Training the amygdala:
The Development of a real-time fMRI Neurofeedback Intervention for Depression

Kymberly Young, PhD
Laureate Institute for Brain Research

April 16th, 2015
Duke University School of Medicine
Central Regional Hospital
Disclosures

None
Roadmap

- Autobiographical memory for positive information is important and impaired in patients with depression

- Positive autobiographical memory has understandable brain targets

- We can target those mechanisms with neurofeedback
Major Depressive Disorder

• **Leading cause** of disability in the United States according to the World Health Organization
  • Lifetime prevalence of 16.5%
  • Cost to US economy $60 billion
  • 30% of patients will attempt suicide

• **Symptoms**
  • Depressed mood; feeling sad, hopeless, worthless
  • Loss of interest or pleasure
  • Fatigue, decreased energy
  • Irritability, restlessness
  • Suicidal thoughts
  • Disturbances in concentration, sleep, appetite, and weight
  • Exaggeration of negative emotion
  • Attenuation of positive emotion

• Advances in technology allow us to target specific brain regions or symptoms we know underlie the illness
Autobiographical Memory

• Memory for personally experienced events

• Test used to assess the degree of specificity of autobiographical memory developed by JMG Williams in 1986
  • Williams & Broadbent (1986) *J Abnorm Psychol*, 95, 144-149

<table>
<thead>
<tr>
<th>Positive Cues</th>
<th>Negative Cues</th>
<th>Neutral Cues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devoted</td>
<td>Grief</td>
<td>Pottery</td>
</tr>
<tr>
<td>Hopeful</td>
<td>Rejected</td>
<td>Ladder</td>
</tr>
<tr>
<td>Amazed</td>
<td>Helpless</td>
<td>Occasion</td>
</tr>
<tr>
<td>Pleased</td>
<td>Blame</td>
<td>Search</td>
</tr>
<tr>
<td>Calm</td>
<td>Awful</td>
<td>Wildlife</td>
</tr>
<tr>
<td>Bright</td>
<td>Mistake</td>
<td>Gigantic</td>
</tr>
</tbody>
</table>
Autobiographical Memory

• Levels of Specificity:
  • Specific – I failed an exam last Tuesday
  • Categorical – I failed a lot of exams in college
  • Extended – The week I spent studying for finals
  • Semantic – I am a failure

Difficulty recalling specific memories a cardinal feature of affective disorders

## Autobiographical Memory

<table>
<thead>
<tr>
<th>Function of specific autobiographical memory</th>
<th>Impairment in depression</th>
</tr>
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## Autobiographical Memory

<table>
<thead>
<tr>
<th>Function of specific autobiographical memory</th>
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<tbody>
<tr>
<td>Problem Solving</td>
<td>Overgeneral memory correlated with impaired problem solving in depression</td>
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## Autobiographical Memory

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Develop and maintain social bonds<br>**Bluck et al (2005) Soc Cogn, 23(1), 91-117**

*Parents have fewer social experiences; unknown if correlated with autobiographical memory<br>Peeters et al 2003, *J Abnorm Psychol, 112, 203-211* |

Social withdrawal predicts depressive symptoms<br>Morgan et al (2013) *J Youth Adolesc, 42, 1117-1127*
## Function of specific autobiographical memory

<table>
<thead>
<tr>
<th>Function</th>
<th>Impairment in depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem Solving</td>
<td></td>
</tr>
</tbody>
</table>

Overgeneral memory correlated with impaired problem solving in depression  
Raes et al (2005) *J Affect Disord, 87, 331-335*

| Maintaining optimism /euthymia in the face of stress and monotony |

Overgeneral memory correlated with increased feelings of hopelessness in depression  

| Emotion Regulation |

Overgeneral memory correlated with higher scores on emotional avoidance and affective reaction to failure  

| Develop and maintain social bonds |

Patients have fewer social experiences; unknown if correlated with autobiographical memory  
Social withdrawal predicts depressive symptoms  
Morgan et al (2013) *J Youth Adolesc, 42, 1117-1127*
# Autobiographical Memory Task

Think of a memory for the word: **PARTY**

<table>
<thead>
<tr>
<th>Was your memory:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific</td>
</tr>
<tr>
<td>Categorical</td>
</tr>
<tr>
<td>Extended</td>
</tr>
<tr>
<td>Semantic</td>
</tr>
<tr>
<td>Repeat</td>
</tr>
<tr>
<td>No Memory</td>
</tr>
</tbody>
</table>

# Semantic Control Task

Think of 7 examples of: **FLOWERS**

<table>
<thead>
<tr>
<th>How easy was it for you to come up with examples?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Easy</td>
</tr>
<tr>
<td>Somewhat Easy</td>
</tr>
<tr>
<td>Easy</td>
</tr>
<tr>
<td>Somewhat difficult</td>
</tr>
<tr>
<td>Difficult</td>
</tr>
<tr>
<td>Very Difficult</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How many examples did you think of?</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
<tr>
<td>1-2</td>
</tr>
<tr>
<td>3-4</td>
</tr>
<tr>
<td>5-6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8 or more</td>
</tr>
</tbody>
</table>

# Riser Detection Baseline Task

<table>
<thead>
<tr>
<th>Was the number of risers:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Even</td>
</tr>
<tr>
<td>Odd</td>
</tr>
</tbody>
</table>

tlpna
Autobiographical Memory Test using fMRI

- Memory or Category Cue Word (12 sec)
  - Riser Task (avg. 6 sec jittered)
  - Riser even/odd? (2 sec)
  - Ratings (10 sec each)
  - Riser Task (avg. 6 sec; jittered)

- 10 Runs – 7 min each. Within each run:
  - 6 autobiographical memory cue words
  - 3 category cue words
  - 18 Riser presentations
  - 9 even/odd questions

- Post Scan Interview: Memories coded by experimenter blind to diagnosis to corroborate participants’ ratings

- fMRI Parameters
  - GE Discovery MR750 3T MRI, 8-channel receive-only head coil array
  - EPI: 40 x 3mm acquired axially, TR/TE = 2000/25ms, SENSE acceleration R = 2, flip angle = 90°, image matrix = 96x96, FOV = 240mm, voxel size = 3 x 2.5 x 2.5 mm³
  - MPRAGE: 120 x 1.2mm slices acquired axially, TR/TE = 5/1.93ms, SENSE acceleration R = 2, flip angle = 8°, image matrix = 256x256, FOV = 240mm, in plane resolution = 0.94mm²
Autobiographical Memory in MDD

- Would our fMRI autobiographical memory task replicate behavioral findings of overgeneral autobiographical memory recall?
- Is autobiographical memory overgenerality a trait or state marker?
- Are there differences in the valence of the recalled specific memories in depressed patients?
- Are any of these deficits related to mood?
Autobiographical Memory in MDD

- Patients with MDD have fewer specific and more categorical autobiographical memories

**Participants**

- **HC** n=14; medically and psychiatrically healthy; 50% females; age 29±9 years
- **MDD** n=12; unmedicated at least 3 weeks; meet DSM-IV-R criteria for a current major depressive episode; 33% females; age 34±11 years; HDRS 21 ± 8.30

* Indicates a significant difference between groups at p<0.05

Young et al., (2012). *Psychological Medicine, 42, 345-357*
Autobiographical Memory in MDD

• Would our fMRI autobiographical memory task replicate behavioral findings over overgeneral autobiographical memory recall?  
  YES!

• Is autobiographical memory overgenerality a trait or state marker?

• Are there differences in the valence of the recalled specific memories in depressed patients?

• Are any of these deficits related to mood?
Autobiographical Memory in MDD

- Overgeneral autobiographical memory is a trait marker of MDD

**Participants**

- **HC** n=16; medically and psychiatrically healthy; 63% females; age 27±8 years
- **rMDD** n=16; unmedicated at least 3 weeks; HDRS score < 7; no impairing depressive symptoms for > 3 months; 63% females, age 34±9 years; HDRS 3.06 ± 4.17
- **MDD** n=16; unmedicated at least 3 weeks; meet DSM-IV-R criteria for a current major depressive episode; 63% females; age 32±12 years; HDRS 20 ± 6.82

* Indicates a significant difference from the HC group at p<0.05

Young et al., (2014). *Psychological Medicine, 44*, 2951-2963
Autobiographical Memory in MDD

- Overgeneral autobiographical memory is a trait marker of MDD

Participants

- **HC** n=16; medically and psychiatricly healthy; 69% females; age 36±10 years
- **HR** n=16; medically and psychiatricly healthy; first degree family relative w/ MDD; 69% females; age 33±11 years
- **MDD** n=16; unmedicated at least 3 weeks; meet DSM-IV-R criteria for a current major depressive episode; 69% females; age 38±10 years; HDRS 17.1 ± 5.92

Present in High Risk Participants

* Indicates a significant difference from the HC group at p<0.05

Autobiographical Memory in MDD

• Would our fMRI autobiographical memory task replicate behavioral findings over overgeneral autobiographical memory recall?

• Is autobiographical memory overgenerality a trait or state marker?

  TRAIT marker of MDD

• Are there differences in the valence of the recalled specific memories in depressed patients?

• Are any of these deficits related to mood?
Autobiographical Memory in MDD

- Fewer specific positive autobiographical memories in MDD and rMDD groups compared to HR and HC groups

**Participants**
- **HC** n=60; medically and psychiatrically healthy; 50% females; age 30±9 years
- **HR** n= 27; medically and psychiatrically healthy; first degree family relative w/ MDD; 70% females; age 30±9 years
- **rMDD** n= 25; unmedicated at least 3 weeks; HDRS score < 7; no impinging depressive symptoms for > 3 months; 60% females, age 31±11 years; HDRS 3.88 ± 4.22
- **MDD** n= 42; unmedicated at least 3 weeks; meet DSM-IV-R criteria for a current major depressive episode; 64% females; age 33±9 years; HDRS 19.2 ± 6.11

* Indicates a significant difference between groups at p<0.05
Autobiographical Memory in MDD

• Would our fMRI autobiographical memory task replicate behavioral findings over overgeneral autobiographical memory recall?

• Is autobiographical memory overgenerality a trait or state marker?

• Are there differences in the valence of the recalled specific memories in depressed patients?

  YES! Decreased positive specific memories in depressed and remitted patients

• Are any of these deficits related to mood?
Recalling Specific and Positive autobiographical memories improves ‘stable’ trait measures in MDD and rMDD participants only.

- STAI: State-Trait Anxiety Inventory
- Test-retest reliability = 0.89
- Spielberger (1989) State-Trait Anxiety Inventory: Bibliography (2nd ed.)

* Indicates a significant difference between groups at p<0.05

Young et al., under revision American Journal of Psychiatry
Autobiographical Memory and MDD

- Improvement in ‘stable’ trait measure of anxiety correlated with ability to recall specific positive autobiographical memories in MDD participants

\[ y = -0.1076x + 2.9101 \]
\[ R^2 = 0.2286 \]
\[ p = 0.016 \]

- In contrast, no significant correlation was found in the other groups

\[ y = 0.0386x + 0.3709 \]
\[ R^2 = 0.02099 \]

\[ y = 0.0438x + 3.2074 \]
\[ R^2 = 0.0549 \]

\[ y = 0.039x + 3.2089 \]
\[ R^2 = 0.03357 \]

* Indicates a significant difference between groups at p<0.05

Young et al., under revision *American Journal of Psychiatry*
Autobiographical Memory in MDD

• Would our fMRI autobiographical memory task replicate behavioral findings over overgeneral autobiographical memory recall?

• Is autobiographical memory overgenerality a trait or state marker?

• Are there differences in the valence of the recalled specific memories in depressed patients?

• Are any measures of autobiographical performance related to mood?

YES! Recalling positive memories improves trait measures of anxiety in MDD patients
Treatments for MDD

- Conventional treatments do not address autobiographical memory
  - Antidepressants

- Cognitive-behavioral therapy (CBT)
- Electroconvulsive therapy (ECT)
Treatments for MDD

- Conventional treatments do not address autobiographical memory
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Treatments for MDD

- Conventional treatments do not address autobiographical memory
  - Antidepressants
  - Cognitive-behavioral therapy (CBT)
  - Electroconvulsive therapy (ECT)
    - Side effects include amnesia, impaired autobiographical memory retrieval. Lindsey et al (2000) Arch Gen Psychiatry, 57, 581-590
    - Recent presentation found reduced specificity of AMs following ECT. McClintock et al (2014) Neuropsychopharmacology, 39, s556

Need to better address autobiographical memory
Why not treat autobiographical memory directly?

Training aimed at increasing autobiographical memory specificity

- Treatment as usual does not alter autobiographical memory specificity

- Recalling positive events does not have a benefit on mood for currently depressed or those with a history of depression
Why not treat autobiographical memory directly?

Memory Specificity Training (MEST)

- Decreases depressive symptoms in adolescents
  - Suffering from severe trauma (but not an MDD diagnosis)
  - Only measured changes in self-report symptoms which did not differ at post-training but did at 2 months follow-up
- Decreases depressive symptoms in the elderly
- High drop out rates (~50%)
- Only small immediate improvements that did not differ from the control group at follow-up
Roadmap

• Autobiographical memory for positive information is important and impaired in patients with depression

• **Positive autobiographical memory has understandable brain targets**

• We can target those mechanisms with neurofeedback
fMRI of autobiographical memory

• Current treatments do not alter autobiographical memory specificity

• Understanding the underlying pathophysiology of positive autobiographical memory overgenerality is the path to discovering how to change it

• fMRI: measures brain activity by detecting changes in blood flow
  • Neuronal activation is coupled with cerebral blood flow and oxygenation
  • When an area of the brain is in use, blood flow and oxygen use to that region also increases

• What are the neural systems underlying the behavioral effects of reduced positive specific autobiographical memories?
  • Compared positive specific memory recall to positive example generation
  • 3dANOVA (using AFNI) to identify regional differences in the hemodynamic signal between groups
    • Young et al., (2014). *Psychological Medicine*, 44, 2951-2963
    • Young et al., (2013). *JAMA: Psychiatry*, 70(7), 698-708
  • One region of particular interest…..
The Amygdala

- Critical role in emotional processing and response
  - Phelps et al. (2005) Neuron, 48, 175-187
- Part of a core set of regions recruited during autobiographical memory recall in healthy populations
  - Svoboda et al. (2006). Neuropsychologia, 44, 2189-2208
- Particularly for positive autobiographical memories

Happy > Negative Memories

Piefke et al (2003) Brain, 126, 650-668
The Amygdala and MDD

- Left amygdala responses are exaggerated to negative stimuli and **attenuated to positive stimuli** in MDD
  - Victor et al (2011) *Arch Gen Psychiatry*, 67, 1128-1138

- Responsiveness to positive faces correlated inversely with depression severity

Would the amygdala show a similar pattern for positive autobiographical memory recall? We performed a small-volume correction to examine this hypothesis in our data.
The amygdala and autobiographical memory

- Reduced amygdala activity to positive autobiographical memories in MDD group only

**Participants**

- **HC** n=60; medically and psychiatrically healthy; 50% females; age 30±9 years
- **HR** n= 27; medically and psychiatrically healthy; first degree family relative w/ MDD; 70% females; age 30±9 years
- **rMDD** n= 25; unmedicated at least 3 weeks; HDRS score < 7; no impairing depressive symptoms for > 3 months; 60% females, age 31±11 years; HDRS 3.88 ± 4.22
- **MDD** n= 42; unmedicated at least 3 weeks; meet DSM-IV-R criteria for a current major depressive episode; 64% females; age 33±9 years; HDRS 19.2 ± 6.11

* Indicates a significant difference from the MDD group at p<0.05
The amygdala and autobiographical memory

- Amygdala activity to positive autobiographical memories is inversely correlated with depressive severity in MDD participants

\[ y = -9.8301x + 18.797 \]
\[ R^2 = 0.20036 \]
\[ p = 0.003 \]

- Relationship not seen for negative or specific memories

\[ y = 2.6802x + 18.631 \]
\[ R^2 = 0.01124 \]
\[ p = 0.003 \]
Targeting the Amygdala

Most treatments suppress the amygdala response to negative stimuli

- **Antidepressants**

- **Cognitive Therapy**
- **Other Therapies**
  - Deep Brain Stimulation
  - Sleep Deprivation
  - Vegas Nerve Stimulation

 graphene

\[ t \text{ Score (PSC x 100)} \]

<table>
<thead>
<tr>
<th>Amygdala</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation</td>
<td>![Activation Graph](Anand et al (2007))</td>
<td></td>
</tr>
<tr>
<td>Connectivity</td>
<td>![Connectivity Graph](Anand et al (2007))</td>
<td></td>
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\[ t = \frac{\text{difference in scores}}{\text{standard error of the difference}} \]
Most treatments suppress the amygdala response to negative stimuli

- Antidepressants
- Cognitive Therapy
- Other Therapies
  - Deep Brain Stimulation
  - Sleep Deprivation
  - Vegas Nerve Stimulation
Targeting the Amygdala

Most treatments suppress the amygdala response to negative stimuli

- Antidepressants
- Cognitive Therapy
- Other therapies
  - Deep Brain Stimulation
    - Mayberg et al. (2005) *Neuron*, 45, 651-660
  - Sleep Deprivation
  - Vagus Nerve Stimulation

Zobel et al. (2005)
Why not Down-regulate the Amygdala?

• Difficulties in down-regulating regions involved in emotion

• Study attempted amygdala down-regulation in healthy controls

Roadmap

• Autobiographical memory for positive information is important and impaired in patients with depression

• Positive autobiographical memory has understandable brain targets

• **We can target those mechanisms with neurofeedback**
Neurofeedback

- **Neurofeedback**: information about brain activity is fed back to the user
  - Spatial specificity of fMRI allows for targeting specific brain regions

- Healthy individuals can learn to control neurophysiological activity in a variety of regions
  - Sulzer et al. (2013) NeuroImage, 76, 386-399

- Evidence of clinical utility in reducing symptoms of
  - Sulzer et al. (2013) NeuroImage, 76, 386-399
    - Chronic pain
    - Tinnitus
    - Parkinson’s Disease
**Goal:** restore the normative positive processing bias evinced in healthy individuals to MDD patients via the use of amygdala neurofeedback **

**Training MDD participants to access and modulate amygdala activity for the purpose of generating positive autobiographical memories and emotions holds potential to improve the emotional state in MDD**
- **Neurofeedback runs** divided into alternating 40-second blocks of rest, happy and count tasks.
- Each run lasts 8 minutes and 40 seconds.
- **Practice** run in which participant uses one memory per Happy block.
- **Transfer** run in which no neurofeedback provided.
• Participants recall positive autobiographical memories that are specific, vivid, and highly arousing in order to activate amygdala.

• Dynamic red bar shows activation as percent signal change.
  • Relative to the amygdala signal for the preceding 40s rest block
  • The red feedback bar is updated every 2 sec.

• Static blue bar acts as a target level that gets higher as the experiment progresses.

• Some common examples of happy memories:
  • Time with a favorite family member or pet
  • Birth of their child
  • A fun vacation or special date
• Mentally count backwards from 300 by a given number.
• Used to distract participant from happy memories and allow amygdala signal to return to baseline.

• Used to determine baseline for the neurofeedback task.
• **ROI Placement:**
  - **Experimental Feedback:**
    Left Amygdala (-21, -5, -16)
  - **Control Feedback:**
    Left HIPS (-42, -48, 48)

• **fMRI Parameters**
  - GE Discovery MR750 3T MRI, 8-channel receive-only head coil array
  - **EPI:**
    - FOV/slice = 240/2.9mm
    - axial slices per volume = 34
    - acquisition matrix = 96x96
    - TR/TE = 2000/30ms
    - SENSE acceleration factor R = 2
    - flip angle = 90°
    - sampling bandwidth = 250kHz
  - **MPRAGE:**
    - FOV = 240mm
    - slice thickness = 1.2mm
    - image matrix = 256x256
    - TR/TE = 5/19.ms
    - SENSE acceleration R = 2
    - flip angle = 10°
    - TD = 1400ms
    - TI = 725ms
    - sampling bandwidth = 31.2kHz
Pilot Study: MDD Experiment

- Can depressed individuals use rtfMRI-nf to enhance their amygdala hemodynamic response to positive memories?
  - **Hypothesis**: patients receiving amygdala neurofeedback (relative to HIPS neurofeedback) will elevate their amygdala activity during positive memory recall following a single training session

- Does regulating amygdala activity alter mood?
  - **Hypothesis**: patients receiving amygdala neurofeedback (relative to HIPS neurofeedback) will have decreased scores on state measures of negative affect and increased scores on state measures of positive affect
  - **How to test**: Profile of Mood States (POMS), Visual Analogue Scale (VAS), State-Trait Anxiety Inventory (STAI) pre- and post-neurofeedback (same day)

**Participants**

- N=21; 14 experimental group, 7 control group
  - DSM-IV-R diagnosis of major depressive disorder
  - Currently experiencing a major depressive episode
    - MADRS = 27.1 ± 6.69 Experimental Group; 31.4 ± 6.71 Control Group
  - Unmedicated for at least 3 weeks prior to the study
  - Age 37 ± 9 years; 86% females

Young et. al. (2014) *PLoS One*, 9(2), e88785
Pilot Study: MDD Experiment

Left Amygdala

* Indicates a significant difference from 0 at p <0.05;  
# Indicates a significant difference from the Experimental group at p<0.05

Error bars indicate +/- one standard error of the mean

Young et. al. (2014) *PLoS One*, 9(2), e88785
Pilot Study: MDD Experiment

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>State</strong></td>
<td>-3.36 (12.9)</td>
<td>1.10 (8.44)#</td>
</tr>
<tr>
<td><strong>Trait</strong></td>
<td>-4.18 (5.44)*</td>
<td>-1.60 (5.78)#</td>
</tr>
<tr>
<td>POMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>-5.00 (6.66)*</td>
<td>-2.50 (8.45)#</td>
</tr>
<tr>
<td>Tension</td>
<td>-1.27 (8.71)</td>
<td>-2.70 (2.91)*</td>
</tr>
<tr>
<td>Anger</td>
<td>-1.00 (7.11)</td>
<td>-3.10 (5.15)*</td>
</tr>
<tr>
<td>Vigor</td>
<td>3.73 (8.75)</td>
<td>1.50 (5.46)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>-3.82 (5.06)*</td>
<td>-0.80 (7.97)</td>
</tr>
<tr>
<td>Confused</td>
<td>-1.27 (2.45)</td>
<td>-0.90 (4.18)</td>
</tr>
<tr>
<td>Friendly</td>
<td>1.64 (5.84)</td>
<td>-1.00 (5.91)#</td>
</tr>
<tr>
<td>Total</td>
<td>-17.0 (31.9)</td>
<td>-10.6 (26.7)</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Happy</strong></td>
<td>1.77 (2.44)*</td>
<td>0.50 (1.51)*#</td>
</tr>
<tr>
<td>Restless</td>
<td>-0.68 (2.19)</td>
<td>-0.40 (3.69)</td>
</tr>
<tr>
<td>Sad</td>
<td>-1.82 (2.36)</td>
<td>-0.50 (4.30)</td>
</tr>
<tr>
<td>Anxious</td>
<td>-0.09 (3.30)</td>
<td>-0.60 (2.84)</td>
</tr>
<tr>
<td>Irritated</td>
<td>0.41 (2.87)</td>
<td>-0.90 (1.60)</td>
</tr>
<tr>
<td>Drowsy</td>
<td>-0.96 (2.52)</td>
<td>0.00 (3.37)</td>
</tr>
<tr>
<td>Alert</td>
<td>-0.14 (0.95)</td>
<td>0.10 (1.10)</td>
</tr>
</tbody>
</table>

Ability to regulate amygdala correlated positively with change in happiness ratings in the experimental group

* Indicates a significant difference from 0 at p <0.05
# Indicates a significant difference from the experimental group at p<0.05
Numbers in parentheses indicate one standard deviation of the mean

y = 0.0776x + 0.0572
R² = 0.28961

Young et. al. (2014) *PLoS One*, 9(2), e88785
Ability to regulate amygdala correlated inversely with the length of the current depressive episode, and positively with alertness.

\[ y = -0.0034x + 0.3672 \]
\[ R^2 = 0.42286 \]
\[ p = 0.025 \]

\[ y = 0.0176x - 0.4979 \]
\[ R^2 = 0.25991 \]
\[ p = 0.035 \]
Pilot Study: MDD Experiment

• Can depressed individuals use rtfMRI-nf to enhance their amygdala hemodynamic response to positive memories?
  • MDD participants can learn to regulate their amygdala using neurofeedback within a single training session.
  • The observed training effect generalized to the Transfer run, in which neurofeedback was no longer provided.
  • Important individual differences in who can successfully be trained to regulate their amygdala.

• Does regulating amygdala activity alter mood?
  • Improvements evident in state measures of mood and anxiety.

Young et. al. (2014) *PLoS One*, 9(2), e88785
Pilot Study: Unresolved Questions

• **Do additional sessions improve amygdala response or depression scores?**
  - **Hypothesis**: an additional session of amygdala neurofeedback will result in decreased severity of depression ratings and increased amygdala activity in response to training
    - **How to test**: 2 rtfMRI-nf sessions, 1 week apart

• **Can amygdala neurofeedback improve more than temporary mood states?**
  - **Hypothesis**: amygdala neurofeedback will result in decreased severity of both clinician-administered and self-report measures of depression severity
    - **How to test**: Administer Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), and Beck Depression Inventory (BDI) at baseline, each neurofeedback session, and one week following the 2nd session

• **Can amygdala neurofeedback alter autobiographical memory specificity?**
  - **Hypothesis**: amygdala neurofeedback will result in an increased percent of specific memories, particularly of positive valence compared to baseline
    - **How to test**: Baseline and follow-up scores on the 18 cue Autobiographical Memory Test
MDD: Clinical Trial

Differences from Pilot Study:

- Transfer run at the beginning and end of the study
  - Does training elevate amygdala beyond baseline ability?

- Registered as a clinical trial: NCT02079610
  - Randomized, double-blind
- Research supported by the National Institute Of Mental Health of the National Institutes of Health under Award Number K99MH101235
### Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th><strong>Experimental Group</strong></th>
<th></th>
<th><strong>Control Group</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre Training</td>
<td>Post Training</td>
<td>Pre Training</td>
<td>Post Training</td>
</tr>
<tr>
<td>Age</td>
<td>35 (12)</td>
<td></td>
<td>33 (8)</td>
<td></td>
</tr>
<tr>
<td>MDE Length in months</td>
<td>21.1 (21.8)</td>
<td></td>
<td>17.6 (18.1)</td>
<td></td>
</tr>
<tr>
<td>MADRS</td>
<td>30.2 (9.24)</td>
<td>17.8 (11.0)</td>
<td>25.0 (7.93)</td>
<td>23.1 (9.76)</td>
</tr>
<tr>
<td>HDRS</td>
<td>24.0 (6.63)</td>
<td>13.6 (7.35)</td>
<td>18.1 (5.22)</td>
<td>15.9 (5.57)</td>
</tr>
<tr>
<td>BDI</td>
<td>30.9 (7.80)</td>
<td>19.0 (10.2)</td>
<td>26.5 (11.6)</td>
<td>26.3 (11.9)</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate one standard deviation of the mean

MDE = major depressive episode
MADRS = Montgomery-Asberg Depression Rating Scale
HDRS = Hamilton Depression Rating Scale (21 item)
BDI = Beck Depression Inventory

**Recruitment Goal:** 40 participants by April 2016 (20/group)
MDD: Clinical Trial

Error bars indicate +/- one standard Error of the mean; * significant difference from 0 at p<0.05; # significant difference from the active group at p<0.05
MDD: Clinical Trial

Amygdala activity for positive memories during transfer runs pre- and post-neurofeedback training for each subject

Length of current episode = 2 years, others in active group average 15 months (range 3-19)
Starting MADRS score = 40, one of the more severely depressed participants
# Indicates a significant difference from the Experimental group at p<0.05
MDD: Clinical Trial

Individual Data

![Graph showing MADRS Score over time for Experimental amygdala rtfMRI-nf and Control HIPS rtfMRI-nf](image)
MDD: Clinical Trail

Change in amygdala functional connectivity from baseline Happy condition to the final transfer run following training

<table>
<thead>
<tr>
<th>Amygdala Connectivity After Training</th>
<th>Area</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Caudate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Putamen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Putamen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Thalamus</td>
<td>Relay Station</td>
<td>Sherman &amp; Guillery (2000) <em>Exploring the Thalamus</em></td>
</tr>
<tr>
<td>L Superior Temporal Gyrus / BA 22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p<0.05, cluster size > 30

MDD: Clinical Trail

Change in amygdala-VLPFC functional connectivity from baseline to final transfer run following training correlates with improvements in MADRS scores.

**L Ventrolateral PFC / BA 44***

![Brain Images]

$X=-53, Y=9$

**Enjoyment, emotional expression**


\[ y = -86.214x - 5.3278 \]
\[ R^2 = 0.74002 \]

\[ p=0.01 \]

\[ p<0.05, \text{ cluster size } > 30 \]

MDD: Clinical Trial

Amygdala rtfMRI-nf intervention is changing autobiographical memory recall for *Positive Specific Memories*!

* Indicates a significant difference from Baseline at p<0.05
MDD: Clinical Trial

Correlations between change in memory specificity, change in MADRS scores, and average amygdala activity during training

**Experimental Group**

\[ Y = -0.52x - 23.3 \]
\[ R^2 = 0.33, p=0.02\]

**Control Group**

\[ Y = -66.4x - 22.1 \]
\[ R^2 = 0.53, p=0.01\]

\[ Y = 56.7x + 2.76 \]
\[ R^2 = 0.31, p=0.025\]
Conclusions

• Do additional sessions improve amygdala response or depression scores?
  YES: While changes could be seen following one session, the additional session resulted in even greater symptom improvement

• Can amygdala neurofeedback improve more than temporary mood states?
  YES: Both clinician-administered and self-report measures of depressive symptoms decreased in the experimental group

• Can amygdala neurofeedback alter autobiographical memory specificity?
  YES!!! Autobiographical memory specificity, particularly for positive events, increased from baseline following amygdala neurofeedback
Major Depressive Disorder is a debilitating and difficult to treat illness.

Autobiographical memory overgenerality is a trait maker of MDD that is not addressed by current treatments.

The amygdala is under-responsive to positive stimuli in MDD.
  - Including to positive autobiographical memories

Individuals with depression are able to use real-time fMRI neurofeedback to increase their amygdala response to positive autobiographical memories.

Learning to regulate the amygdala response to positive memories improves symptoms and autobiographical memory recall in MDD participants.
Advantages:

- **Non-invasive**
- Translational approach informed by research into the biological mechanisms underlying onset and recovery from MDD
- Uses principles of CBT to teach strategies that will eventually become self-sustainable
- Enhances feelings of self-efficacy (important for cognitive restructuring)
- Leads to better understanding of brain processes underlying MDD

Disadvantages:

- **Cost**
- **Environment**
- Potential that maladaptive plasticity could be induced if dysfunctional strategies are used
- Not suitable for claustrophobic patients or those with metal implants

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14 Farahbod et al. 2010 *Clinical EEG and Neuroscience* 41(1): 19-23
Future Directions

Planned Analyses with Current Data Set

- Determine who will benefit from amygdala neurofeedback
  - Demographic factors, motivation, duration of illness
- Concurrent EEG identifying correlates of amygdala regulation
  - **Develop and test EEG intervention for use outside of the scanner**
    - Reduce cost, expand environment in which intervention can be performed
- Examine changes in functional connectivity
  - **Allow for development of network-based rtfMRI-nf**
Future Directions

Future Studies

• Determine other populations that might benefit from amygdala neurofeedback
  • NIMH RDoC approach: cognitive and positive valence systems
• Adapt procedure for use with adolescent populations
• Determine whether standard treatments might benefit from augmentation with amygdala neurofeedback
  • Cognitive-behavioral therapy, antidepressants
• Determine optimal number of sessions and duration of antidepressant effects
This work was supported by the Laureate Institute for Brain Research and the William K. Warren Foundation, through the National Institutes of Mental Health Award K99MH101235, and by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation.
MDD: Clinical Trial – HIPS Activity

Error bars indicate +/- one standard Error of the mean
Amygdala rtfMRI-nf intervention is changing autobiographical memory recall!
MDD: Clinical Trial

Amygdala rtfMRI-nf intervention is NOT changing negative autobiographical memory recall
MDD: Clinical Trial

Amygdala time course (relative to rest) for first and final transfer runs
MDD: Clinical Trail

Control Group: Amygdala rtfMRI-nf visit following completion of the study

Left Amygdala (happy - rest)

% Signal Change

-0.2  -0.1  0  0.1  0.2  0.3  0.4  0.5  0.6
Pre-Training Transfer  Practice  Training Run 1  Training Run 2  Training Run 3  Post-Training Transfer