr>
<tr>
<td>• Supportive Therapy</td>
<td>• Interpersonal Therapy (IPT)</td>
<td>• Medication + CBT or IPT</td>
</tr>
</tbody>
</table>

Hypothetical model of functional changes in amygdala and the main prefrontal areas involved in anxiety disorders and major depressive disorder.

Quide, Witteveen, El-Hage, et al., 2011
Limitations of EBTs

- The impact of EBTs will fall short if a one-size fits all assumptions continues to be made when utilizing EBTs
II. The Solution of Personalization
Current Treatments have Response/Recovery Rates of 43%-71%
Current Treatments have Response/Recovery Rates of 43%-71%

TADS Team (2004)
The Cost of Choosing the “Wrong” Treatment

- Personal / Societal Problem
  - Loss of productivity (Global Burden of Dz)
  - Continued distress / Suicide risk
  - Discouragement from help-seeking
- Wasted resources
  - Health-care costs
  - Practitioner time/money which could be treating those who will respond

McGrath et al, 2013
Solution Options

- Dosage change?
- Components adjust?
- Treatment add?
- Personalization?
  - Preference
    - (Mergl, et al, 2011)
  - Clinical Predictors

- Biological Markers
Personalizing Treatment

- The next step: to move beyond determining what treatments work to identifying which treatments work for whom

- Identifying patient characteristics that predict or interact with (moderate) treatment can guide clinicians in selecting a treatment that more rapidly and efficiently manages depression for a specific group of individuals

Insel, 2009, National Institute of Mental Health Strategic Plan, 2008
Current Status of Search for Tailoring Variables

- Infinite Possibilities?
- Psychosocial
  - not yielded the wealth of findings
- Biological
  - There is excitement about the possibility of identifying indexes linked with underlying biological mechanisms (biomarkers) that can guide treatment decisions
Main Approaches for Biological Predictors

- Brain (circuits)
  - Neuroimaging
  - Neuropsychological testing
  - Neurotransmitters
- Body (physiology)
  - HPA Axis
- Genes
  - Molecular genetics
  - Epigenetics
IV. Biological Markers Predicting Treatment Response
Neurobiology of Depression

- Hypersecretion of CRF
- Impaired negative feedback by cortisol
- Adrenal hypertrophy
- Excess cortisol released
- Cortisol in circulation
- Impaired negative feedback by cortisol
- Desensitisation of cortisol receptors leads to disturbances in noradrenaline and serotonin transmission
- Neurotransmitters
- Neuropeptides
- Desensitisation of cortisol receptors, increased activity of macrophages and increased release of pro-inflammatory cytokines
SSRIs:
Common Choice of Medication for Depression

- Exact mechanisms of SSRIs are still fully not understood
  - extracellular increases in serotonin levels
    (partially do to SSRI blocking reabsorption due to abnormalities in 5-HT1A receptor)
- SSRIs may alter brain functioning
  - decreased limbic activation
  - increased cortical activation (ACC, PFC)
- SSRIs may alter HPA axis functioning
  - antidepressants increase GR function, thus leading to resolution of glucocorticoid resistance

Fronto-limbic Neural Circuitry

Red: dFr = dorsolateral prefrontal; inf Par = inferior parietal; dCg = dorsal anterior cingulate; pCg = posterior cingulate. Blue: Cg 25 = subgenual (infralimbic) cingulate; vlins = ventral anterior insula, Hc = hippocampus; vFr = ventral frontal; Hth = hypothalamus. Yellow: rCg = rostral anterior cingulate. White: mb-p = midbrain-pons; BG = basal ganglia; Th = thalamus; Am = amygdala.
**Table 2. Treatment by Outcome Interaction Results and Post hoc Analyses of Extracted Regions of Interest**

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI Coordinates, Peak</th>
<th>Cluster Size, a Voxels</th>
<th>Effect Sizesb</th>
<th>Average Marginal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td>Side</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>+30.0</td>
<td>+24.0</td>
<td>−13.5</td>
<td>R</td>
</tr>
<tr>
<td>Inferior temporal</td>
<td>+42.0</td>
<td>−33.0</td>
<td>−25.5</td>
<td>R</td>
</tr>
<tr>
<td>(BA 20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>−27.0</td>
<td>−7.5</td>
<td>−27.0</td>
<td>L</td>
</tr>
<tr>
<td>Premotor (BA 6)</td>
<td>−27.0</td>
<td>+1.5</td>
<td>+58.5</td>
<td>L</td>
</tr>
<tr>
<td>Motor (BA 4)</td>
<td>+25.5</td>
<td>−27.0</td>
<td>+60.0</td>
<td>R</td>
</tr>
<tr>
<td>Precuneus (BA 7)</td>
<td>−18.0</td>
<td>−67.5</td>
<td>+43.5</td>
<td>L</td>
</tr>
</tbody>
</table>

Abbreviations: BA, Brodmann area; CBT, cognitive behavior therapy; CBT—sCIT, mean difference between CBT and escitalopram Montreal Neurological Institute; NR, nonresponders; REM, remitters; REM—NR, mean difference between remitters and nonrespc escitalopram oxalate.

aWhole-brain 2-way analysis of variance with P < .001 uncorrected; voxel size, 1.5 mm × 1.5 mm × 1.5 mm.

bEffect size = mean difference divided by pooled standard deviation.
Mayberg:

Mayberg:

Mayberg:

Mayberg:

Research on Adolescent Depression

• Aim: To identify whether neurobiological functioning is associated with favorable antidepressant response in adolescents with depression

  • Frontolimibic (rest and task) functioning at baseline will predict a decline in depressive symptoms

  • Neuroendocrine functioning at baseline will predict a decline in depressive symptoms

Klimes-Dougan, Cullen et al., in preparation
Antidepressant Intervention Pilot Study

- 8 Week Trial of Antidepressant Medication (SSRIs)

**Baseline Demographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
</tr>
<tr>
<td>Age (mean years, SD)</td>
<td>15.5, 2.3</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>4/9 (69% female)</td>
</tr>
<tr>
<td>Right Handed-n(%)</td>
<td>12 (92%)</td>
</tr>
<tr>
<td><strong>Ethnicity - n(%)</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>13 (100%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (31%)</td>
</tr>
<tr>
<td><strong>Current Comorbidities - n(%)</strong></td>
<td></td>
</tr>
<tr>
<td>Attention Deficit and Hyperactive Disorder</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Generalized Anxiety Disorder</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Post-traumatic Stress Disorder</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Social Anxiety</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Anxiety NOS</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Med-Naive-n(%)</td>
<td>11 (85%)</td>
</tr>
<tr>
<td>Duration of illness (mean months, SD)</td>
<td>15.5, 16.1</td>
</tr>
<tr>
<td>Global Assessment of Functioning (mean, SD)</td>
<td>55, 77</td>
</tr>
<tr>
<td>Positive Family History</td>
<td>11 (85%, n = 13)</td>
</tr>
<tr>
<td>CDRS-R (mean T-score, SD)</td>
<td>73.2, 7.3</td>
</tr>
<tr>
<td>BDI-II (mean, SD)</td>
<td>28.7/9.3 (n=13)</td>
</tr>
</tbody>
</table>

- Baseline
- Circuits
- Neuropsych
- Physiology

Task Based fMRI Differences

**Left Amygdala Activation**

**Right Amygdala Activation**

Klimes-Dougan, et al, 2014
Neurocircuits – SSRI Results

- Emotion task: Responders showed greater limbic activation (more different from HC) than non-responders.

Klimes-Dougan, Cullen et al, in preparation
Neurocircuits – SSRI Results

Klimes-Dougan, Cullen et al., in preparation
Adolescents’ Pre-Treatment Cortisol Trajectories Predict Suicide Ideation Patterns Across an 8-week trial of SSRIs

Klimes-Dougan, Cullen et al, in preparation
Summary and Conclusions

- The goal of this line of work is to provide some practical solutions for determining who will respond best from which treatment.
  - Identify Biological Predictors
    - Brain functioning
    - Physiological functioning
    - Genetic functioning

- Cautions
  - How predictive of treatment response?
  - How feasible would these procedures be?

- EXCITING POSSIBILITIES!!!
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    Melinda Westlund Schreiner, ABD
    Michelle Thai, B.A.
    Many other graduate and undergraduate students

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Thank You!
### Ongoing Recruitment of Studies: University of Minnesota

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Coordinator</th>
<th>Email</th>
<th>Phone</th>
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<tbody>
<tr>
<td><strong>Ketamine:</strong></td>
<td>Ketamine infusion efficacy for 12-18 year olds with treatment resistant depression</td>
<td>Palistha Amatya</td>
<td><a href="mailto:amaty008@umn.edu">amaty008@umn.edu</a></td>
<td>612-626-8534</td>
</tr>
<tr>
<td>Mood</td>
<td>Neurological functioning of 13-18 year olds with a diagnosis of a bipolar disorder, depressive disorder, or mood disorder not otherwise specified</td>
<td>Nathan Horek</td>
<td><a href="mailto:nahorek@umn.edu">nahorek@umn.edu</a></td>
<td>612-626-7635</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation for 12-18 year olds with treatment resistant depression</td>
<td>Palistha Amatya</td>
<td><a href="mailto:amaty008@umn.edu">amaty008@umn.edu</a></td>
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<tr>
<td>BRIDGES</td>
<td>Brain development in young adolescent girls (12-14 years old) with and without a history of self-injury</td>
<td>Palistha Amatya</td>
<td><a href="mailto:kamp0182@umn.edu">kamp0182@umn.edu</a></td>
<td>612-626-8534</td>
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<tr>
<td>High Field</td>
<td>High-field brain imaging in 13-17 year old adolescents with Major Depressive Disorder</td>
<td>Nathan Horek</td>
<td><a href="mailto:nahorek@umn.edu">nahorek@umn.edu</a></td>
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**HEALTHY CONTROLS:**

**AGES 12 to 19**