Brain Imaging in Bipolar Disorder: A Window into Mind and Mood

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Many Faces of Bipolar Disorder

- **Different mood states**
  - Mania/hypomania
  - Depression
  - Euthymia

- **Different patterns of cycling**
  - Bipolar I
  - Bipolar II
  - Cyclothymia
  - Rapid cycling

- **Different accompanying symptoms / conditions**
  - Psychosis
  - Substance dependence
  - Eating disorders
  - ADHD
  - Personality disorders

- **Different treatments**
In search of...

- **Quicker and more accurate diagnosis**
  - 5.9 years to correct Bipolar I diagnosis
  - 11.6 years to correct Bipolar II diagnosis
  - Spectrum of disorders, continuity with normal mood lability

- **Treatments that work and improve quality of life**
  - Mood stabilizers work but not for all
  - Bipolar depression difficult to treat
  - Little attention to cognition and functional outcome

- **Ways to prevent disabling symptoms from occurring in the first place**
  - Need to understand pathophysiology
  - How do genes and environment interact to lead to symptom expression?
Why use neuroimaging?

- **Primary disordered organ of bipolar disorder is the brain**
- **Behavioral measures and clinical observations are imperfect and far away from the underlying biological causes**
  - Influence of motivation
  - Self-report and clinician biases
  - Compensation may lead to normal performance even if brain is abnormal
- **Neuroimaging allows direct examination of disordered organ**
  - Volume and shape of brain structures
  - Integrity and path of white matter connections
  - Brain response to cognitive challenge
Bipolar Disorder Circuits

Phillips et al, 2009
Bipolar Disorder Circuits

Adapted from Davidson et al, 2000

Strakowski et al, 2005
Structural Neuroimaging

- MRI with T1-weighted images
  - Volume
  - Shape
  - Thickness

Fischl et al. 2002; 2004
Desikan et al., 2006
Structural Neuroimaging

- Diffusion Tensor Imaging
  - Integrity of white matter
  - Tractography
**Volumetric Findings**

- *Decreased* volume of left anterior cingulate
  - Found in both unipolar and bipolar depression with family history
  - Not seen in schizophrenia

*Drevets et al., 1997*
**Volumetric Findings**

- *Increased volume of the amygdala in adults*
  - *Decreased* ↓ volumes seen in pediatric, adolescent, 1\(^{st}\) episode samples; positive relationship to age

- *Increased striatal volume*

- *Subtle alteration of shape in subregions of the right hippocampus* (Bearden et al, 2008)
Voxel-based Findings

- *Mixed* findings, perhaps related to medication status
- *Increased* cortical density only among lithium-treated (Bearden et al, 2007)
White Matter Findings

- *Increased* prevalence of white matter hyperintensities (particularly among old, but even among young bipolars)

- DTI abnormalities
  - *Decreased* fiber organization particularly in frontal cortex
  - *Increased* number of fibers connecting subgenual ACC to hippocampus / amygdala (Houenou et al, 2007)
  - *Increased* organization in these same tracts (uncinate fasciculus) on the left but *decreased* on the right (Versace et al, 2008)
Functional Neuroimaging

- **Positron Emission Tomography**
  - Metabolism
  - Blood flow
  - Receptor binding

- **Functional Magnetic Resonance Imaging**
  - Blood oxygenation
  - Blood flow
Design Issues

- **Mood state**
  - Depressed
  - Manic
  - Euthymic

- **Brain state**
  - Resting
  - Emotional challenge
  - Cognitive challenge
  - Emotio-cognitive challenge

- **Medication state**
Bipolar Depression

- **Resting studies**
  - *Decreases*
    - PFC and subgenual metabolism
    - Caudate metabolism
  - *Increases*
    - Amygdala metabolism
  - Deficits improve with anti-depressant / mood stabilizer treatment

*Drevets et al., 2001*
Bipolar Depression

- Emotional challenge studies
  - Mood induction
    - *Decreases* in cortical regions
      - Dorsal-ventromedial frontal, posterior cingulate, inferior parietal, temporal, and *lateral prefrontal* in response to sad mood induction (Kruger et al, 2003)
    - *Increases* in subcortical regions
      - Thalamus, amygdala, hypothalamus, and *globus pallidus* to positive-captioned pictures (Malhi et al, 2004)
      - Insula, cerebellum (Kruger et al, 2003)
Bipolar Depression

- Emotional challenge studies (continued)

  - Facial affect recognition
    - *Decreases* in cortical and subcortical regions depending on which emotion
      - DLPFC to mild happy faces (Hassel et al., 2008)
      - Parahippocampus and thalamus to negative (Almeida et al., 2009)
    - *Increases* in other cortical and subcortical regions
      - Subcortical and ventral PFC (Lawrence et al., 2004)
      - Fronto-striatal-thalamic regions to happy faces and somatosensory and motor to fearful faces (Chen et al., 2006)
      - Left ventral striatum (Hassel et al., 2008) and amygdala (Almeida et al., 2010)
      - DLPFC to positive (Almeida et al., 2009)
Bipolar Depression

- **Cognitive challenge studies**
  - **Stroop task**
    - *Decreases* in prefrontal areas
      - *Left rostral ventral PFC* (mood independent) (Blumberg et al, 2003)
      - *Dorsal Cingulate* (Marchand et al, 2007)
      - *Ventrolateral PFC* (Kronhaus et al, 2006)
    - *Increases* also found
      - *Left ventral PFC* (Blumberg et al, 2003)
  - **Motor task**
    - *Decreases* in some subcortical regions
      - *Right globus pallidus* (Caligiuri et al, 2006)
    - *Increases* in other subcortical regions and some cortical areas
      - Unwanted ipsilateral activation in right supplementary motor area (Caligiuri et al, 2004)
      - *Ventral striatum, sensorimotor, anterior cingulate during paced motor task* (Marchand et al, 2007)
Bipolar Depression

- Emotio-cognitive challenge studies

- N-back following sad mood induction
  - Decreases
    - Dorsal anterior cingulate (Deckersbach et al, 2008)
  - Increases
    - DLPFC (Deckersbach et al, 2008)
Bipolar Depression versus Unipolar Depression

- Increased amygdala activation to happy faces
- Lack of normalization of limbic overactivation with remission
- Increased lateral prefrontal activity during cognitive challenge in depressed but not remitted state
Mania

- **Resting studies**
  - *Decreases* in prefrontal
    - Subgenual PFC metabolism
    - Orbitofrontal flow
  - *Increases* in other areas and subcortical
    - Anterior cingulate blood flow
    - Basal ganglia
  - *Mixed* findings in temporal lobe
  - No differences in D$_2$ receptor binding

*Drevets et al., 2001*
Mania

- Emotional challenge
  - Mood induction
    - Increases
      - Caudate and thalamus to negative-captioned pictures (hypomania) (Malhi et al, 2004)
  - Affective faces
    - Decreases
      - Subgenual anterior cingulate and amygdala (Lennox et al, 2004)
    - Increases
      - Posterior cingulate and posterior insula (Lennox et al, 2004)
      - Fusiform gyrus (Chen et al, 2006) to sad faces; somatosensory and motor to fearful faces (Chen et al, 2006)
      - Amygdala (Altshuler et al, 2005)
Mania

- **Cognitive challenge studies**
  - **Stroop task**
    - *Decreases in prefrontal response*
      - Right ventral frontal response, left rostral ventral PFC (mood independent) (Blumberg et al, 2003)
  - **Decision making**
    - *Decreases in frontal response*
      - Inferior frontal and right frontopolar (Rubinsztein et al, 2001)
    - *Increases in other regions*
      - Anterior cingulate (Rubinsztein et al, 2001)
Mania

- Cognitive challenge studies
  - Go-No Go
    - Decreases
      - Right orbitofrontal cortex, right hippocampus, and left cingulate
  - Motor
    - Increases
      - Globus pallidus; untreated show more overactivation (Caligiuri et al, 2003);
      - Unwanted ipsilateral supplementary motor activation (Caligiuri et al, 2004)
  - Working memory
    - Failure to de-activate medial prefrontal region; related to poorer performance (Pomarol-Clotet et al, 2011)
Mania

- Emotio-cognitive challenge tasks
  - Affective go-no go
    ♦ Increases
      • Left ventrolateral PFC to emotional targets (Elliott et al, 2004)
Euthymia / Remission

- Emotional challenge tasks
  - Facial affect discrimination
    - *Decreases* in lateral prefrontal cortex
      - Dorsal PFC response to fearful faces (Yurgelun-Todd et al, 2000 [mixed mood states])
      - DLPFC to mildly happy faces (Hassel et al, 7th ICBD)
    - *Increases* in limbic areas
      - Amygdala activation to fearful faces (Yurgelun-Todd et al, 2000 [mixed mood states])
      - Left ventral striatum to mild happy faces (Hassel et al, 7th ICBD)
      - Hippocampal activation to fearful faces (Malhi et al, 2007)
Euthymia / Remission

- Emotional challenge tasks (continued)
  - Sad mood induction
    - **Decreases**
      - Dorsal-ventromedial frontal, posterior cingulate, inferior parietal, and temporal (Kruger et al, 2003)
    - **Increases**
      - Insula, cerebellum, dorsal anterior cingulate, premotor cortex (Kruger et al, 2003)
**Euthymia / Remission**

- **Cognitive challenge tasks**
  - **Working memory**
    - *Decreases* in lateral frontal and other cortical regions
      - DLPFC and anterior cingulate (Frangou et al, 2005)
      - Left frontal, middle temporal, cuneus/precuneus, and cerebellum (Monks et al, 2004)
      - Inferior and lateral prefrontal activation during all parts of working memory (encode, delay, response execution) (Lagopoulos et al, 2007)
      - Connectivity of amygdala with other cortical areas (Gruber et al, 2010)
    - *Increases* in cortical and medial frontal
      - Fronto-polar, temporal and parietal cortex and basal ganglia (Adler et al, 2004)
      - Superior frontal (Frangou et al, 2005)
      - Precentral, supramarginal, and medial frontal (Monks et al, 2004)
      - Medial prefrontal during delay (Lagopoulos et al, 2007)
Euthymia / Remission

- **Failure to deactivate** default mode regions during working memory

Healthy Comparison

1-back

-31.5 -11.5 8.5

Euthymic Bipolar Patients

1-back

-31.5 -11.5 8.5

-0.2% 0.2%

- Related to worse performance

Eyler Lab, In preparation
Euthymia / Remission

- **Cognitive challenge tasks (continued)**
  - **Stroop task**
    - *Decreases in many cortical regions*
      - Cerebellar, middle temporal, putamen, and middle frontal gyrus; no difference in DLPFC (Strakowski et al, 2005)
      - Fusiform, DLPFC, ventrolateral PFC, and precuneus and greater deactivation of orbital and medial prefrontal cortex (Kronhaus et al, 2006)
      - Right dorsal attention to action division of anterior cingulate (Gruber et al, 2004)
      - Medial and inferior frontal, posterior cingulate, parahippocapal, fusiform middle occipital, and pons (Roth et al, 2006)
    - *Increases*
      - Occipital (Strakowski et al, 2005)
      - DLPFC (Gruber et al, 2004)
Euthymia / Remission

- **Cognitive challenge tasks (continued)**
  - Continuous performance task
    - *Decreases* in some regions
      - Orbitofrontal and fusiform (Strakowski et al, 2004)
    - *Increases* in emotional regions
      - Limbic, paralimbic, ventrolateral PFC (Strakowski et al, 2004)
  - Verbal fluency
    - *Increases*
      - Prefrontal response (Curtis et al, 2001)
Euthymia / Remission

- Cognitive challenge tasks (continued)
  - Learning and memory
    - Decreases in cortical and medial temporal
      - Left DLPFC response, inferior prefrontal, hippocampus, and inferior temporal during verbal learning (Deckersbach et al, 2006)
      - Hippocampal and parahippocampal activation in face-name encoding and recall, decreased DLPFC in encoding (Glahn et al, 7th ICBD)
    - Increases in other regions
      - Ventrolateral, parahippocampal, temporal, and occipital during verbal learning (Deckersbach et al, 2006)
Euthymia / Remission

- Emotio-cognitive challenge tasks
  - Iowa Gambling Task
    - Decreases
      - Ventral PFC activation (Frangou et al, 2005)
  - Affective Go-No Go
    - Increases
      - Temporal during emotional go-no go; increased orbitofrontal and caudate to emotional vs. neutral distractors (Wessa et al, 2007)
Euthymia / Remission

- Emotio-cognitive challenge tasks
  - Emotional Stroop
    - Decreases
      - Cortical and subcortical activation, particularly in ventral prefrontal cortex (Malhi et al, 2005)
  - Working memory for affective words
    - Decreases
      - Cingulate, prefrontal and parahippocampus regardless of valence; valence-specific decreases in additional more posterior regions (Malhi et al, 2007)
<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Volume</th>
<th>White Matter Connections</th>
<th>Resting</th>
<th>Emotional</th>
<th>Cognitive</th>
<th>Emotion-Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>↑↓</td>
<td>↑</td>
<td>↑Dep</td>
<td>↑Dep</td>
<td>↓Man</td>
<td>↑↓ Eut</td>
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<tr>
<td>Striatum</td>
<td>↑</td>
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<td>↓Dep</td>
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<td>↑Man</td>
<td>↑↓ Dep</td>
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<tr>
<td>Anterior Cingulate</td>
<td>--</td>
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<td>↑Man</td>
<td>↓Man</td>
<td>↑Eut</td>
<td>↑↓ Man</td>
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<tr>
<td>Orbito- / Ventral Frontal</td>
<td>↓</td>
<td>↓</td>
<td>↓Dep</td>
<td>↑↓Dep</td>
<td>↓Man</td>
<td>↑↓ Man</td>
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<tr>
<td>DLPFC</td>
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<td>↑↓Dep</td>
<td>↑↓ Dep</td>
<td>↑↓Eut</td>
<td>↑↓ Eut</td>
</tr>
</tbody>
</table>
Bipolar Disorder Circuits

Strakowski et al, 2005
Confounders & Comorbidities

**Treatment**

- **Lithium**
  - Grows your brain
  - Anticholinergic effects

- **Pharmacologic Treatment**
  - Motor: treated have more normal striatal hyperactivation (Caligiuri et al, 2004)
  - Emotional faces: treated have lower amygdala activation and normal rostral anterior cingulate activation (Blumberg et al, 2005)

- **Total sleep deprivation with light therapy**
  - Responders showed opposite change in brain response to valenced words compared to non-responders (Benedetti et al, 2007)
Confounders & Comorbidities

- **Clinical subtypes**
  - Rapid cycling
    - Smaller VPFC (Blumberg et al, 2006)
  - Bipolar II
    - Few direct comparisons of BPI and BPII
    - Few structural differences
    - BPI > BPII in resting metabolism of anterior cingulate, middle frontal, inferior parietal lobule (Ketter et al, 2001)

- **Comorbid conditions**
  - Substance use/dependence generally excluded
  - White matter findings exacerbated by cardiovascular, but still present after controlling
  - No studies of effect of anxiety or personality disorder comorbidity
Confounders & Comorbidities

- Developmental issues
  - Continuity between pediatric and adult-onset?
  - **Amygdala** smaller in pediatric, larger in adults
  - Cognitive deficits worse in older adults

- More negative correlation of total gray matter volume and age in bipolar group (Brambilla et al, 2001)

- Steeper declines over 4 years in hippocampal, fusiform, and cerebellar grey in bipolar group (Moorhead et al, 2007)

Depp et al, 2007
Take Home Messages

- Neurobiology of bipolar disorder involves anterior limbic circuits, including amygdala, ventral striatum, anterior cingulate, ventral PFC, and dorsolateral PFC.
- General pattern of hyper-response in limbic areas and hypo-response in cortical monitoring and control areas.
- Still unclear what role mood state plays and difference between unipolar and bipolar.
- More research to be done to understand role of treatment, mood state, cycling patterns, associated disorders, and development.
Ongoing Studies

- Structural and Functional Brain Aging in Bipolar Disorder
- Role of sleep and sleep cycles
- Role of smoking / nicotine in brain’s response to attention
Structural and Functional Brain Aging in Bipolar Disorder

- White Matter Integrity / Organization
- Inter-Regional Communication
- Cognitive Performance

- Gray Matter Integrity
- Regional Brain Function
- Vascular Tone

AGE
Participants

- 85 participants with bipolar disorder
- 85 individuals without mental illness
- Age range 30-79
- Criteria for bipolar group:
  - Bipolar I diagnosis and no other mental disorder
  - Stably medicated
  - No current mood episode
  - First episode at age 13-30
  - Right handed
  - No uncontrolled diabetes or high blood pressure
  - Native English speaker
- Additional criteria for comparison group:
  - No current mental disorder
  - No immediate family members with bipolar, depression, or schizophrenia
- If you want more information, call 858-552-8585, ext 2774.
Sleep

- Disrupted in bipolar disorder
- Sleep disruptions can lead to cognitive difficulties
- Little research on how sleep relates to cognition and brain function in bipolar
- Actigraphy measurement for one week
Smoking and Nicotine

- Rates of smoking much higher among individuals with bipolar than general population
- Nicotine can improve cognitive performance, particularly attention
- Part of increased smoking in bipolar may be self-medication for attention problems
- Little is known about how smoking affects cognition and brain function in bipolar disorder
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