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

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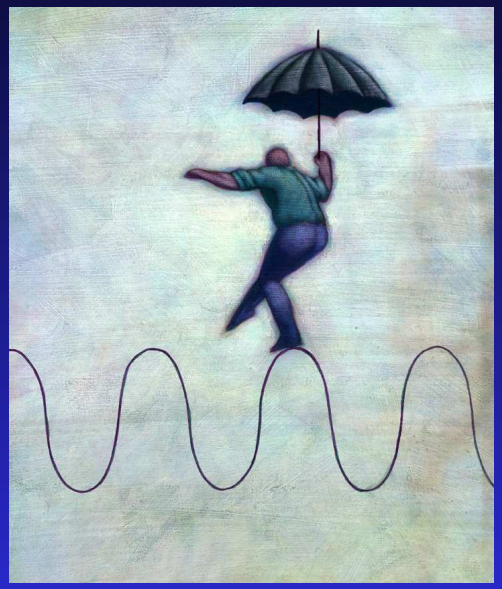
Many Faces of Bipolar Disorder



- 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

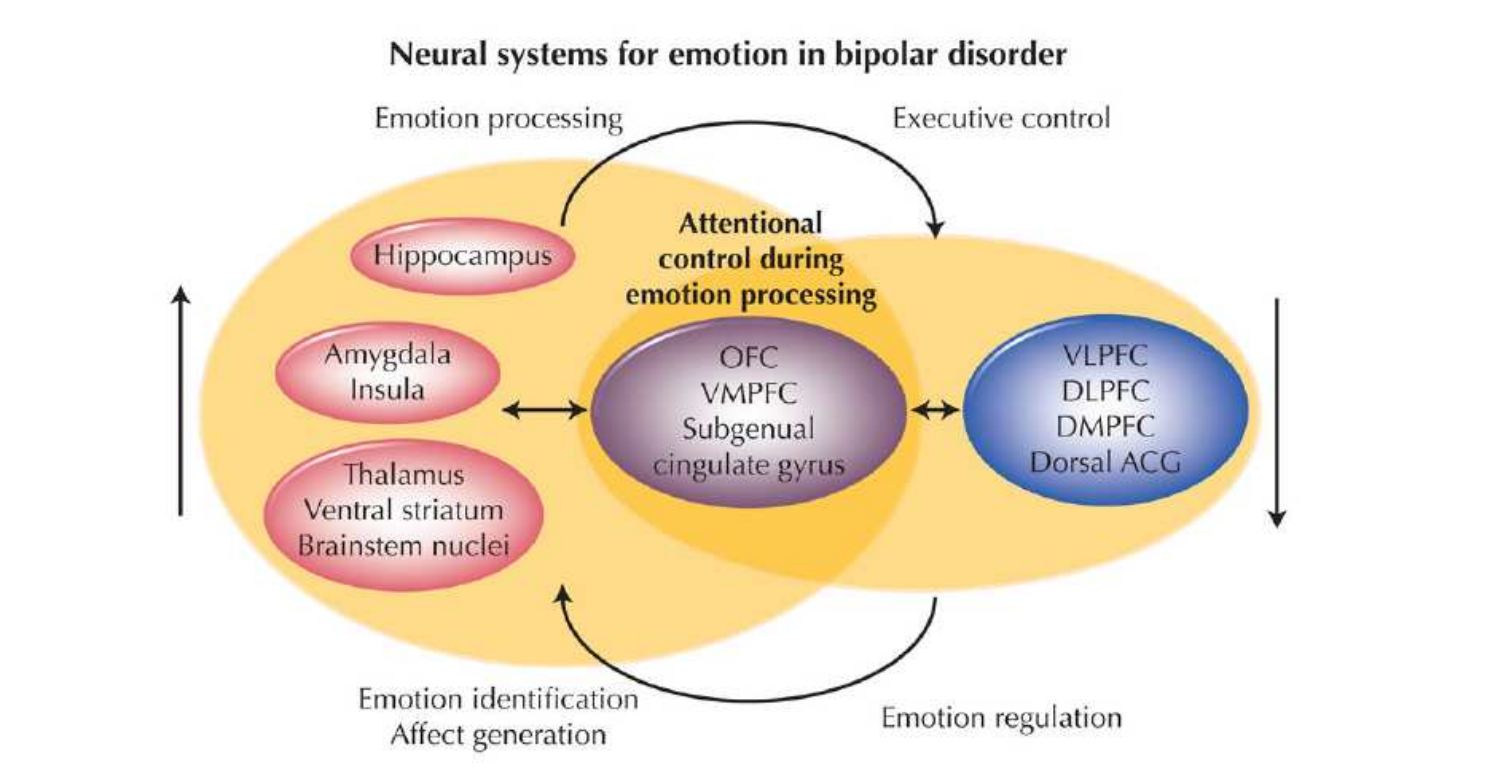
In search of…

- 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?

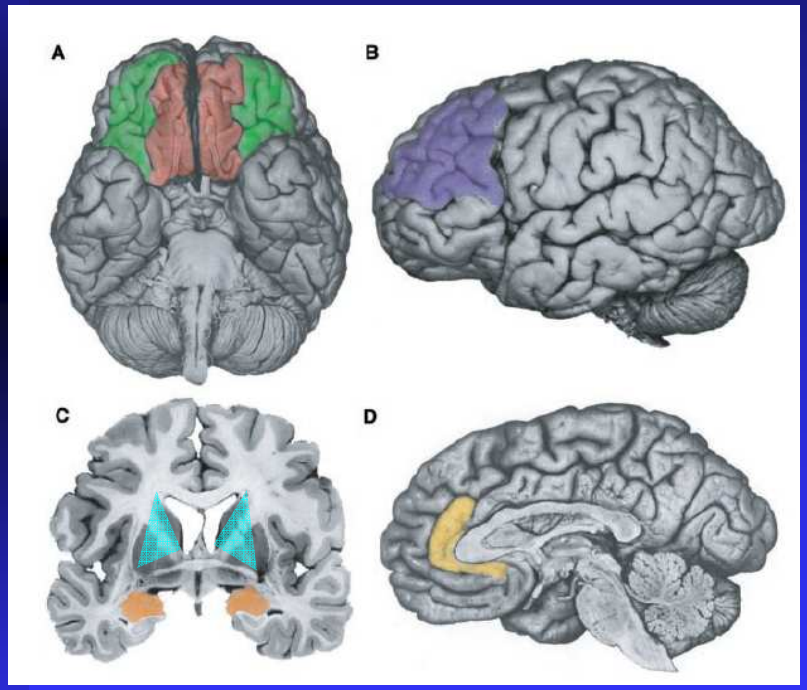
- Primary disordered organ of bipolar disorder is the brain
- Behavioral measures and clinical observations are imperfect and far away from the underlying biological causes
  - Influence of motivation
  - Self-report and clinician biases
  - Compensation may lead to normal performance even if brain is 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

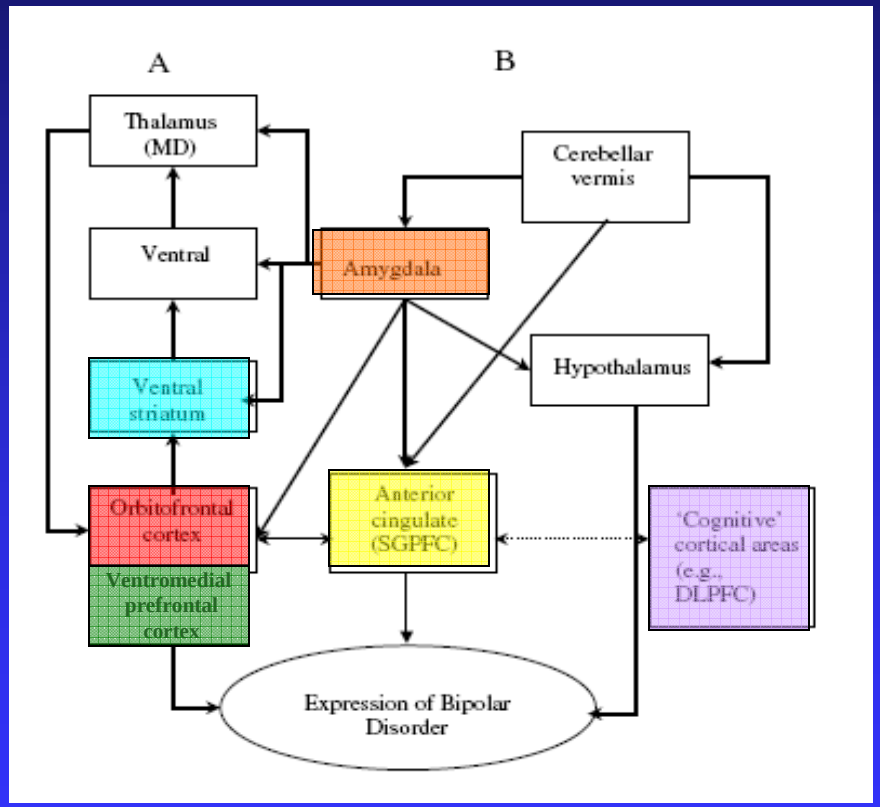


Phillips et al, 2009

Bipolar Disorder Circuits



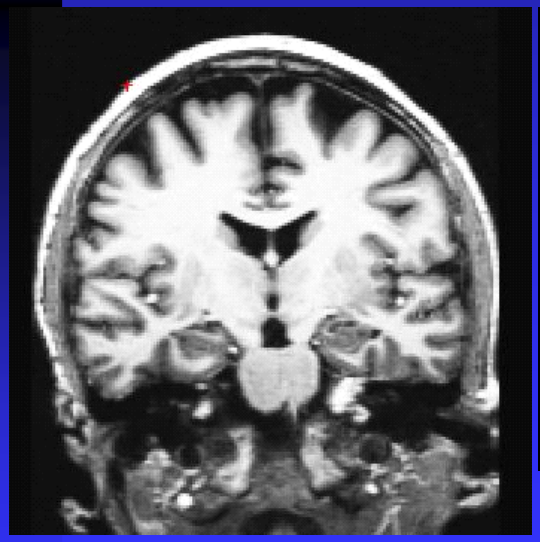
Adapted from Davidson et al, 2000

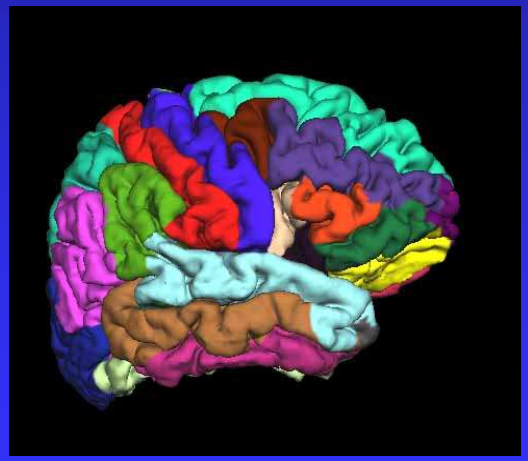


Strakowski et al, 2005

Structural Neuroimaging

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



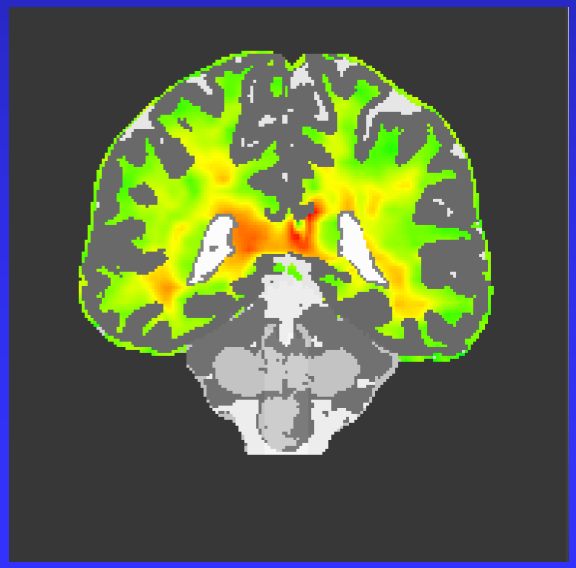


Fischl et al. 2002; 2004

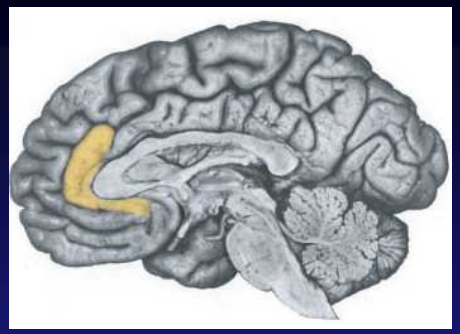
Desikan et al., 2006

Structural Neuroimaging

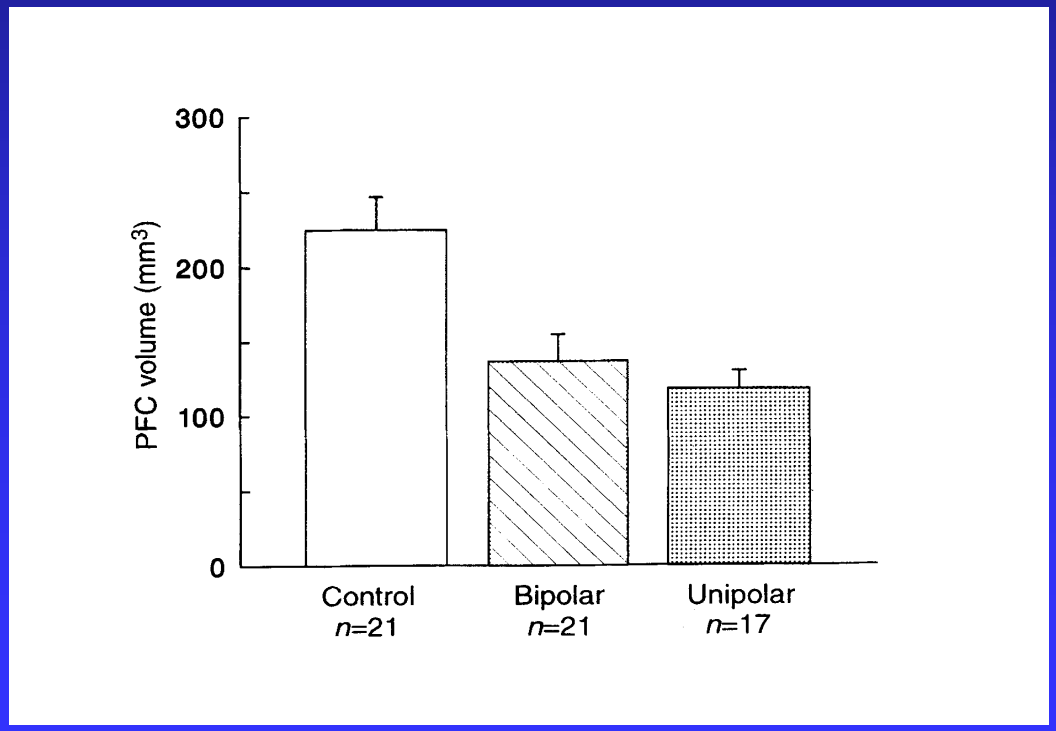
- Diffusion Tensor Imaging
  - Integrity of white matter
  - Tractography



Volumetric Findings

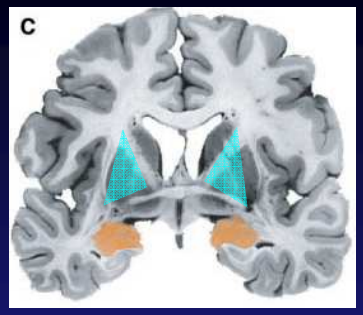


- *Decreased* volume of left anterior cingulate
  - Found in both unipolar and bipolar depression with family history
  - Not seen in schizophrenia

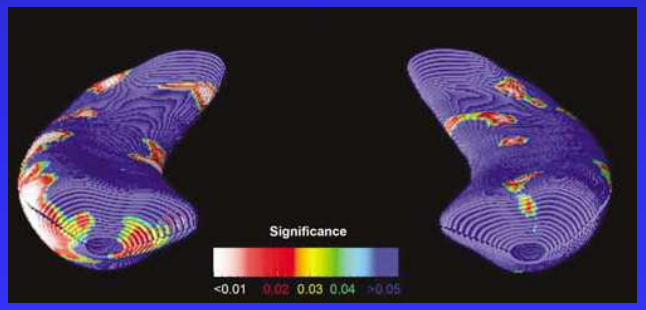


Drevets et al., 1997

Volumetric Findings



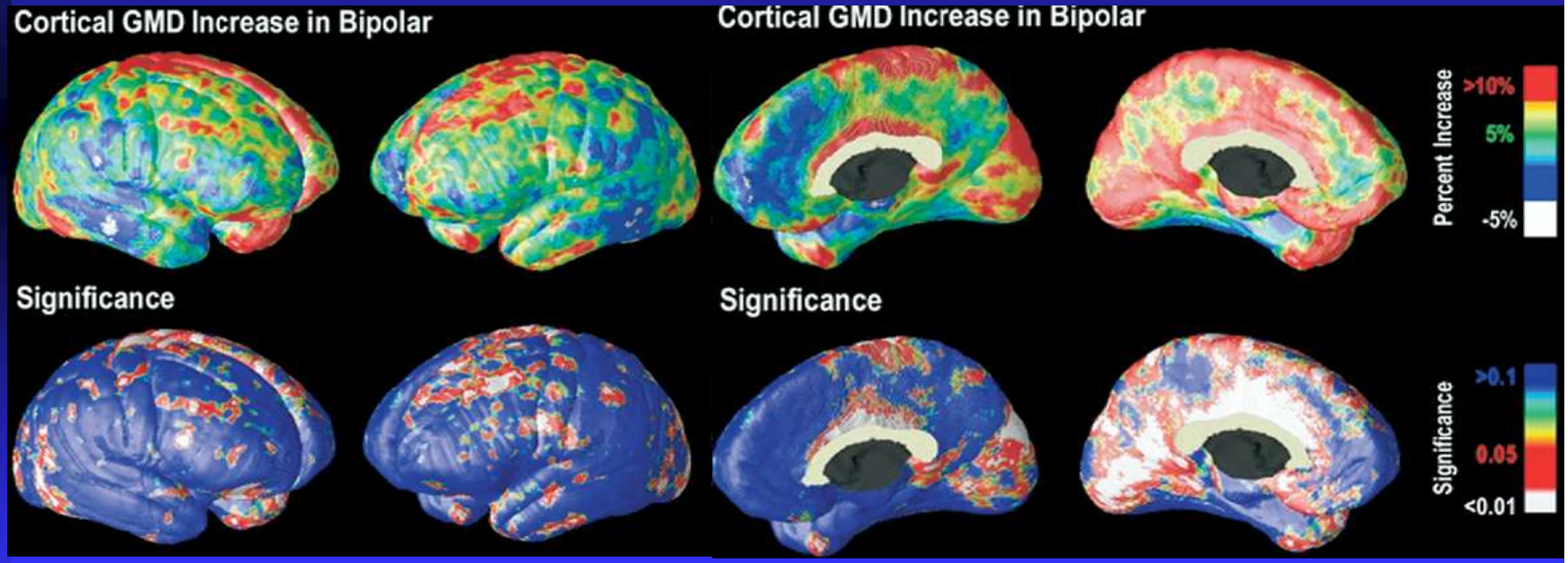
- *Increased* volume of the amygdala in adults
  - *Decreased* ↓ volumes seen in pediatric, adolescent, 1st episode samples; positive relationship to age
- *Increased* striatal volume
- Subtle *alteration* of shape in subregions of the right hippocampus (Bearden et al, 2008)



Right Left

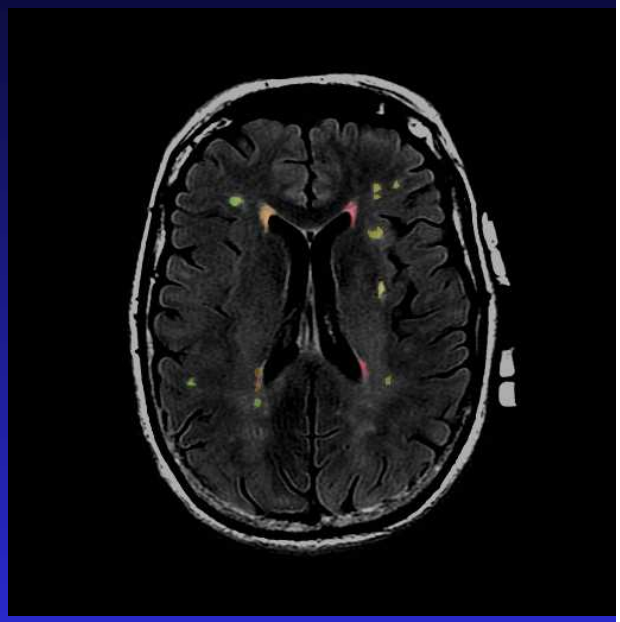
Voxel-based Findings

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

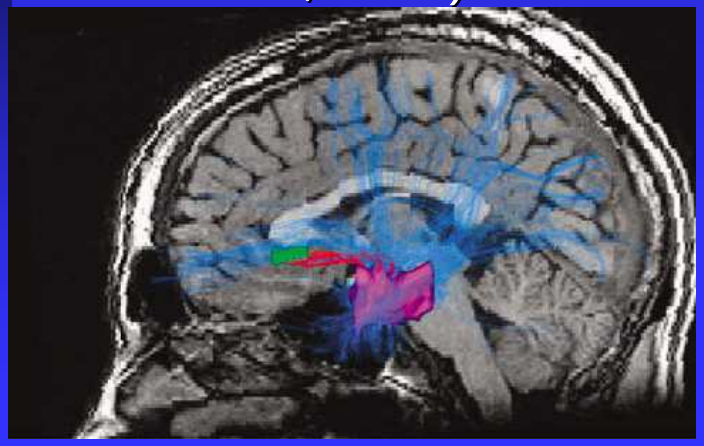


White Matter Findings

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



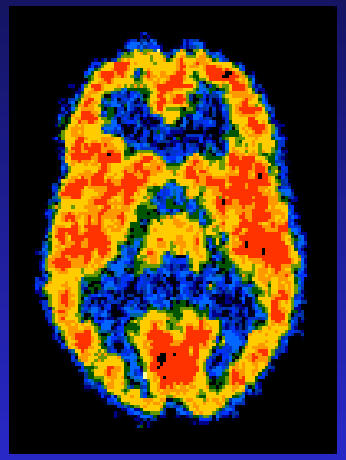
- DTI abnormalities
  - *Decreased* fiber organization particularly in frontal cortex
  - *Increased* number of fibers connecting subgenual ACC to hippocampus / amygdala (Houenou et al, 2007)

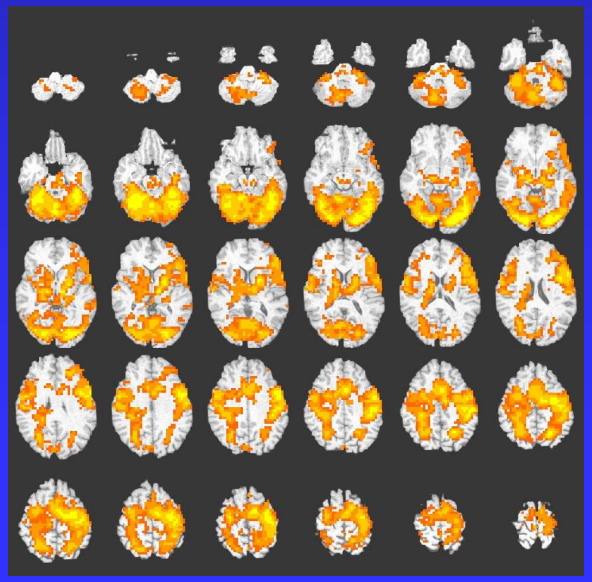


  - *Increased* organization in these same tracts (uncinate fasciculus) on the left but *decreased* on the right (Versace et al, 2008)

Functional Neuroimaging

- Positron Emission Tomography
  - Metabolism
  - Blood flow
  - Receptor binding
- Functional Magnetic Resonance Imaging
  - Blood oxygenation
  - Blood flow



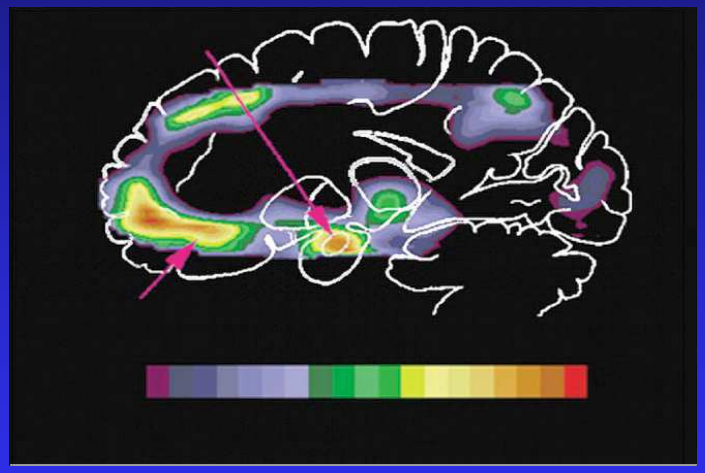


Design Issues

- Mood state
  - Depressed
  - Manic
  - Euthymic
- Brain state
  - Resting
  - Emotional challenge
  - Cognitive challenge
  - Emotio-cognitive challenge
- Medication state

Bipolar Depression

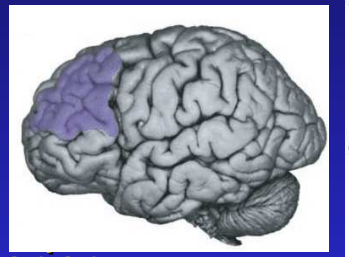
- Resting studies
  - *Decreases*
    - PFC and subgenual metabolism
    - Caudate metabolism
  - *Increases*
    - Amygdala metabolism
  - Deficits improve with anti-depressant / mood stabilizer treatment

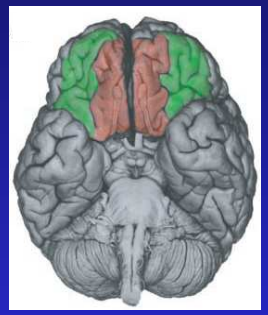


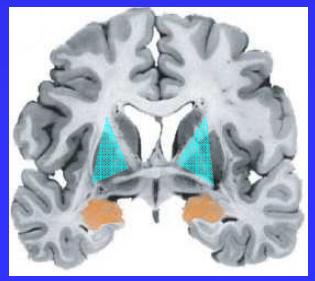
Drevets et al., 2001

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)



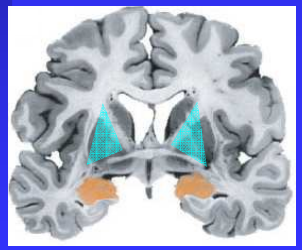


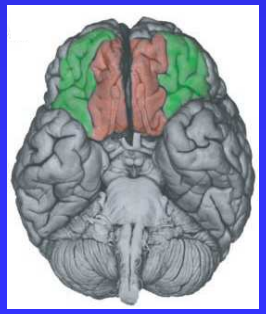


Bipolar Depression

- Emotional challenge studies (continued)
  - Facial affect recognition

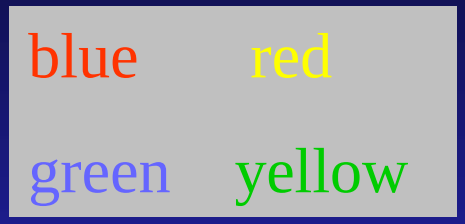
    - *Decreases* in cortical and subcortical regions depending on which emotion
      - DLPFC to mild happy faces (Hassel et al, 2008)
      - Parahippocampus and thalamus to negative (Almeida et al, 2009)
    - *Increases* in other cortical and subcortical regions
      - Subcortical and ventral PFC (Lawrence 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)

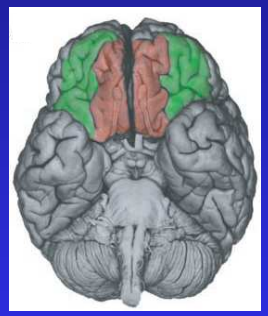


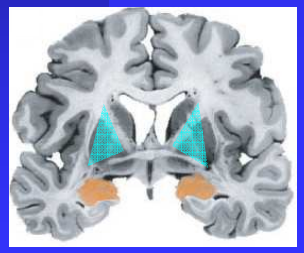


Bipolar Depression

- 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)

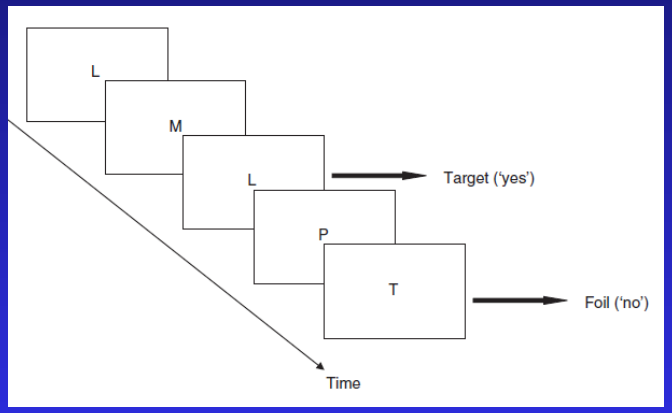






Bipolar Depression

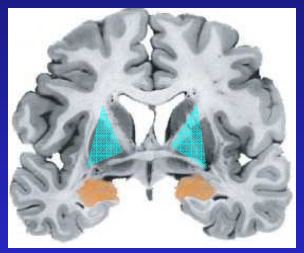
- Emotio-cognitive challenge studies



  - 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

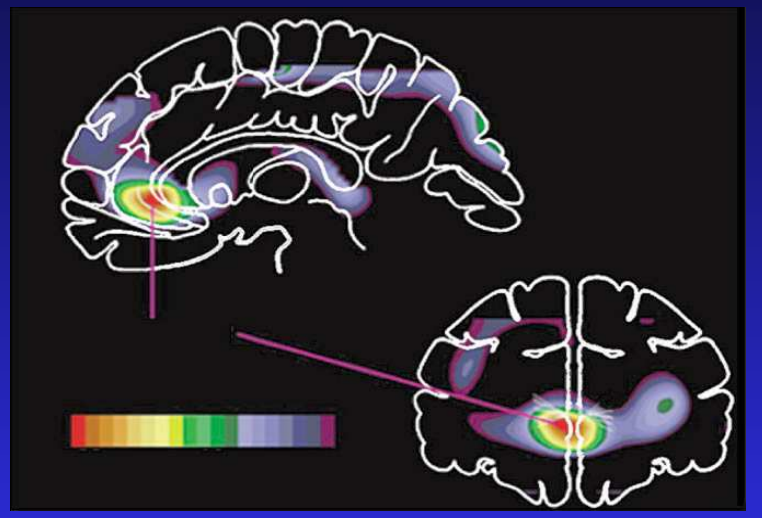
- Increased amygdala activation to happy faces



- Lack of normalization of limbic overactivation with remission
- Increased lateral prefrontal activity during cognitive challenge in depressed but not remitted state

Mania

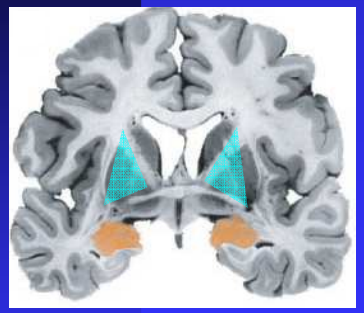
- Resting studies
  - *Decreases* in prefrontal
    - Subgenual PFC metabolism
    - Orbitofrontal flow
  - *Increases* in other areas and subcortical
    - Anterior cingulate blood flow
    - Basal ganglia
  - *Mixed* findings in temporal lobe
  - No differences in D_2 receptor binding



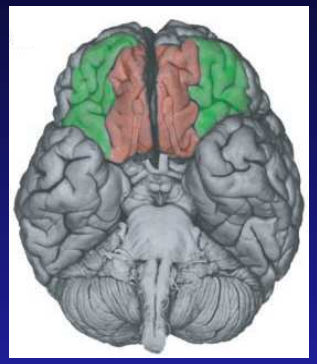
Drevets et al., 2001

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)



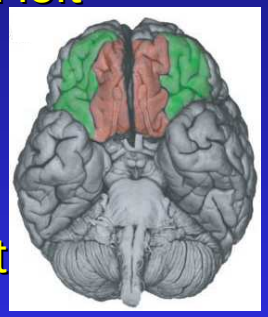
Mania



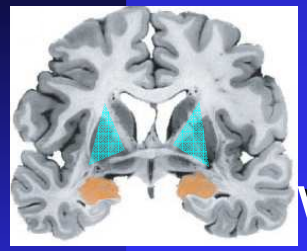
- Cognitive challenge studies
  - Stroop task
    - *Decreases* in prefrontal response
      - Right ventral frontal response, left rostral ventral PFC (mood independent) (Blumberg et al, 2003)
  - Decision making
    - *Decreases* in frontal response
      - Inferior frontal and right frontopolar (Rubinsztein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



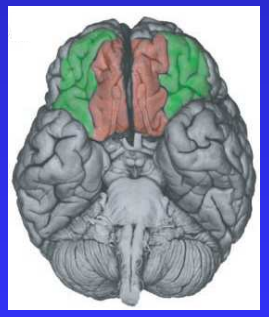
  - Motor
    - *Increases*
      - Globus pallidus; untreated show more overactivat (Caligiuri et al, 2003);
      - Unwanted ipsilateral supplementary motor activation (Caligiuri et al, 2004)



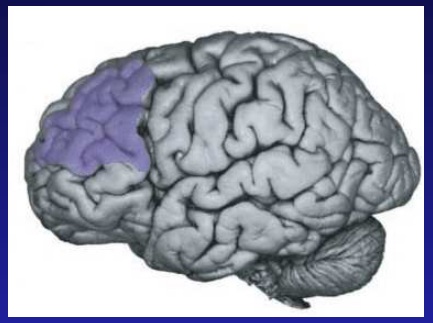
  - Working memory
    - *Failure to de-activate* medial prefrontal region; related to poorer performance (Pomarol-Clotet et al, 2011)

Mania

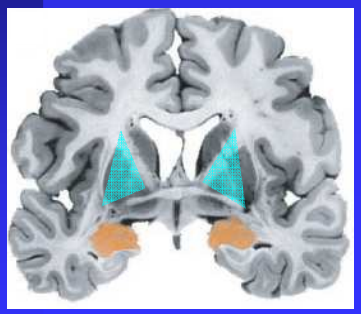
- Emotio-cognitive challenge tasks
  - Affective go-no go
    - *Increases*
      - Left ventrolateral PFC to emotional targets (Elliott et al, 2004)



Euthymia / Remission

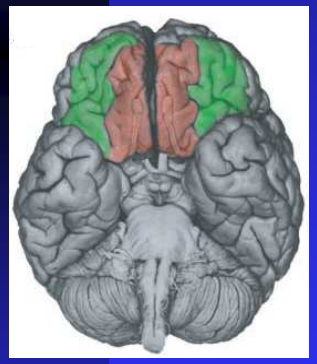


- Emotional challenge tasks
  - Facial affect discrimination
    - *Decreases* in lateral prefrontal cortex
      - Dorsal PFC response to fearful faces (Yurgelun-Todd et al, 2000 [mixed mood states])
      - DLPFC to mildly happy faces (Hassel et al, 7th ICBD)
    - *Increases* in limbic areas
      - 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)

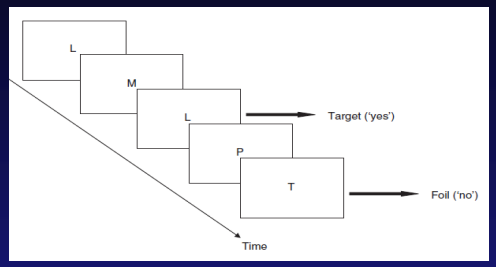


Euthymia / Remission

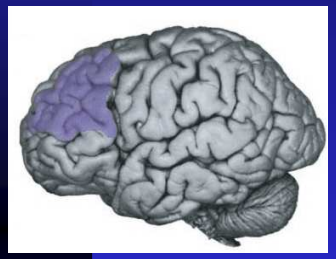
- Emotional challenge tasks (continued)
  - Sad mood induction
    - *Decreases*
      - Dorsal-ventromedial frontal, posterior cingulate, inferior parietal, and temporal (Kruger et al, 2003)
    - *Increases*
      - Insula, cerebellum, dorsal anterior cingulate, premotor cortex (Kruger et al, 2003)



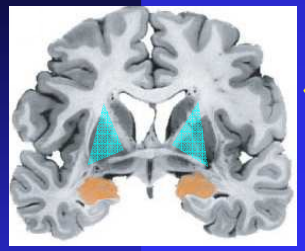
Euthymia / Remission



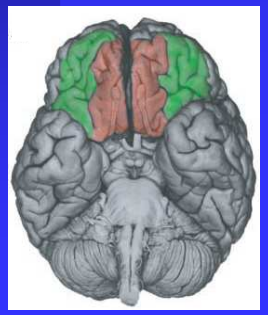
- Cognitive challenge tasks
  - Working memory
    - *Decreases* in lateral frontal and other cortical regions



      - 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)

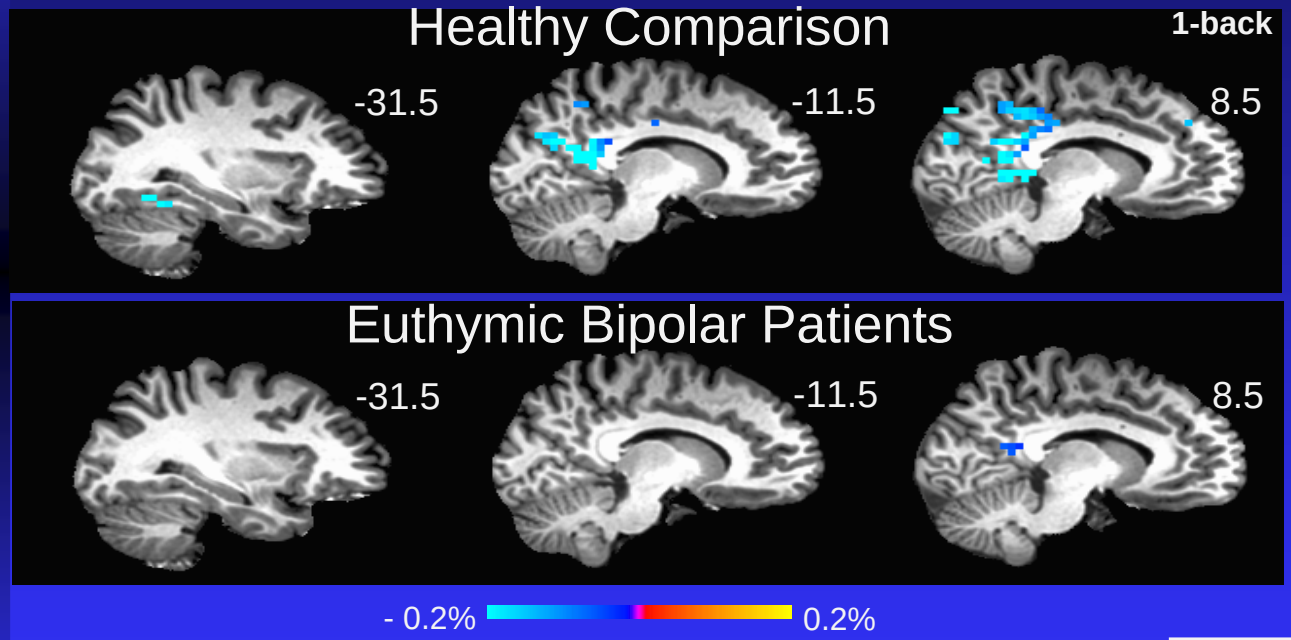


    - *Increases* in cortical and medial frontal
      - Fronto-polar, temporal and parietal cortex and basal ganglia (Adler et al, 2004)
      - Superior frontal (Frangou et al, 2005)
      - Precentral, supramarginal, and medial frontal (Monks et al, 2004)
      - Medial prefrontal during delay (Lagopoulos et al, 2007)

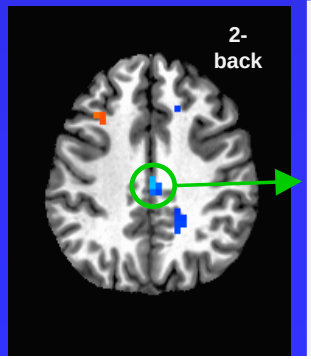


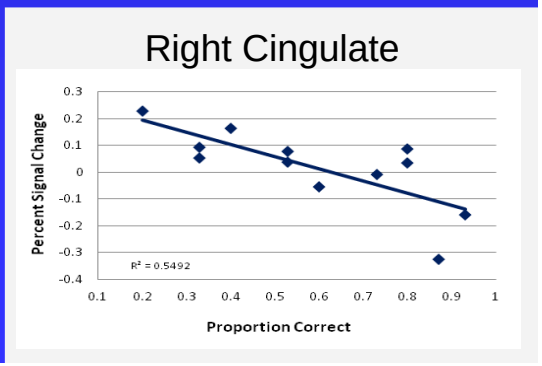
Euthymia / Remission

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



- Related to worse performance

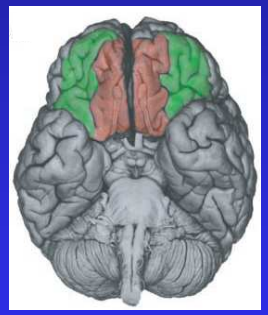


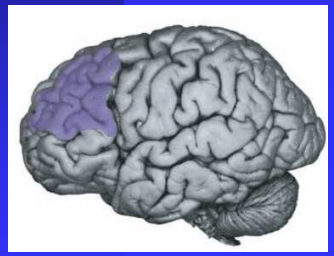


Eyler Lab, In preparation

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

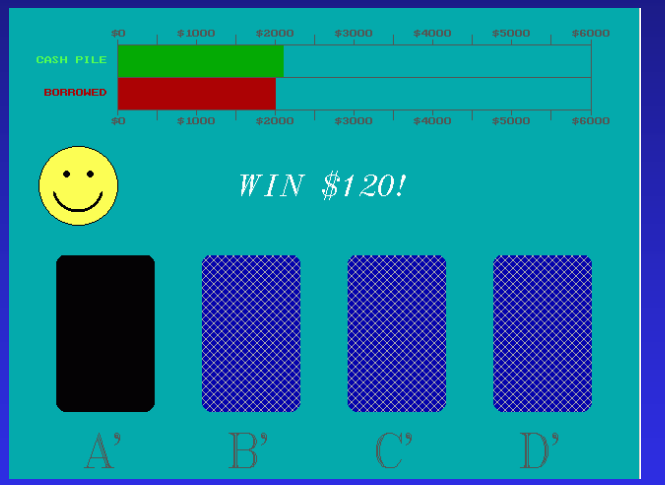
- Cognitive challenge tasks (continued)
  - Continuous performance task
    - *Decreases* in some regions
      - Orbitofrontal and fusiform (Strakowski et al, 2004)
    - *Increases* in emotional regions
      - Limbic, paralimbic, ventrolateral PFC (Strakowski et al, 2004)
  - Verbal fluency
    -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

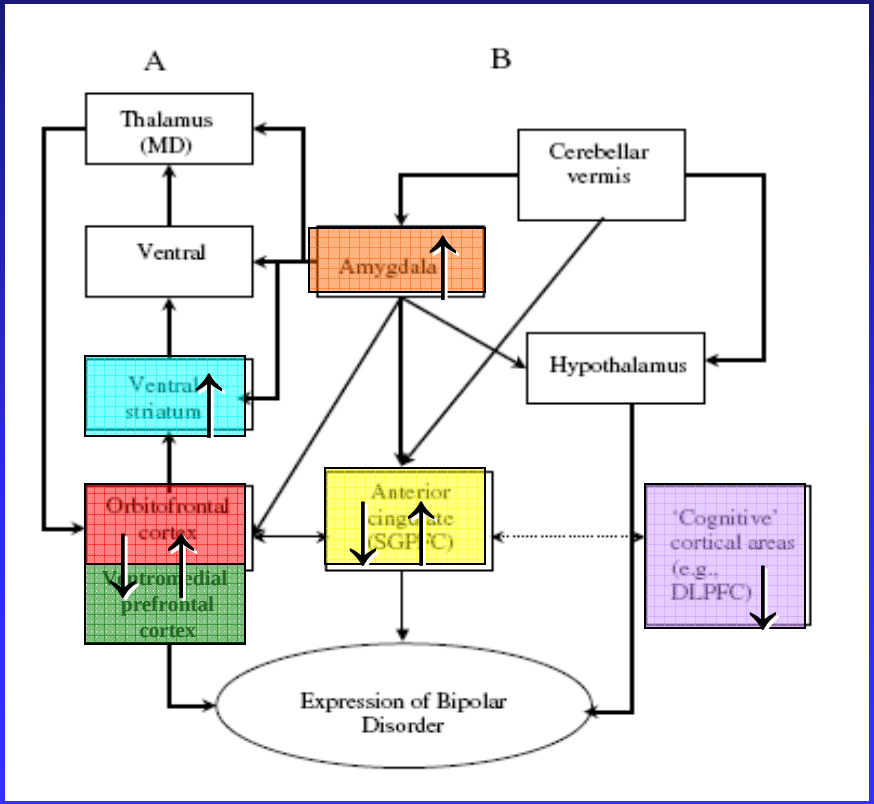


Euthymia / Remission

- 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)

Brain Region	Volume	White Matter Conn-ections	Resting	Emotional	Cognitive	Emotio-Cognitive
Amygdala	↑↓	↑	↑Dep	↑Dep ↓Man ↑Eut	↑↓Eut	
Striatum	↑	--	↓Dep ↑Man	↑Dep ↑Man ↑Eut	↑↓Dep ↑Man ↑Eut	↑Eut
Anterior Cingulate	--	↑	↑Man	↓Man ↑Eut	↑Dep ↑↓ Man ↓Eut	↓Dep ↓Eut
Orbito- / Ventral Frontal	↓	↓	↓Dep ↓Man	↑↓Dep ↓Eut	↑↓Dep ↓Man ↑↓Eut	↑Man ↑↓Eut
DLPFC	--	--		↑↓Dep ↓Eut	(↑)↓Eut	↑↓Dep

Bipolar Disorder Circuits



Strakowski et al, 2005

Confounders & Comorbidities

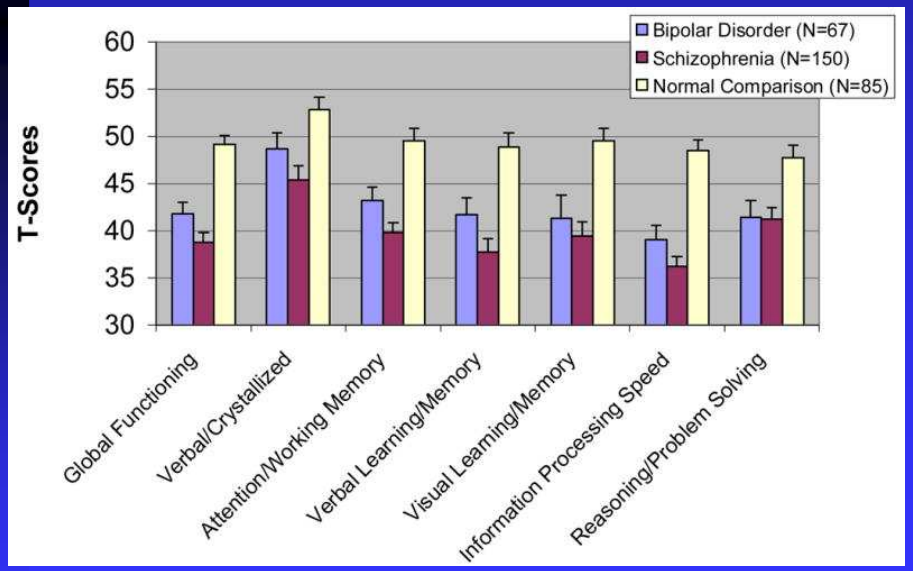
- Treatment
  - Lithium
    - Grows your brain
    - Anticholinergic effects
  - Pharmacologic Treatment
    - Motor: treated have more normal striatal hyperactivation (Caligiuri et al, 2004)
    - Emotional faces: treated have lower amygdala activation and normal rostral anterior cingulate activation (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



Depp et al, 2007

- 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)

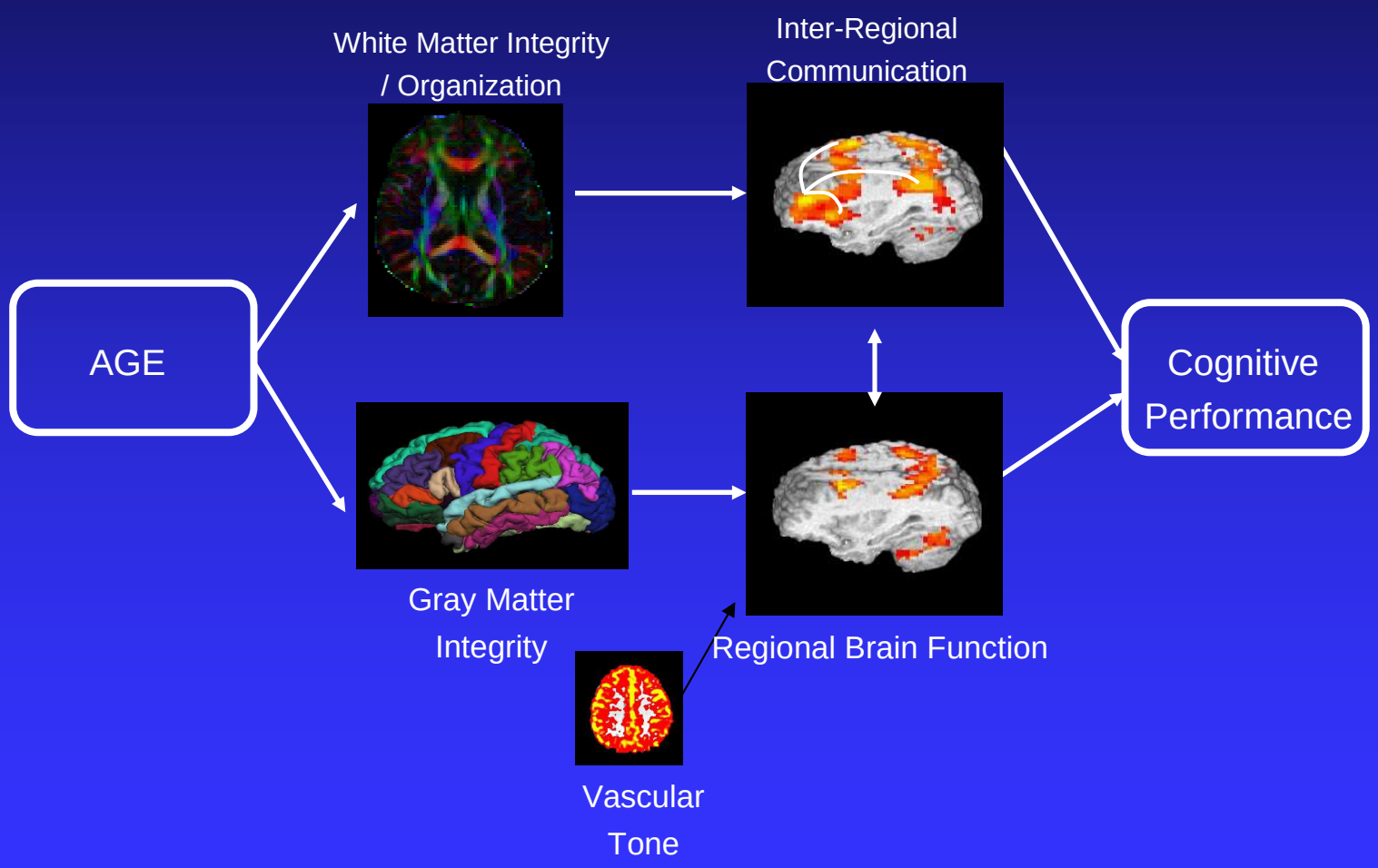
Take Home Messages

- 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



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

Acknowledgments

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Any questions?