Brain Imaging in Mood Disorders
Terence A. Ketter, M.D.

Disclosure Information
Research Support / Consultant / Speaker
Abbott Laboratories
Bristol-Myers Squibb
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Eli Lilly & Co.
GlaxoSmithKline
Janssen Pharmaceutica
Nancy Pritzker Research Network
National Institute of Mental Health
Pfizer, Inc.

Commercial Scanning?

Temporal Domains of Affective Experiences

<table>
<thead>
<tr>
<th>Duration</th>
<th>Emotions</th>
<th>Moods</th>
<th>Temperaments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seconds</td>
<td>Acute</td>
<td>Subacute /</td>
<td>Chronic / genetic</td>
</tr>
<tr>
<td>to minutes</td>
<td>robust</td>
<td>absent</td>
<td>Absent / subtle</td>
</tr>
<tr>
<td>Hours</td>
<td>Variable</td>
<td>Cognitions</td>
<td>Cognitive-affective</td>
</tr>
<tr>
<td>to months</td>
<td>/ subtle</td>
<td>interactions</td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>Anterior</td>
<td>Anterior</td>
<td>Anterior cortical /</td>
</tr>
<tr>
<td>to decades</td>
<td>cortical</td>
<td>cortical</td>
<td>anterior limbic /</td>
</tr>
<tr>
<td></td>
<td>/ brainstem</td>
<td>/ anterior</td>
<td>brainstem</td>
</tr>
</tbody>
</table>

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Neuroanatomical Models

- Limbic lobe (Broca 1878)
- Corticothalamic circuit (Papez 1937)
- Limbic system (MacLean 1952)
- Basal ganglia – thalamocortical loops (Yakovlev '66, Alexander '86)
- Anterior paralimbic model (MacLean '53, Mesulam '88, Vogt '92, Devinsky '95)

Phylogenetic Limbic Schema

Corticothalamic Limbic Schema

Papez’s Medial Limbic Circuit

Basal Ganglia-Thalamocortical Loops

The Triune Brain

<table>
<thead>
<tr>
<th>Limbic Subdivisions</th>
<th>Anterior</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Affect</td>
<td>Visuospatial</td>
</tr>
<tr>
<td>Limbic</td>
<td>Executive</td>
<td>Memory</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Hippocampus</td>
<td></td>
</tr>
<tr>
<td>Ant cingulate</td>
<td>Post cingulate</td>
<td></td>
</tr>
<tr>
<td>OFC, Septum</td>
<td>Post parahippo</td>
<td></td>
</tr>
<tr>
<td>Striatum</td>
<td>Ventral</td>
<td>Dorsal</td>
</tr>
<tr>
<td>Thalamus</td>
<td>VAmc</td>
<td>LD</td>
</tr>
<tr>
<td>MDmc, AM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Prefrontal & Anterior Paralimbic Hypothesis

- Anterior paralimbic areas
  - Contribute to normal emotion
- Prefrontal areas
  - Contribute to normal mood
- Prefrontal & anterior paralimbic
  - Dysfunction in mood disorders
- Dysfunction covaries with
  - Biochemical parameters
  - Clinical parameters (including Rx response)

### Anterior Paralimbic Loop

![Anterior Paralimbic Loop Diagram]

After Alexander GE, et al. 1990

### Structural Imaging Changes in 1° Mood Disorders

- Increased Lateral Ventricular Enlargement *
- Increased Cortical Sulcal Enlargement *
- Increased Third Ventricular Enlargement
- Increased Subcortical Hyperintensities *
  - (younger & older BD, older MDD)
- Frontal / prefrontal Volume Decreases
- Cerebellar Volume Decreases
- Hippocampal Volume Decreases (in MDD) *
- Similar Global Cerebral Volumes *

* Confirmed with Meta-analyses

### Cerebral Hypoplasia/Atrophy in Mood Disorders

**Summary of 57 Controlled Studies**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Significant Increases</th>
<th>Nonsignificant Increases</th>
<th>Equal / Nonsignificant Decreases / Unspecified NS</th>
<th>Significant Decrease</th>
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<tbody>
<tr>
<td>BD Lateral Ventricular Enlargement</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BD Cortical Sulcal Enlargement</td>
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<td></td>
</tr>
<tr>
<td>BD Third Ventricular Enlargement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MO Deep White</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MO Periventricular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MO Subcortical Gray</td>
<td></td>
<td></td>
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</tbody>
</table>

### Subcortical Hyperintensities in Mood Disorders

**Summary of 57 Controlled Studies**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Significant Increases</th>
<th>Nonsignificant Increases</th>
<th>Equal / Nonsignificant Decreases / Unspecified NS</th>
<th>Unspecified Nonsignificant</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD Deep White</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD Periventricular</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
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<td></td>
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Structural Imaging Changes in 2° Mood Disorders
- Neurological disorders
  - Stroke, Huntington’s, Parkinson’s
  - Trauma, tumors, epilepsy
  - Multiple sclerosis
- Anterior paralimbic structures
  - Prefrontal, temporal
  - Basal ganglia
- Lesion laterality effects?
  - Left - depression
  - Right - mania

Depression Frequency After Stroke

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>R</th>
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<tbody>
<tr>
<td>50%</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>17%</td>
<td></td>
<td></td>
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</tbody>
</table>

PET-MRI Coregistration

Original PET  Reoriented MRI  Fused Image
Reoriented PET  Original MRI  Fused Image

Clinical & rCBF Effects of Procaine
- Dramatic affective & psychosensory experiences
- Anterior paralimbic rCBF activation
- Clinical - rCBF correlations
  - Affect with L amygdala
  - Visual hallucinations with global, occipital
- Blunted rCBF responses in mood disorders

Procaine Activates Anterior Paralimbic CBF
- Cytoarchitectonics
  (Brodman)
- CBF Increases
  (32 Healthy Volunteers)

Procaine Increases Anterior Paralimbic CBF

After Robinson RG, Starkstein SE 1990
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Differential Amygdalar Procaine Responses

Left (but not right) amygdala differentially involved in fear and euphoria

\[ \Delta L \text{Amygdala} \]

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>Normalized</th>
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<tbody>
<tr>
<td>Fear</td>
<td>( r .350 )</td>
<td>( .481 )</td>
</tr>
<tr>
<td>Euphoria</td>
<td>( -.467 )</td>
<td>( .466 )</td>
</tr>
<tr>
<td>Vis Halluc</td>
<td>( .432 )</td>
<td>( .244 )</td>
</tr>
<tr>
<td>Aud Halluc</td>
<td>( .060 )</td>
<td>( .072 )</td>
</tr>
</tbody>
</table>

\[ \Delta R \text{Amygdala} \]

<table>
<thead>
<tr>
<th></th>
<th>Absolute</th>
<th>Normalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear</td>
<td>( .078 )</td>
<td>( .70 )</td>
</tr>
<tr>
<td>Euphoria</td>
<td>( .070 )</td>
<td>( .73 )</td>
</tr>
<tr>
<td>Vis Halluc</td>
<td>( .190 )</td>
<td>( .35 )</td>
</tr>
<tr>
<td>Aud Halluc</td>
<td>( .291 )</td>
<td>( .070 )</td>
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</tbody>
</table>

\* maximal correlations compared to all other ROIs
p<0.125 limits overall type 1 error to .05 for 4 (L & R amygdala for anxiety and euphoria) comparisons


Medial Occipital CBF Increases with Procaine-Induced Visual Hallucinations

Could Amygdalo-Occipital Efferents Mediate Procaine-Induced Visual Hallucinations?

A Potential Cholinergic Mechanism of Procaine’s Limbic Activation

Procaine Increases Anterior Paralimbic Cerebral Blood Flow (K1) in Rhesus Monkeys
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Blunted Procaine-Induced CBF Increases in Mood Disorders

Healthy Controls (N = 18)
Mood Disorder Patients (N = 9)
Mean absolute CBF increases.

17 Healthy Controls
17 Mood Disorders
Controls - Patients

Limbic rCBF Activation with Emotion Induction

Pharmacological
(Procaine-Induced
Dysphoria / Euphoria)
Neuropsychological
(Self-Induced Sadness)

32 Healthy Volunteers
(15 Women, 17 Men)
11 Healthy Volunteers
(All Women)


Anterior Cingulate & Affect

MEAN ABSOLUTE CEREBRAL METABOLISM DURING REST AND SADNESS INDUCTION (30 HEALTHY VOLUNTEERS)
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Absolute Decreases
Normalized Increases
Normalized Decreases
No Regions with Significant Absolute Increases

rCMRglu Changes with Sustained Sadness in 20 Healthy Volunteers

Ability to Induce Mood Varies

Left Insula Metabolic Decreases Correlate with Degree of Induced Sadness

Differential Basal Ganglia-Thalamocortical Cerebral Metabolic Decreases?

Overlapping Changes with Sustained Sadness
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Function Imaging Changes in 1° Mood Disorders

- Decreased global cerebral activity (older, more depressed pts)
- Decreased dorsolateral prefrontal activity
- Decreased temporal cortical activity
- Decreased basal ganglia activity (MDD)
- Variable anterior cingulate / medial prefrontal activity
- Increased amygdala activity
- Decreased prefrontal phosphomonoesters (euthymic BD)*

* Confirmed with Meta-analyses

Prefrontal / Anterior Paralimbic Function in Mood Disorders

- Baseline deficits
  - Hypoactivity
    - Common
    - Correlates with depression severity
  - Hyperactivity
    - Less common
- Treatment effects on baseline deficits
  - Attenuation (sleep deprivation)
  - Exacerbation (ECT)

Prefrontal / Anterior Paralimbic Function in Mood Disorders

Hypofrontality in Primary Depression


Hypofrontality in Mood Disorders


Hypofrontality a Common Pathway to Depression

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CBF & CMR in Mania

- Limited, at times inconsistent data
- Primary Mania
  - ↑ global CMR vs dep/mixed (Schwartz 87)
  - ↑ diffuse $^{11}$C-glu uptake (Kishimoto 87)
  - ↑ TL, ↓ FL & BG CBF (O’Connell 89, 95)
  - ↓ R TL CBF (Migliorelli 93)
- Secondary Mania
  - ↓ R TL CMR (Starkstein 90)

Cerebral Metabolism Cycles with Mood

Subgenual Prefrontal Hypometabolism in Mood Disorders

Li / VPA Neuroprotective in Mood Disorders?

Global CMRglu in Bipolar Subgroups

*The X-rays indicate you're crying on the inside.*
Corticobasal Dysregulation


Correlation between CBZ and NMO response and baseline cerebral metabolism

“This is a second opinion.
At first, I thought you had something else.”
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DVPX in Medication-Naive and Mood Stabilizer-Naive Bipolar II Depression

Baseline Medial Frontal rCMRglu & DVPX Response

Rostral Cingulate Hypermetabolism Predicts Fluoxetine Response in Unipolar Depression

Baseline CMRglu Predicts Responses in Depression

Medial Prefrontal ¹H-MRS GABA

**p < .01, ***p < .001 compared to week 0.


**p < .01, ***p < .001 compared to week 0.

Brodmann area 32 age / gender covaried


12.5 cc Medial Prefrontal Voxel (24 mm x 25 mm x 20 mm)
18.0 cc Occipital Lobe Voxel (30 mm x 30 mm x 20 mm)

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**Increased GABA in Euthymic Bipolar Disorder Patients on GABAergic Medications**

<table>
<thead>
<tr>
<th></th>
<th>Occipital</th>
<th>Prefrontal</th>
</tr>
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<tbody>
<tr>
<td>Patients</td>
<td>0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>Controls</td>
<td>0.10</td>
<td>0.15</td>
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N = 16


**Schema of Brain GABA in Mood Disorders**

Conclusions

- Biological evidence at levels of
  - Genome, biochemistry, anatomy
- No unitary biological abnormality
- Anterior paralimbic structures
  - Important for emotion
- Prefrontal structures
  - Important for mood
- Pathophysiology & therapeutics
  - Advance one another