USING fMRI TO PREDICT TREATMENT RESPONSE IN DEPRESSION AND GAD

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- **Other Financial Interest:** Owner of Promoter Neurosciences, LLC; holds patents for the following: promoter sequences for corticotropin-releasing factor CRF2alpha and method of identifying agents that alter the activity of the promoter sequences (U.S. Patent issued on 07-04-06; patent #7071323, U.S. Patent issued on 05-12-09; patent #7,531,356); promoter sequences for uroctinin II and the use thereof (U.S. Patent issued on 08-08-06; patent #7087385); and promoter sequences for corticotropin-releasing factor binding protein and use thereof (U.S. Patent issued on 10-17-06; patent #7122650)
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LEARNING OBJECTIVE

Identify the role of brain imaging in predicting treatment response in patients with anxiety and depression.
BASICS OF MAGNETIC RESONANCE IMAGING (MRI)

Sensitive to:
- # of protons (H₂O)
- Magnetic environment
  - Tissue structure

Radio Wave

B₀
BASICS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

Measuring brain function with MRI

Task ➔ Neuronal Activity ➔ Hemodynamics ➔ Red Blood Cells ➔ MRI signal

↑ Task ➔ ↑ Blood Flow ➔ ↑ O₂ of blood ➔ ↑ MRI signal
Functional connectivity between brain regions can even be measured when the subject is at rest.
THE BRAIN AND EMOTION

ventral PFC

dorsolateral PFC

insula

amygdala

hippocampus

anterior cingulate
WHAT IS EMOTION REGULATION?

- Adaptive processes by which emotional responses can be increased or decreased in duration or magnitude
- Voluntary emotion regulation
- Automatic regulation
- Hypothesis: Alterations in emotion regulation account for symptoms in patients with affective and anxiety disorders and are characterized by alterations in the circuitry that mediates emotion regulation
PRIMARY COMPONENTS INVOLVED IN EMOTION REGULATION

# ALTERED EMOTION REGULATION IN DEPRESSION AND ANXIETY

<table>
<thead>
<tr>
<th>Underlying Dysregulation</th>
<th>Symptom</th>
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<tbody>
<tr>
<td>Failure to terminate negative responses or negative emotions experienced out of context</td>
<td>Prolonged negative mood</td>
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<tr>
<td>Emotion/cognition interface negatively biased</td>
<td>Negative cognitions and memories</td>
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<tr>
<td>Failure in activating positive emotional responses and reward systems</td>
<td>Inability to experience pleasure</td>
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<tr>
<td>Alterations in motivation and in reward/motor interface</td>
<td>Impaired goal-directed behavior</td>
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USING CONSCIOUS REGULATION TO ALTER RESPONSES TO UNPLEASANT STIMULI

-Time
-Intensity of Unpleasantness

“Fangs plunging in! Legs inching up my arm! Aaargh!!”

“It’s harmless. It’ll all be OK.”

“Eww, creepy!!”
CONSCIOUS EMOTION REGULATION
Modulating Amygdala Activity

vmPFC AND OFC ACTIVITY DURING CONSCIOUS REGULATION (SUPPRESS – ATTEND) NEGATIVELY CORRELATES WITH AMYGDALA ACTIVITY

In depression this faith in deliverance, in ultimate restoration, is absent. The pain is unrelenting...If there is mild relief, one knows that it is only temporary; more pain will follow. It is hopelessness even more than the pain that crushes the soul. So the decision-making of daily life involves not, as in normal affairs, shifting from one annoying situation to another less annoying – or from boredom to activity – but moving from pain to pain. One does not abandon, even briefly, one’s bed of nails, but is attached to it wherever one goes.

William Styron, “Darkness Visible”
ALTERED REGULATION OF THE AMYGDALA BY vmPFC WHEN DEPRESSED PATIENTS ATTEMPT TO DOWN REGULATE NEGATIVE AFFECT

ALTERATIONS IN REWARD CIRCUIT WHEN DEPRESSED SUBJECTS ATTEMPT TO UPREGULATE POSITIVE EMOTION

The inset displays a plot of neuroimaging studies finding involvement of the ACC in the prediction of treatment response. The black asterisk is the local maxima of the sgACC finding reported here. Color indicates imaging methodology: red = PET; blue = fMRI; green = EEG/MEG.
PREFRONTAL REGULATION OF EMOTION
Role in Affective and Anxiety Disorders

- Inverse coupling of vmPFC and amygdala during extinction of conditioned fear response\(^2,3\); during evaluation of affectively ambiguous information\(^4\)

ANTERIOR CINGULATE INVOLVED IN RESOLVING EMOTIONAL CONFLICT

NEURAL SUBSTRATES OF AFFECTIVE PROCESSING IN DEPRESSED PATIENTS

Response of Depressed Patients to Venlafaxine in Relation to Left Anterior Cingulate Activation at Baseline After Exposure to Negative Relative to Neutral Stimuli

Signal Change in Left Anterior Cingulate at Baseline

Score on General Distress Scale of Mood and Anxiety Symptom Questionnaire at 8 Weeks

N = 12
fMRI TO PREDICT RECOVERY FROM UNIPOLAR DEPRESSION WITH CBT

Relationship Between Regional Reactivity to Negative Words and Residual Depressive Severity Following Treatment with Cognitive Therapy

N = 14
ALTERED ANTERIOR CINGULATE ACTIVATION IN GAD

N = 24
ANTICIPATION PARADIGM – A MODEL FOR WORRY AND GAD
Event-Related fMRI

Increased Amygdala Response Prior to Treatment

N = 14

A FUNCTIONAL MAGNETIC RESONANCE IMAGING PREDICTOR OF TREATMENT RESPONSE TO VENLAFAXINE IN GAD

N = 15

rACC (-12, 32, 22) Amygdala (-19, 1, -15)
CLINICAL CONNECTIONS

- Evidence demonstrates that prefrontal-amygdala circuitry is altered in depression and GAD
- Increased activity of the anterior cingulate predicts acute treatment response to antidepressants in MDD and GAD
- Activity in other regions of the prefrontal cortex (OFC) may predict longer-term responses
- In contrast to antidepressant treatment, decreased anterior cingulate activity may predict response to CBT