Allison C Nugent, PhD
Experimental Therapeutics and Pathophysiology Branch
NIMH/NIH/DHHS

MRI OF MOOD DISORDERS

NIH National Institute of Mental Health

Outline

- What are mood disorders?
- How do we treat mood disorders?
- What can imaging teach us about mood disorders and their treatment?

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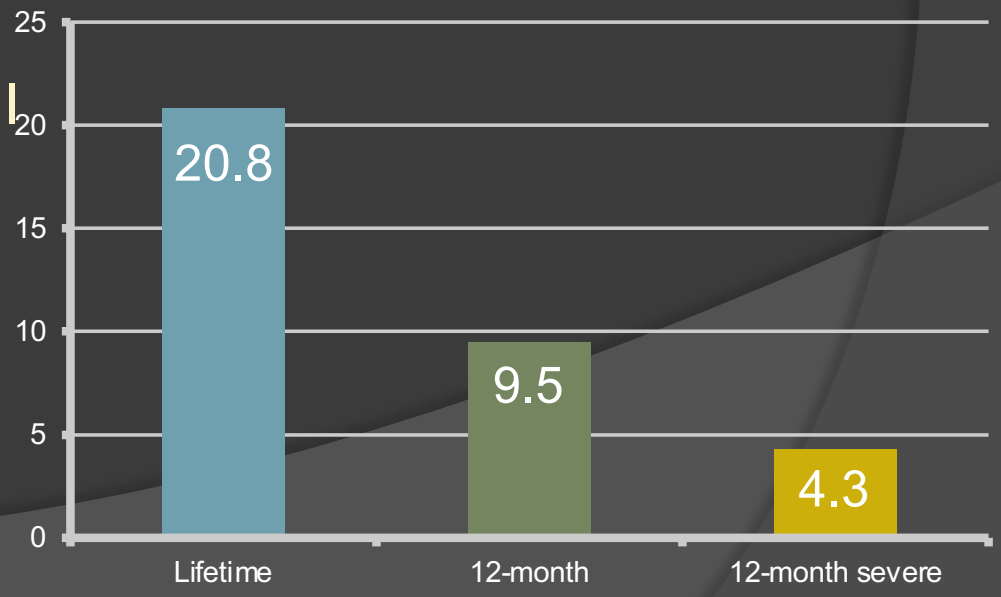
Mood Disorders

- Disorders featuring a disturbance in mood as the primary feature
- Disorders of depressed mood
  - Major depressive disorder, etc.
- Disorders of elevated mood
- Disorders cycling between depressed and elevated moods
  - Bipolar disorder, types I and II
- Highly prevalent



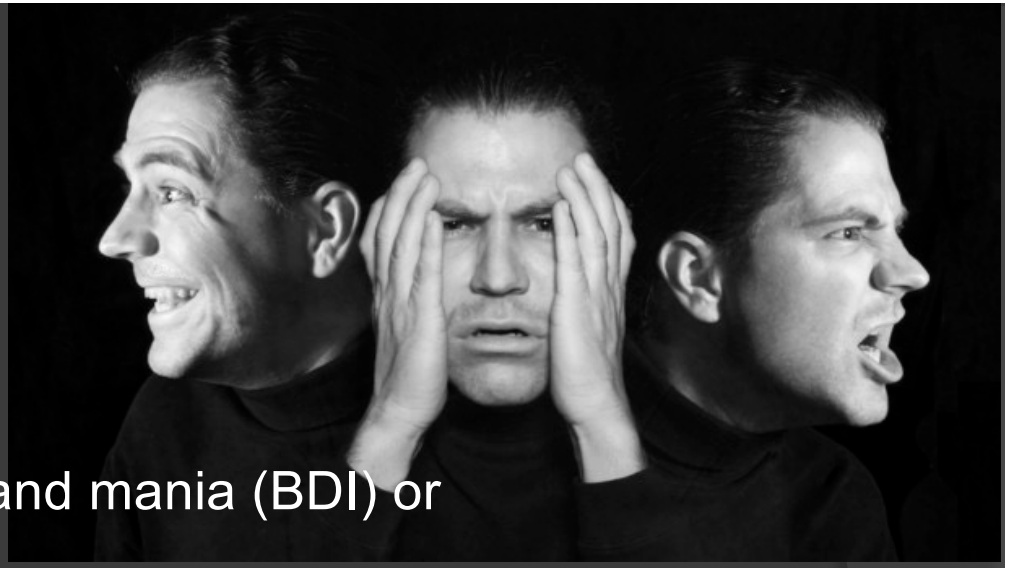
Major Depressive Disorder

- Either depressed mood or anhedonia
- 4 of 7 additional symptoms
  - Weight loss or gain
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation
  - Fatigue
  - Feelings of worthlessness or guilt
  - Cognitive problems
  - Recurrent thoughts of death or suicide
- Symptoms must have lasted more than 2 weeks, cause impairment, and not be due to a medical condition or medication

Major Depressive Disorder

- Highly Heterogeneous
  - Two patients with MDD could overlap on only one symptom
- Heritable, but no clear genetic pattern
- In 2012, 6.9% of US adults had at least one episode in the past year – 16 million

Bipolar Disorder



- Alternating periods of depression and mania (BDI) or hypomania (BDII)
- Manic episode: elevated, expansive, or irritable mood
- 3 of 7 symptoms (4 if only irritable)
  - Inflated self esteem
  - Decreased need for sleep
  - Talkative, pressured speech
  - Racing thoughts
  - Distractibility
  - Increased goal-directed activity
  - Excessive involvement in pleasurable activities
- Present for at least a week, causes impairment, and not due to a medical condition or medication
- Psychosis, requiring hospitalization, and severe impairment are exclusionary for BDII

Bipolar Disorder

- Twelve month prevalence of 2.6%, 82.9% of these cases are severe
- Highly heritable, but no clear genetic pattern
- Frequently disabling, with high prevalence of suicide

Outline

- What are mood disorders?
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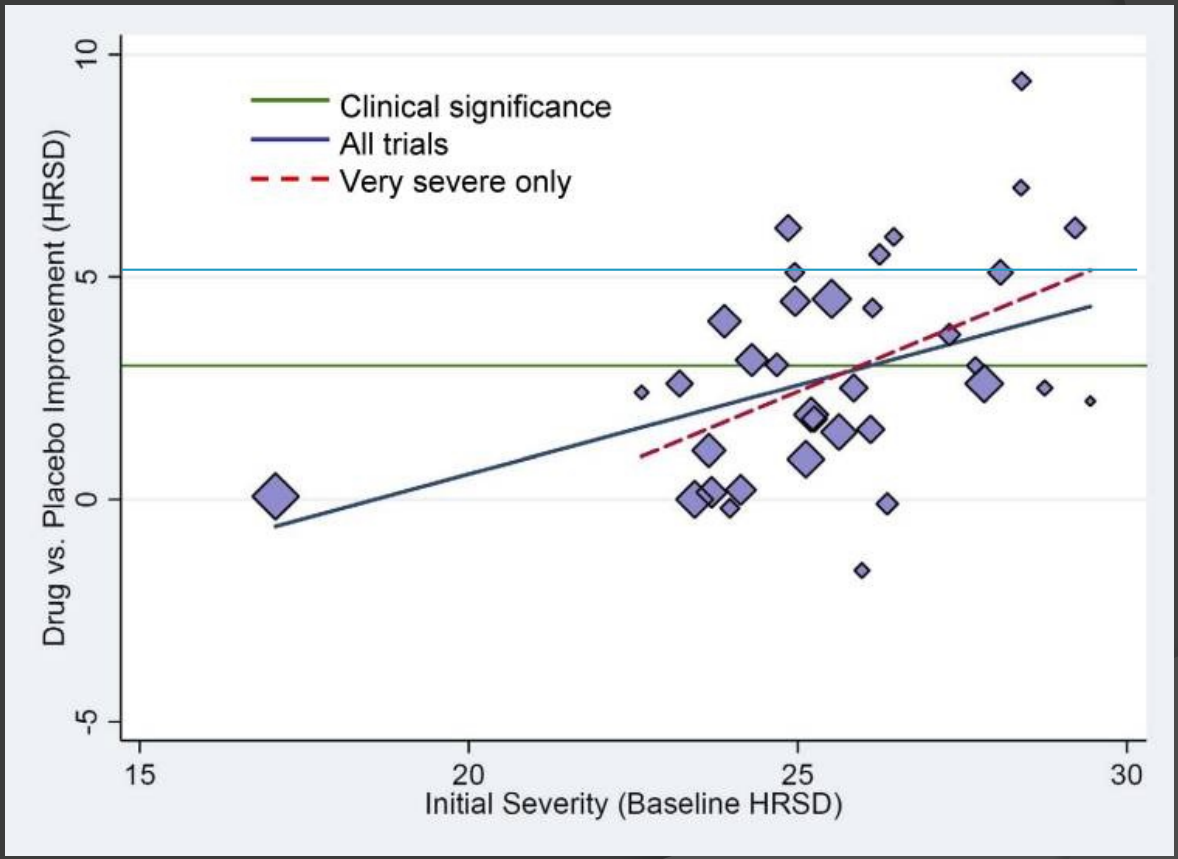
How Do We Treat Depression?

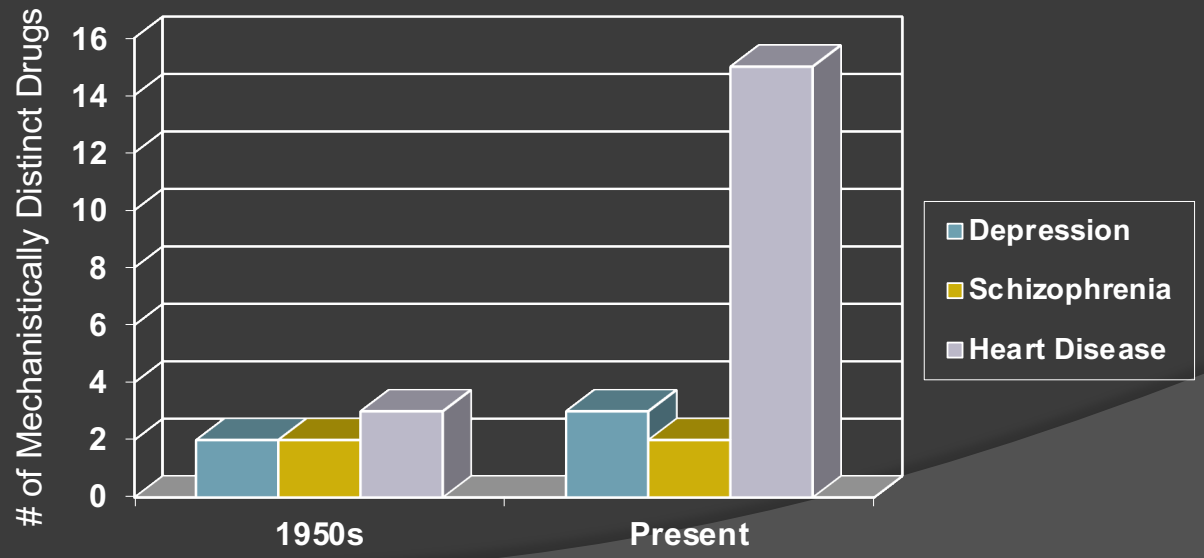
- Not very well
- MDD:
  - SSRI
  - SNRI
  - TCA
  - MAOI
  - ECT, TMS, DBS



Kirsch, et al. PLoS Med (2008) 5(2):e45

How Do We Treat Depression?

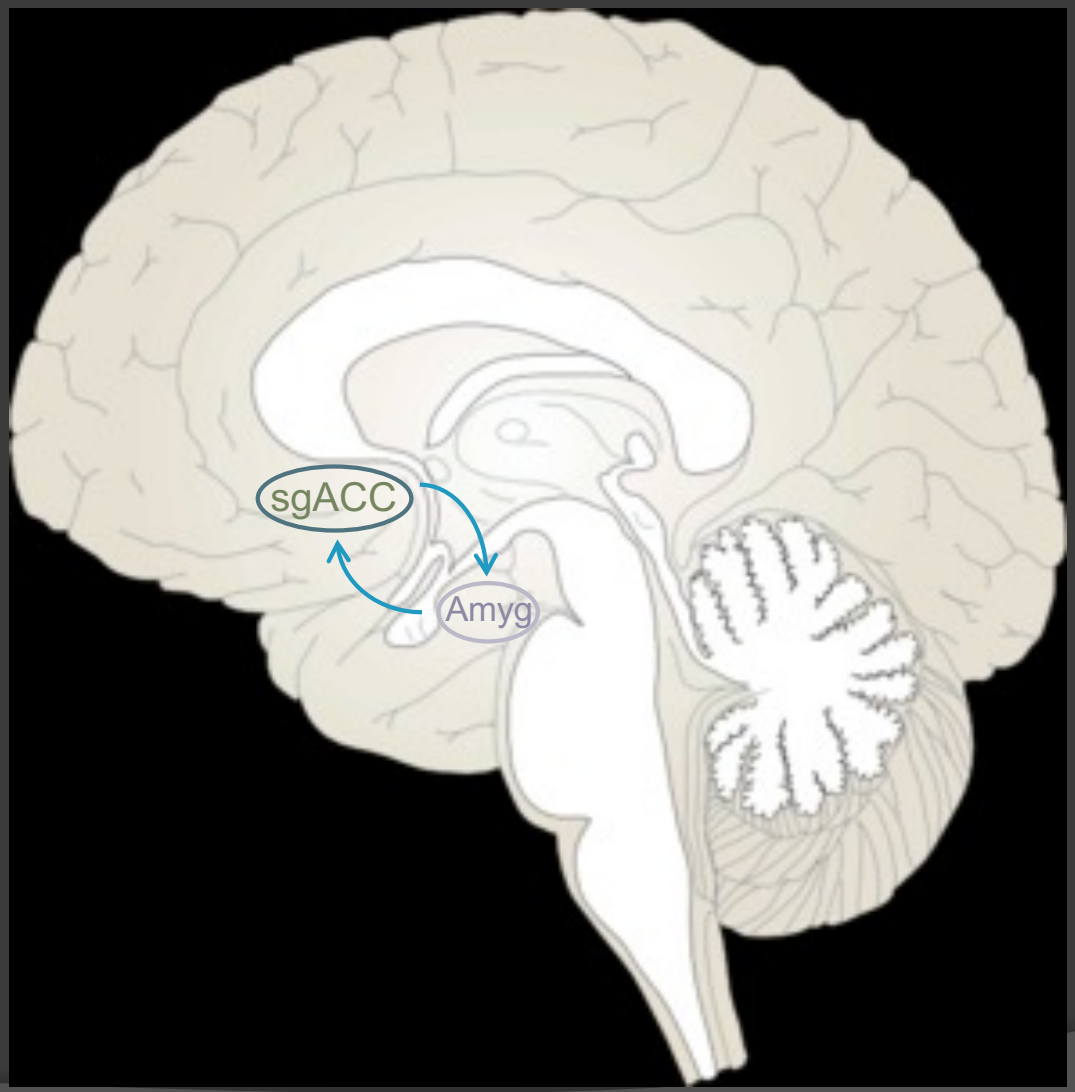
- Only ~35% of patients with depression will respond to the first drug
- Full response is not evident for 6-8 weeks
- There are no markers to guide choice of treatment
- There are no drugs specifically developed to treat depression in the context of BD



How Do We Treat Mania?

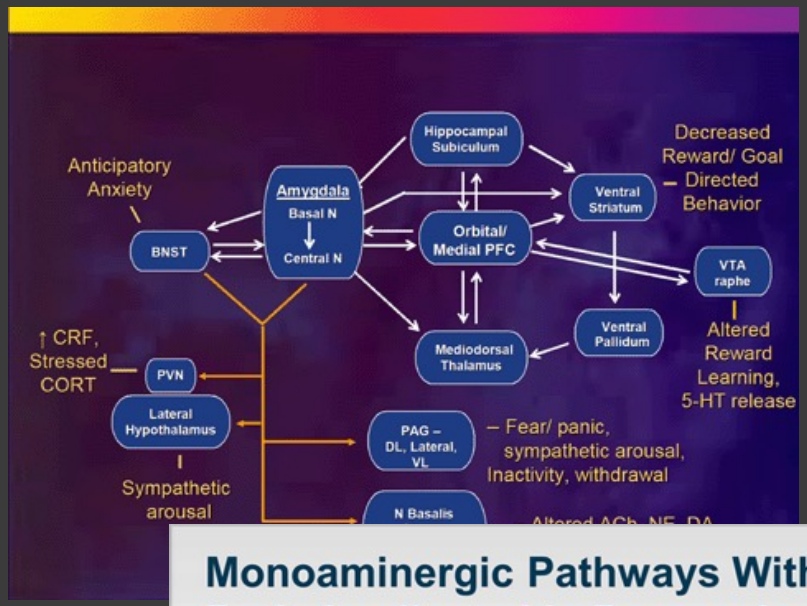
- Only one drug ever developed to treat BD: Lithium
- Alternatively treated with antipsychotics or anticonvulsants
- Frequently severe enough to require hospitalization
- In one study of patients followed after their first hospitalization, only 43% recovered their previous level of occupational and residential function (Tohen 2003).
- Studying bipolar mania is exceedingly difficult

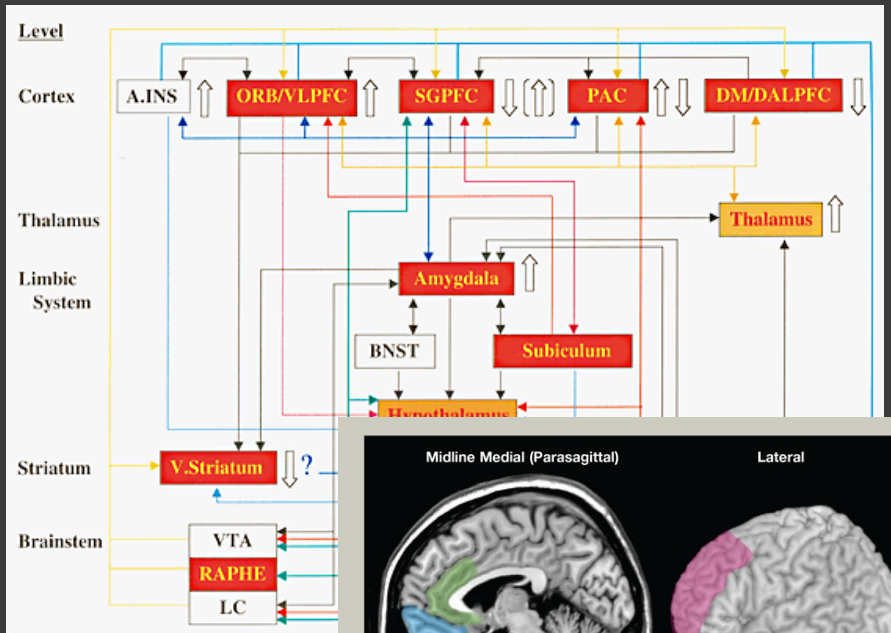
Neurobiology of Depression: Core Brain Regions

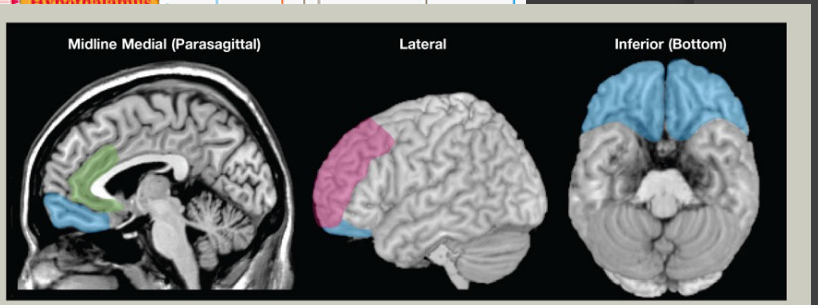


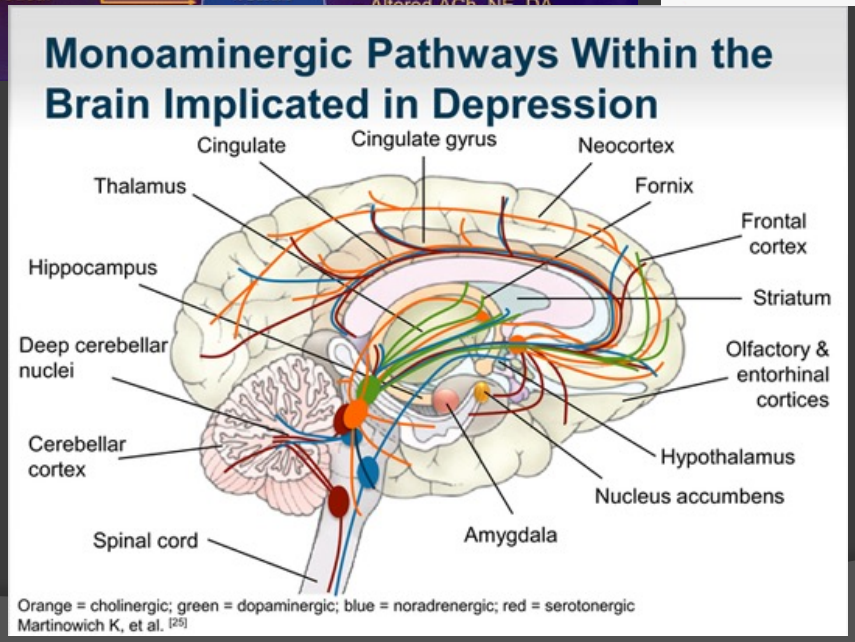
- Subgenual cingulate cortex, BA25
- Amygdala

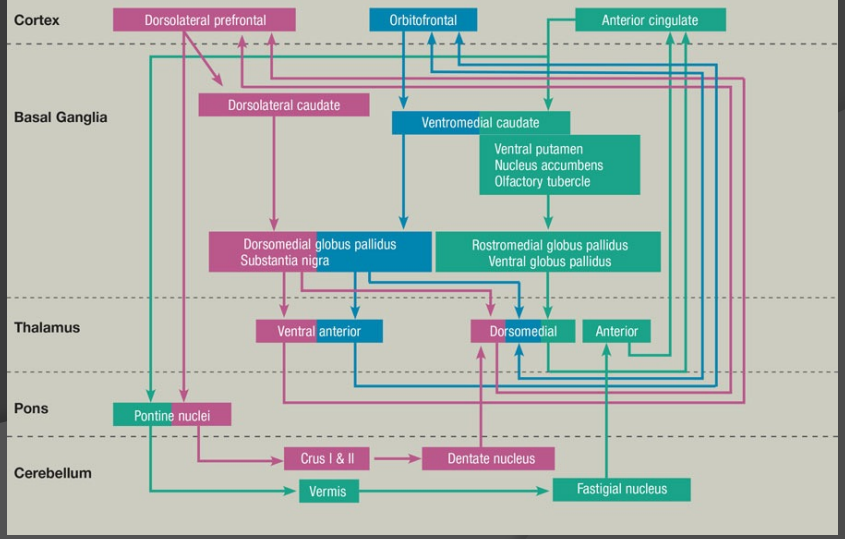
Neurobiology of Depression: Less Simple











Our Approach

- Alternative Targets
  - Monoaminergic drugs rapidly effect the target neurotransmitter system, but effects are delayed
  - Downstream effects can be targeted more efficiently
- Search for correlates of treatment response to identify potential biomarkers of response

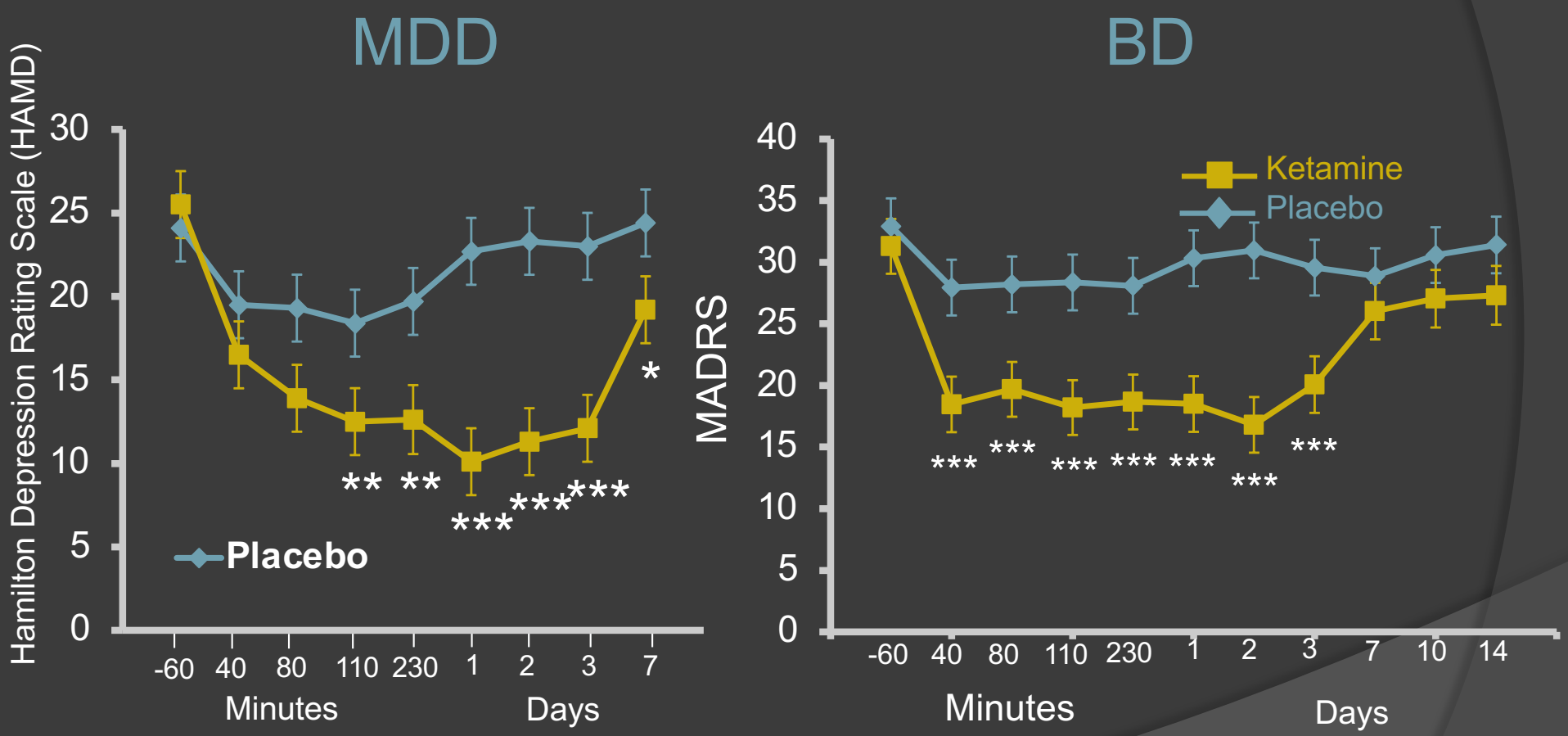
Ketamine

- FDA approved anesthetic and Schedule III controlled substance
- NMDA receptor antagonist
- Potent psychotomimetic effects

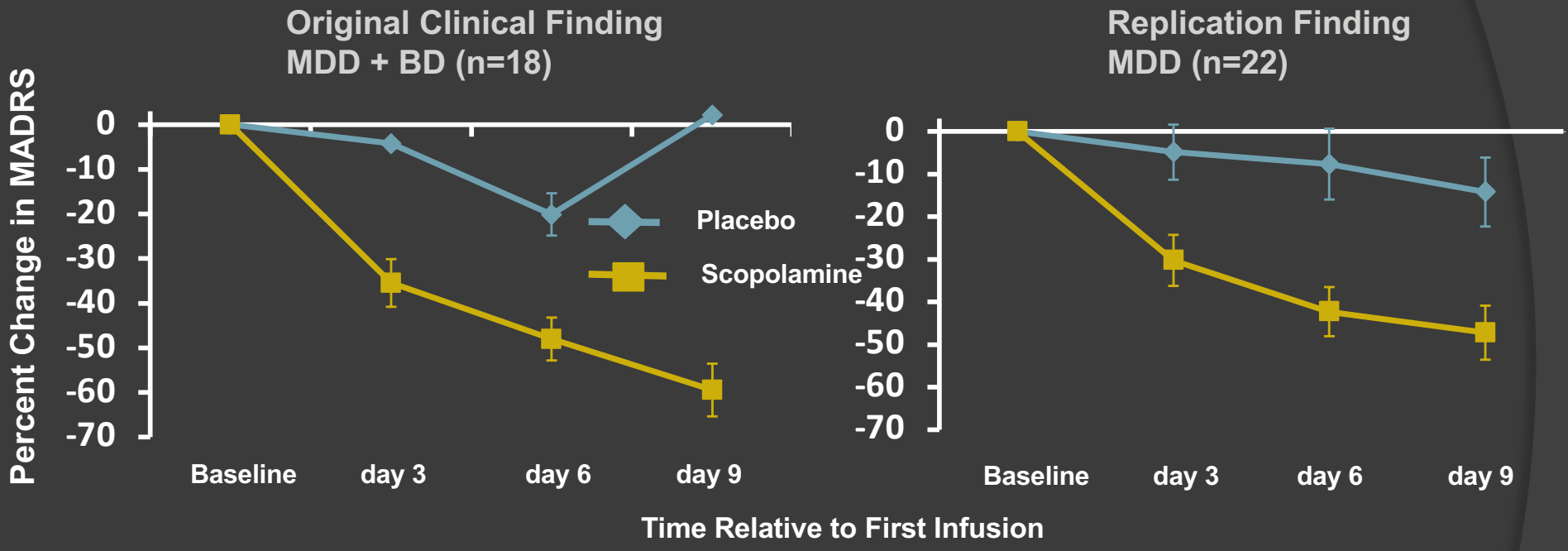
Scopolamine

- Cholinergic muscarinic antagonist
- Can cause delirium in high doses

Ketamine in Severe and Treatment Resistant Depression



Scopolamine: Depressed Outpatients



Furey et al., Arch Gen Psychiatry, 2006

Drevets and Furey, Biol Psychiatry, 2010

Outline

- What are mood disorders?
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How can we use imaging?

- Find brain “biomarkers” that can subdivide MDD and BD into distinct phenotypes
- Find brain “biomarkers” that can reliably predict who will respond to a given intervention
- To be truly useful, any marker should be agent specific
- Markers may change in response to treatment, and display a dose-response relationship

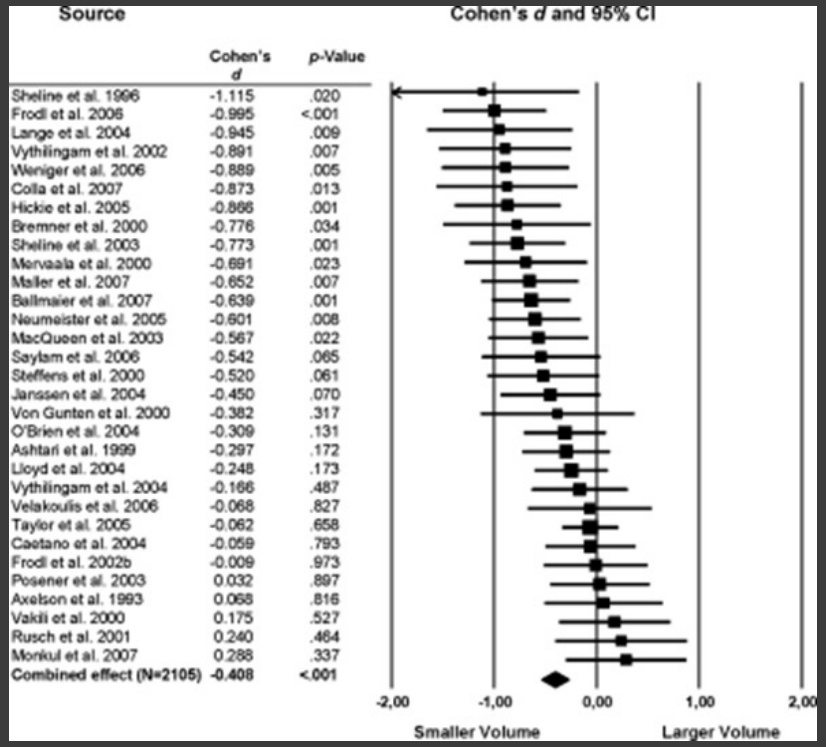
Potential Markers

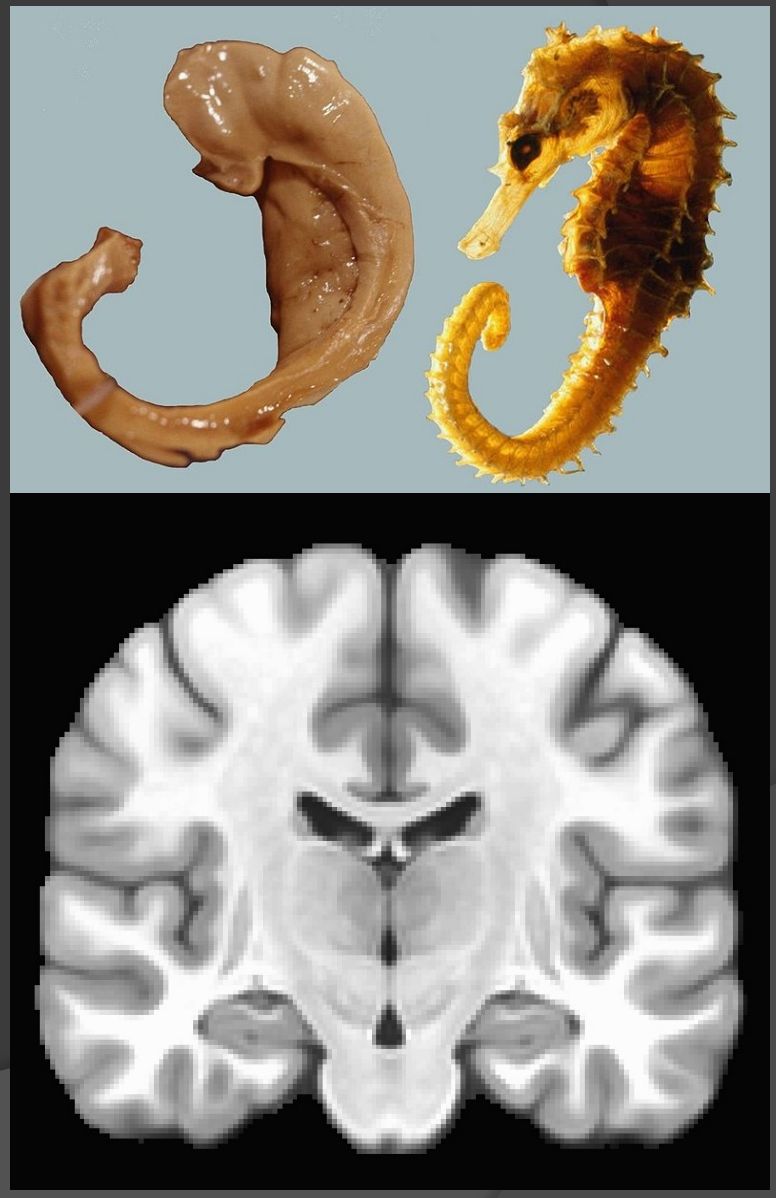
- Structure
  - Volume
  - White Matter
  - Conformation
- Function
  - Cognitive Tasks
  - Resting State

MDD and Brain Structure

- Long history of manual segmentation of structures
- Nearly every structure examined has been shown to be larger, smaller, or no different than in healthy control subjects
- Why? Medication effects, differing segmentation techniques, etc.

MDD and Brain Structure

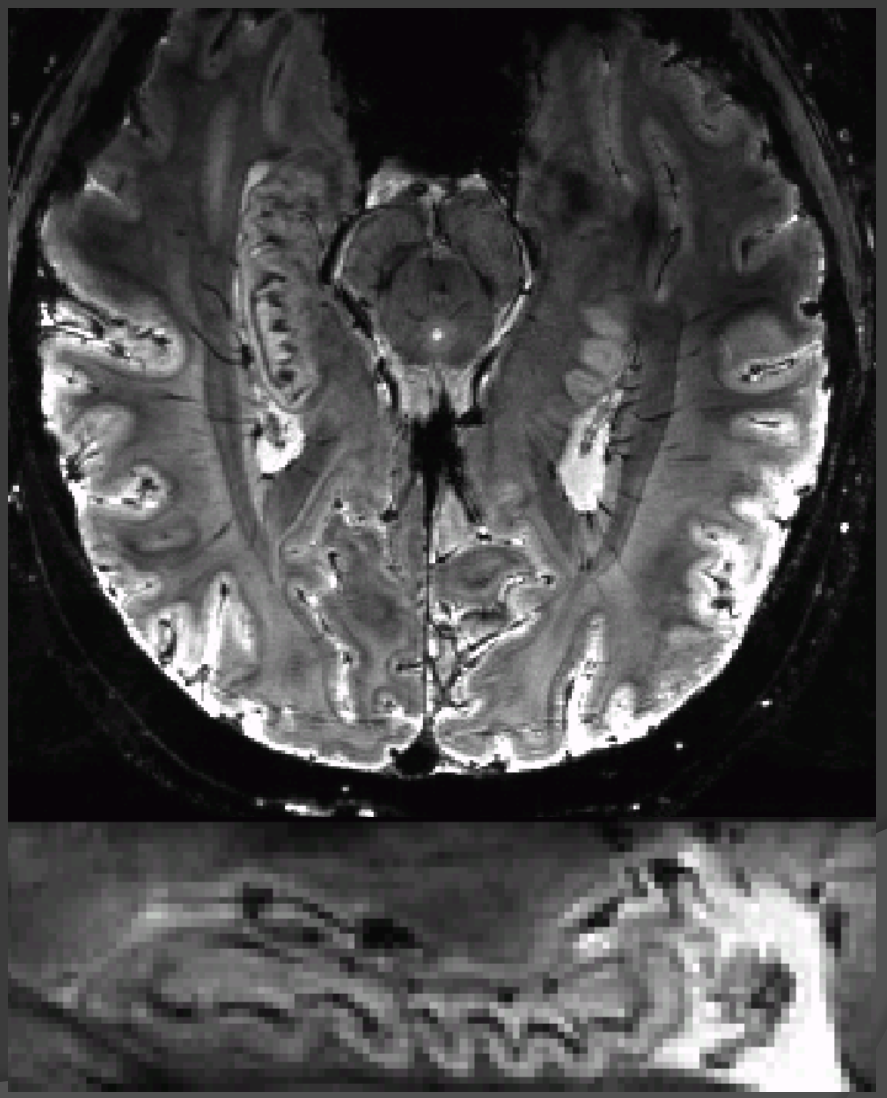




Koolschijn, et al.
Human Brain Mapping (2009) 30(11):3719-3735

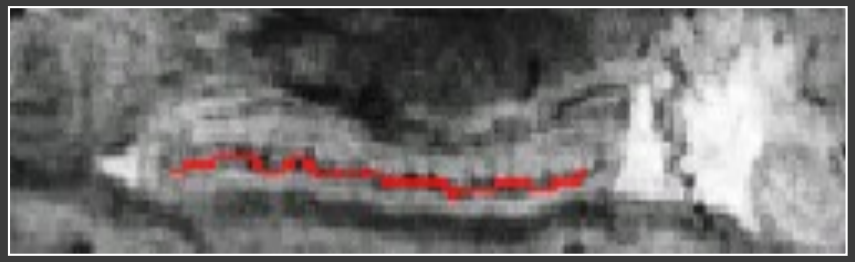
MDD and Brain Structure

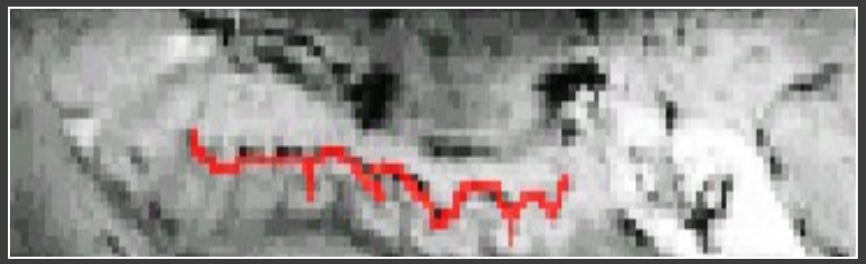
- High resolution hippocampal mapping at 7T
- Assessing curvature, surface area, and shape

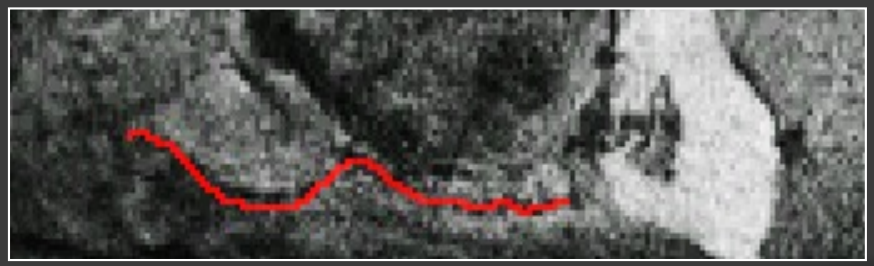


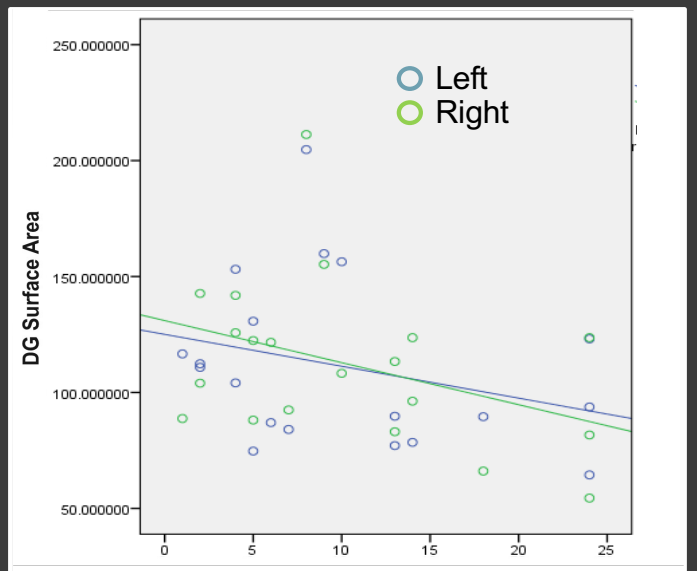
Adam Thomas, et al.

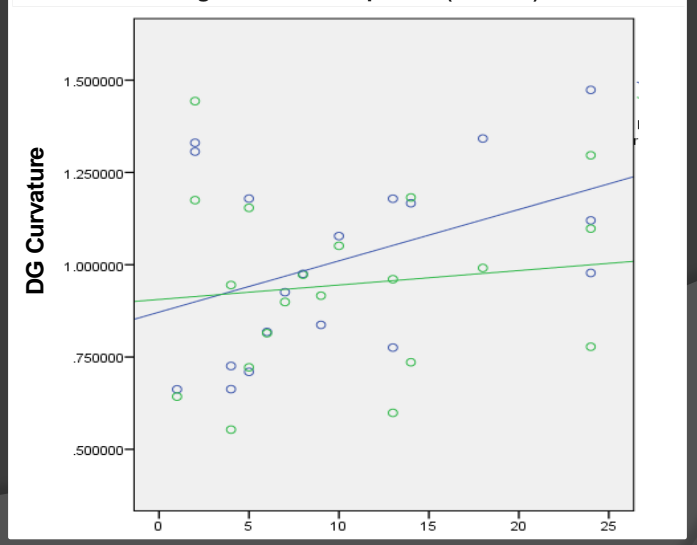
MDD and Brain Structure





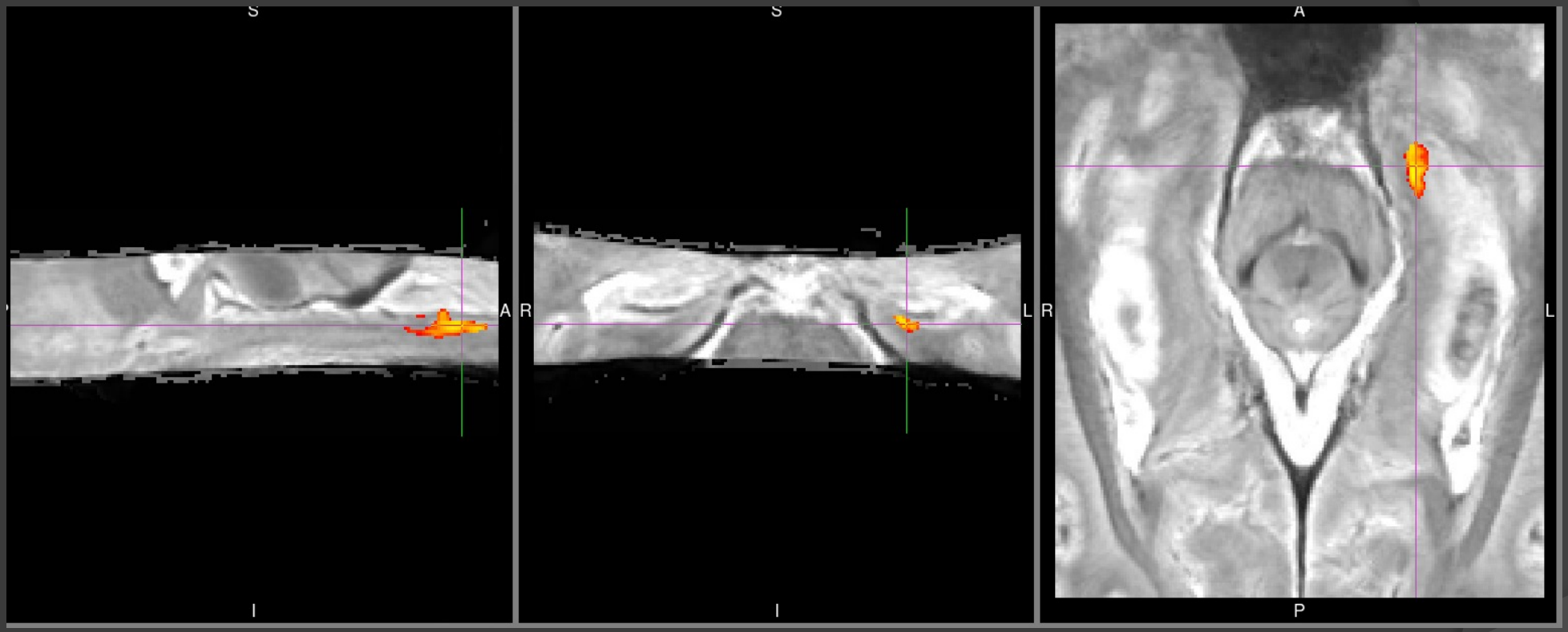






Adam Thomas and Anna Goodwin

MDD and Brain Structure

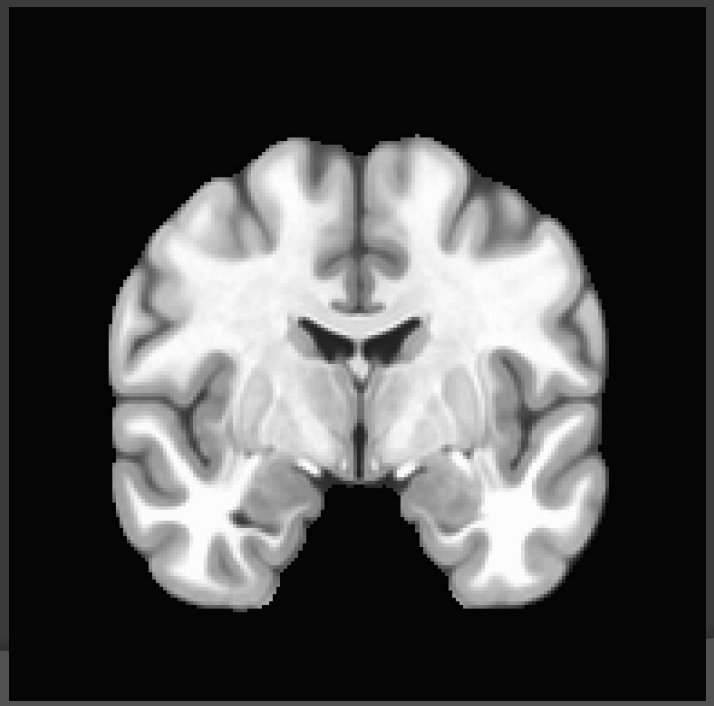


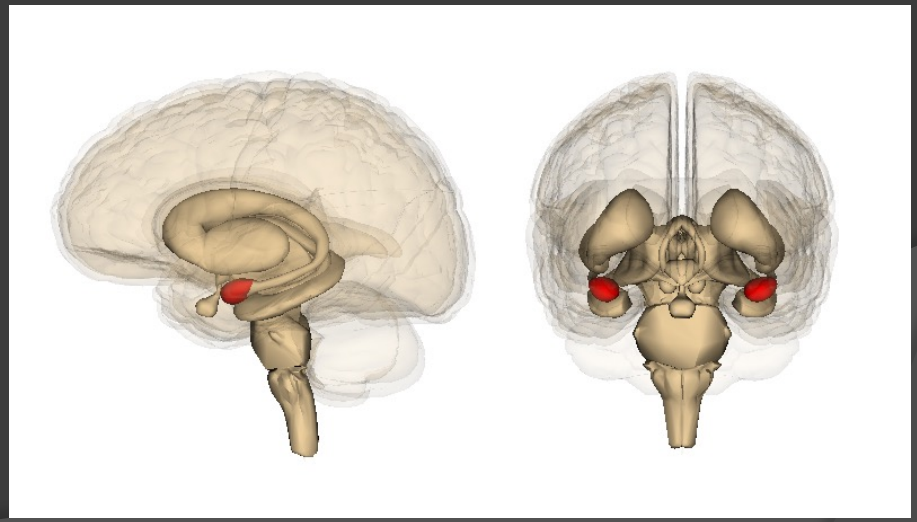
Significant negative association between length of current episode and reduced volume in the subicular subfield of the hippocampus.

Adam Thomas

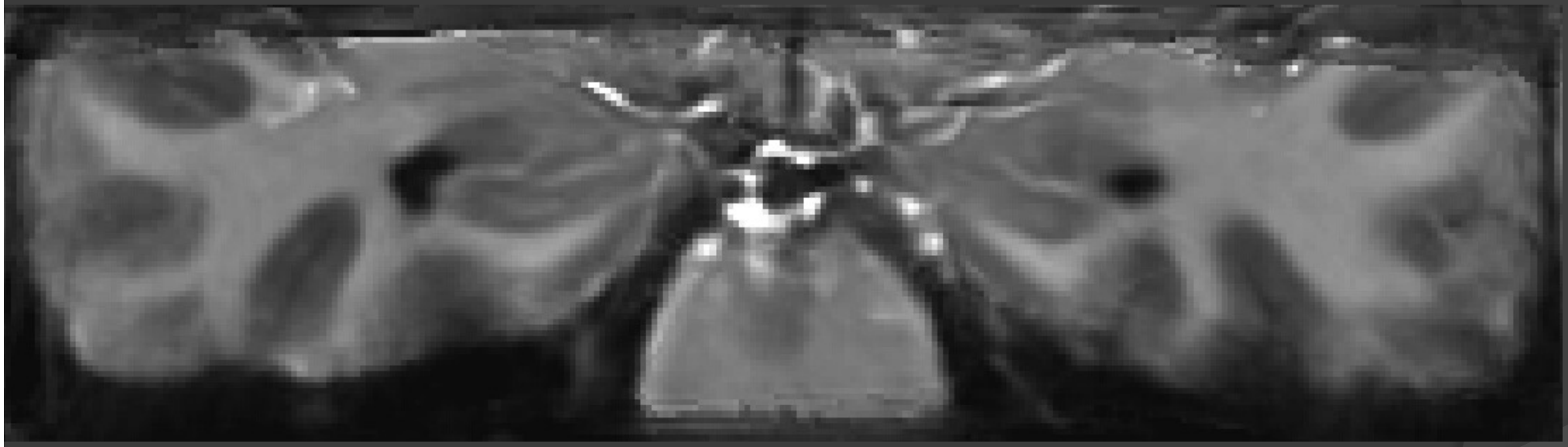
MDD and Brain Structure

- What about the amygdala?
  - Intimately involved in emotional processing and memory
  - Extremely difficult to examine structurally
  - In an area prone to magnetic susceptibility artifacts



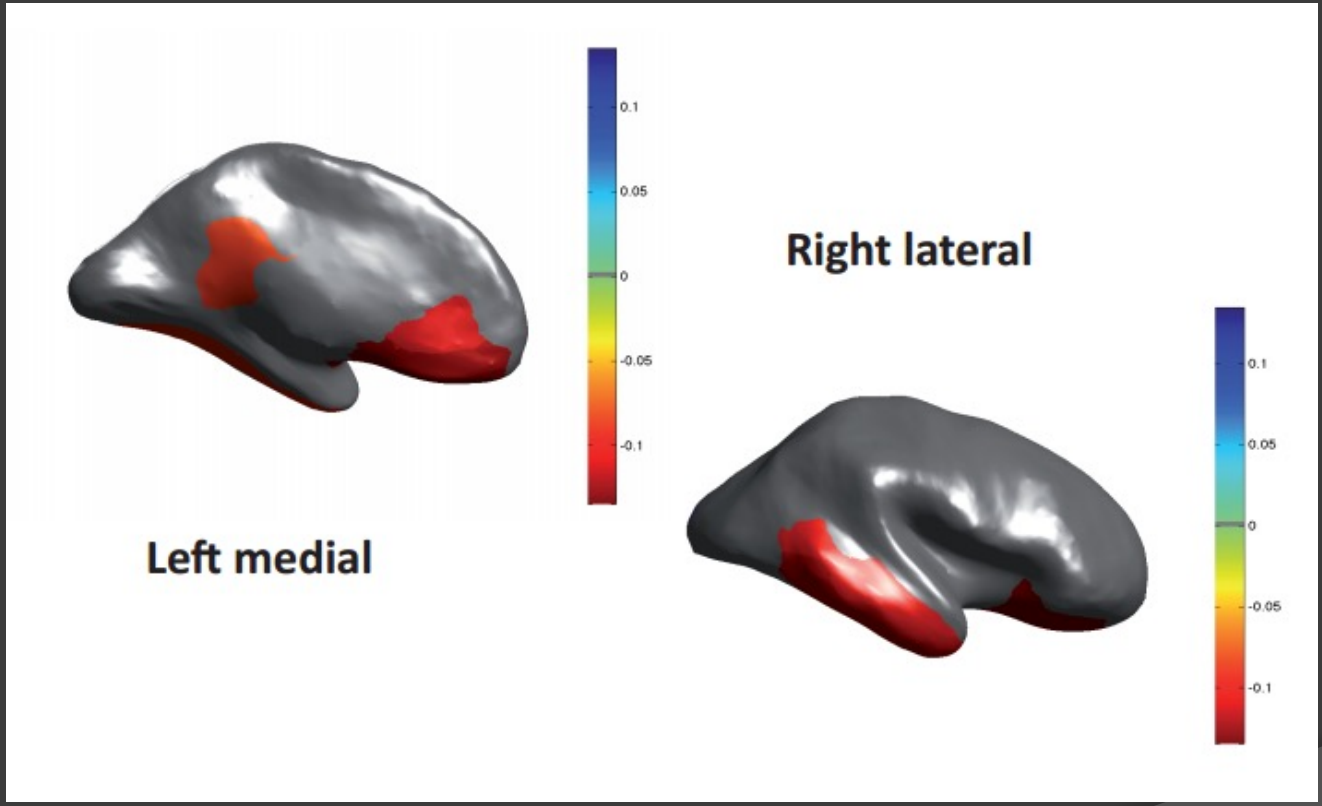


MDD and Brain Structure



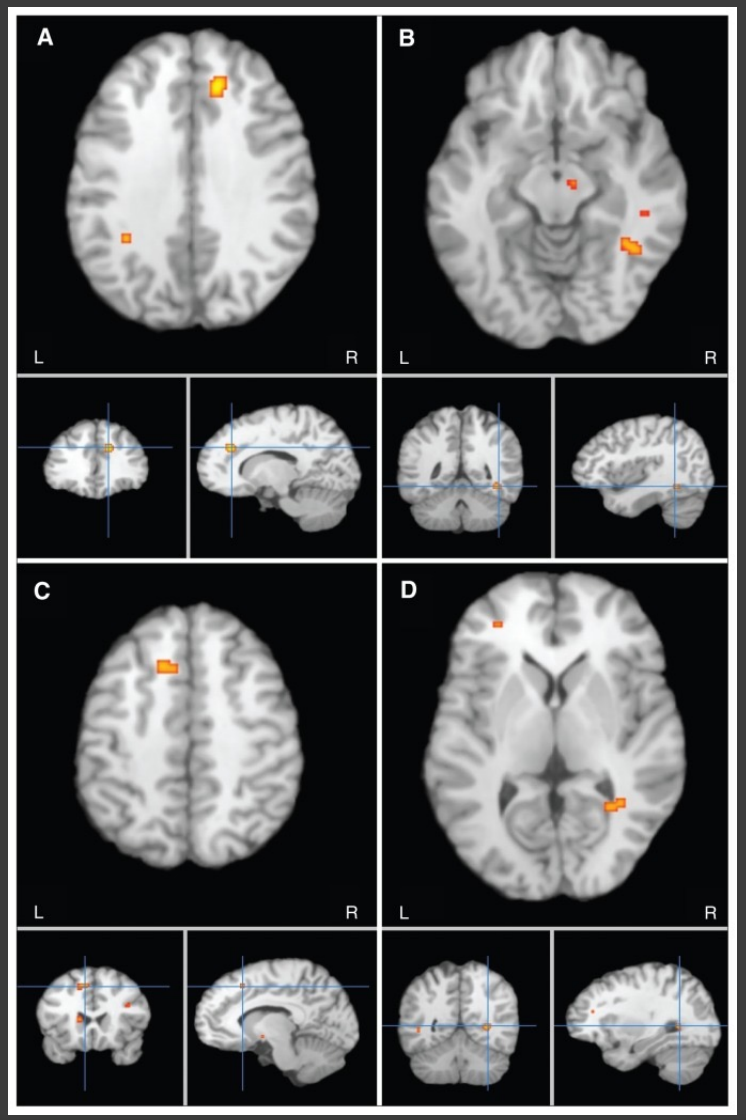
MDD and Brain Structure: Cortex

ENIGMA Major Depressive Disorder Workgroup
N=2104 MDD, N=7971 HC



Schmaal, et al., OHBM 2015

MDD and Brain Structure: DTI



- Meta-analysis
- 3 TBSS studies, and 8 VBA studies
- Reduced FA in CC, longitudinal fasciculus, fronto-occipital fasciculus, and thalamic radiation

Liao, et al. (2013) J Psychiatry Neurosci 38(1):49-56.

MDD and Brain Structure: DTI

- Choi, et al. Neuropsychopharmacology (2014) 39(6):1332-1339.
- MDD (N=134) and HC (N=54)
- 98 treatment naïve MDD
- All medication free
- No differences found

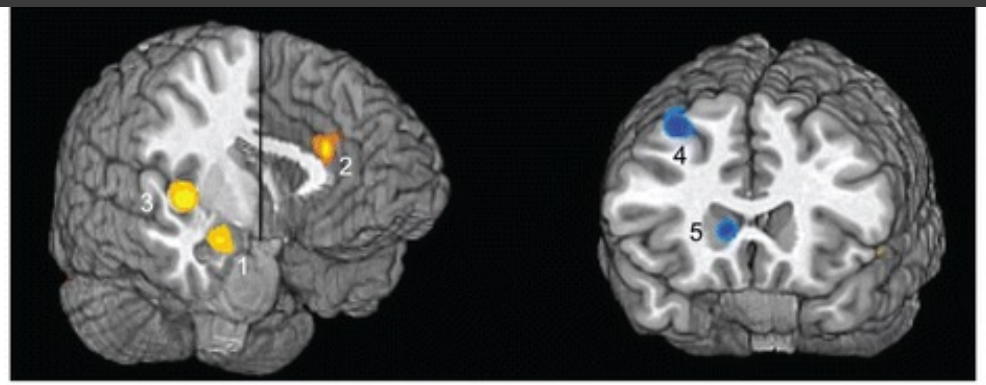
Potential Markers

- Structure
  - Volume
  - White Matter
  - Conformation
- Function
  - Cognitive Tasks
  - Resting State

MDD and cognition

- Affective Processing
  - Bias towards negative stimuli in depression
- Attention
  - Dot probe tasks
- Working memory and executive function
  - N-back task, delayed matching tasks
- Reward processing

Emotion Processing: Depression



Structure	Direction of Effect	Valence Specific Effect?	Talairach Coordinates	Cluster Size (mm^3)	Number
Amygdala	Depressed > Comparison	Yes	24, –4, –13	318	1
Dorsal anterior cingulate cortex	Depressed > Comparison	Yes	–2, 30, 20	196	2
Insula and superior temporal gyrus	Depressed > Comparison	Yes	–38, –6, –8	834	3
Precentral gyrus	Depressed > Comparison	Yes	–30, –15, 44	621	–
Middle temporal gyrus	Depressed > Comparison	Yes	–39, –64, 17	440	–
Dorsolateral prefrontal cortex	Comparison > Depressed	Yes	30, 13, 47	1,380	4
Dorsolateral prefrontal cortex	Comparison > Depressed	No	–22, 27, 42	949	–
Caudate body	Comparison > Depressed	No	10, 20, 6	382	5

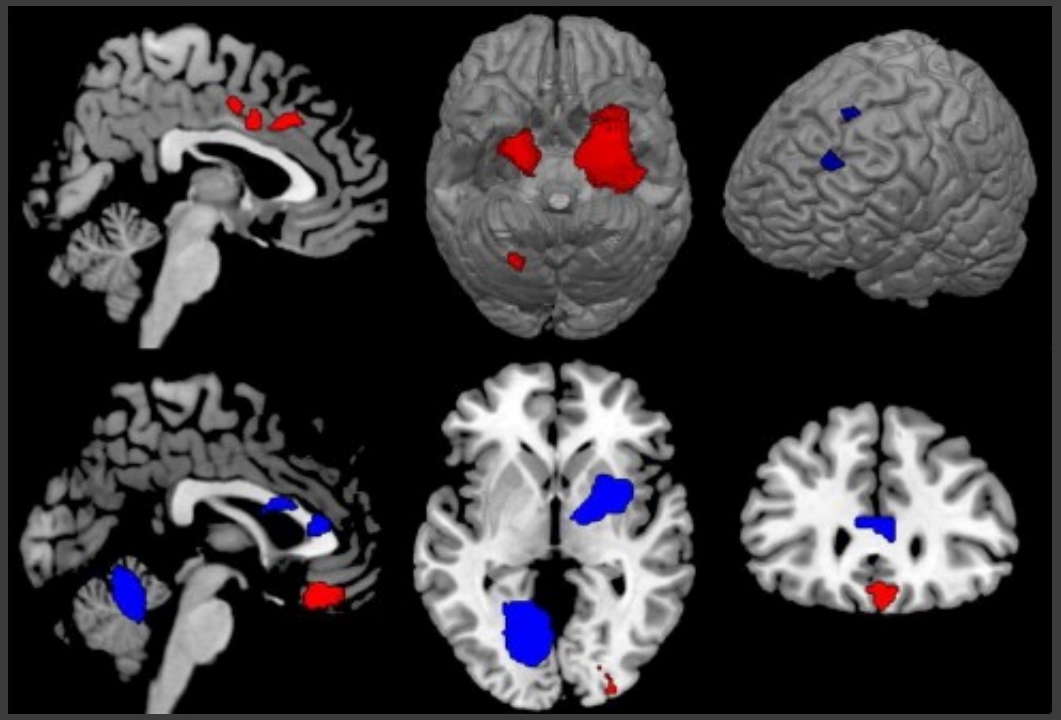
- Meta-analysis
- 14 rCBF and 24 fMRI studies
- Hyper-reactivity in salience network in response to negative stimulus vs. positive or neutral stimulus
- Hypo-reactivity in DLPFC (executive network)
- Depressed subjects also showed reduced striatal response to positive stimuli

Hamilton, et al. (2012) Am J Psychiatry 169(7):693-703

Emotion Processing: Depression

Negative Emotions

Positive Emotions

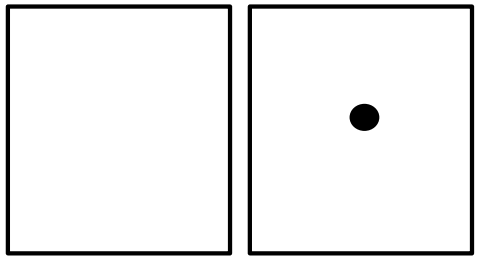


- Meta-analysis
- 44 fMRI studies
- Hyperactivation to negative stimuli and hypoactivation to positive stimuli

Groenewold, et al. (2012) Neurosci and Biobehav Rev 37(2):152-163

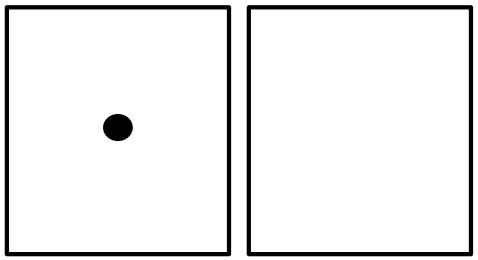
Dot Probe Task

Angry Block:

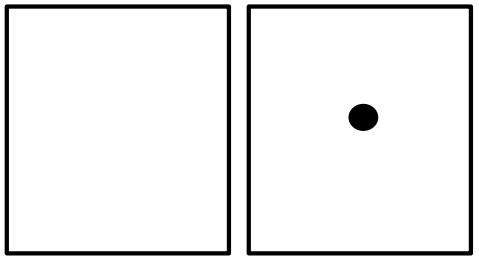
Incongruent Trial

+

Congruent Trial

Happy Block:

Congruent Trial

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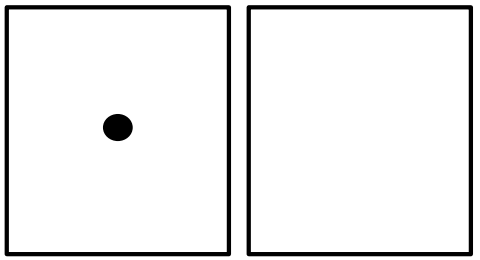
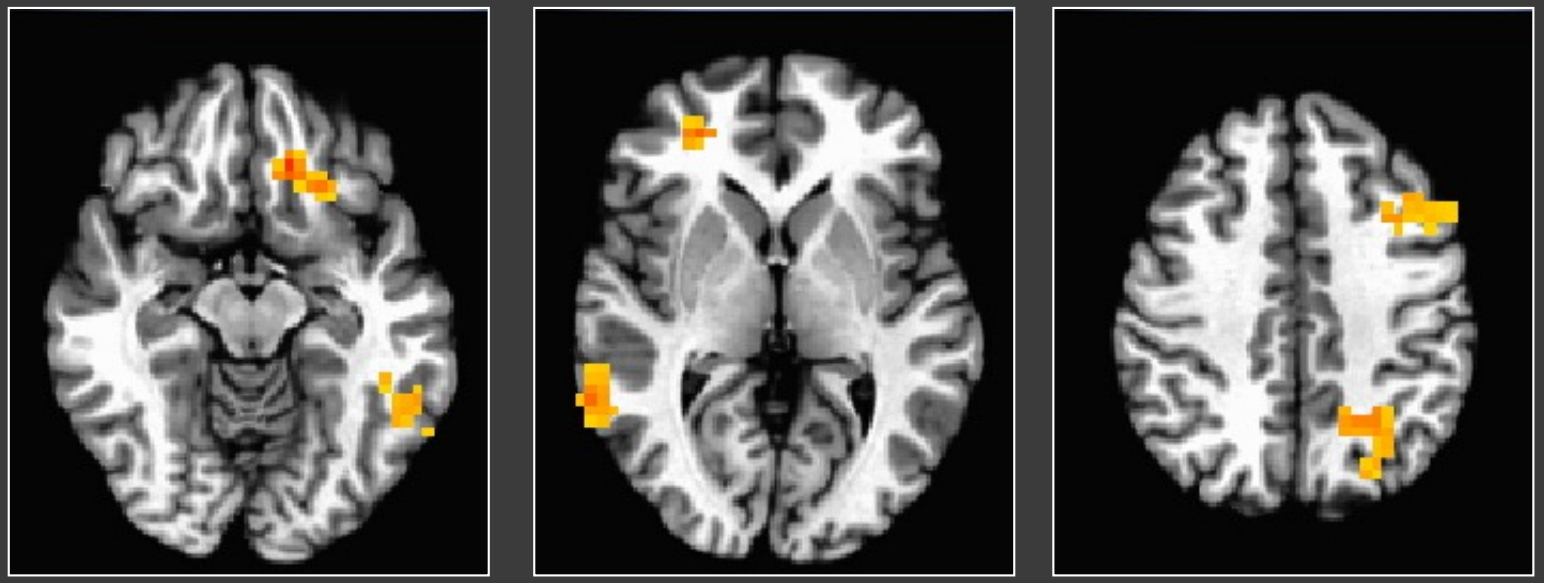


Control Trial

Dot probe task



Mixed Model: Emotion * Diagnosis Interaction

$p_{corr} < 0.10$

Parietal cortex, DLPFC, Middle temporal cortex, orbital cortex / sgACC

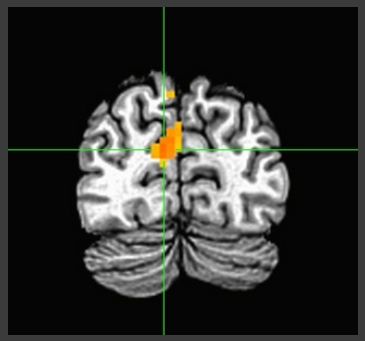
Supports the idea of an emotional processing bias at a systems level

Jessica Ihne, et al.

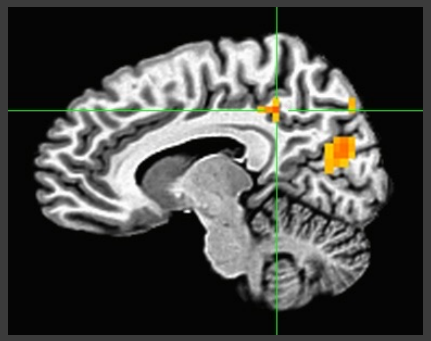
Dot Probe Task: Ketamine

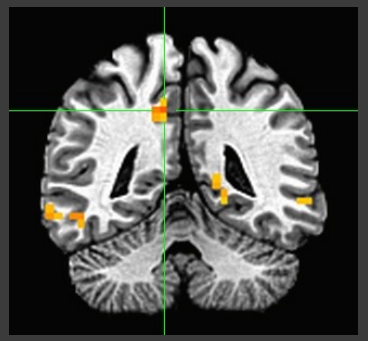
Response to negative stimuli at baseline correlates with subsequent antidepressant response



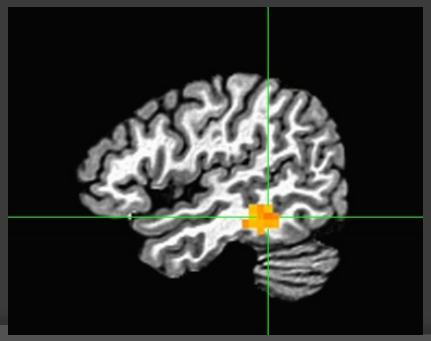
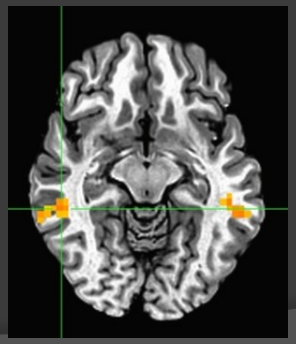
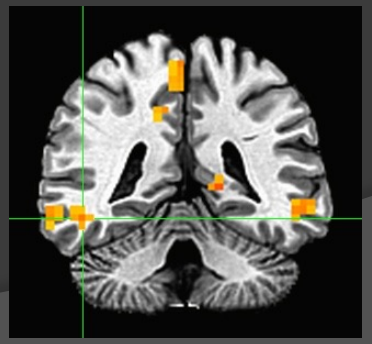


Right Cuneus
K=51
P<0.01





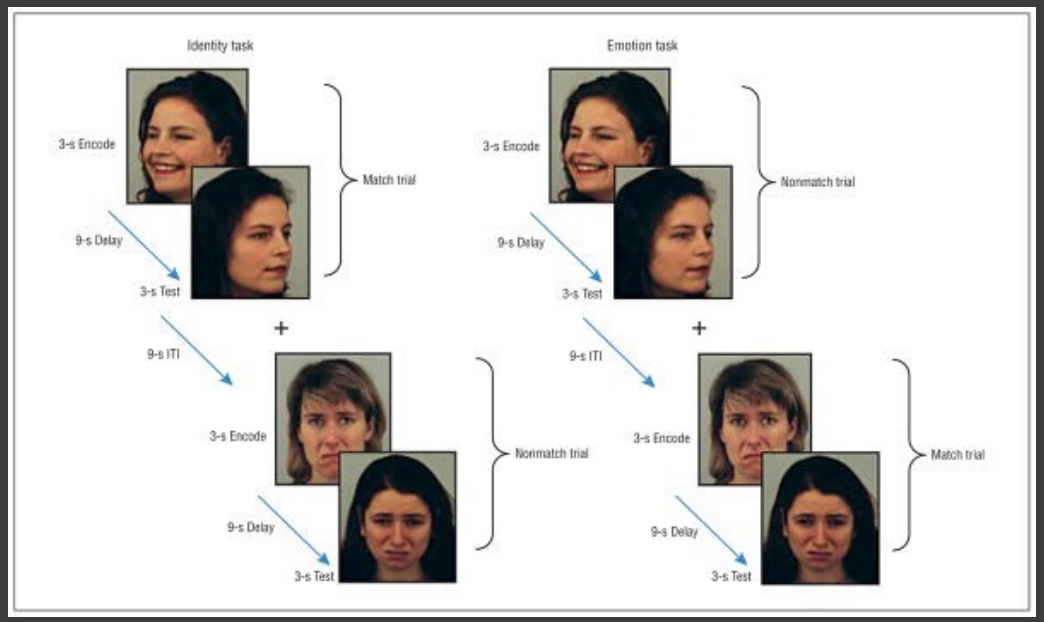
Posterior Cingulate
K=33
P<0.03

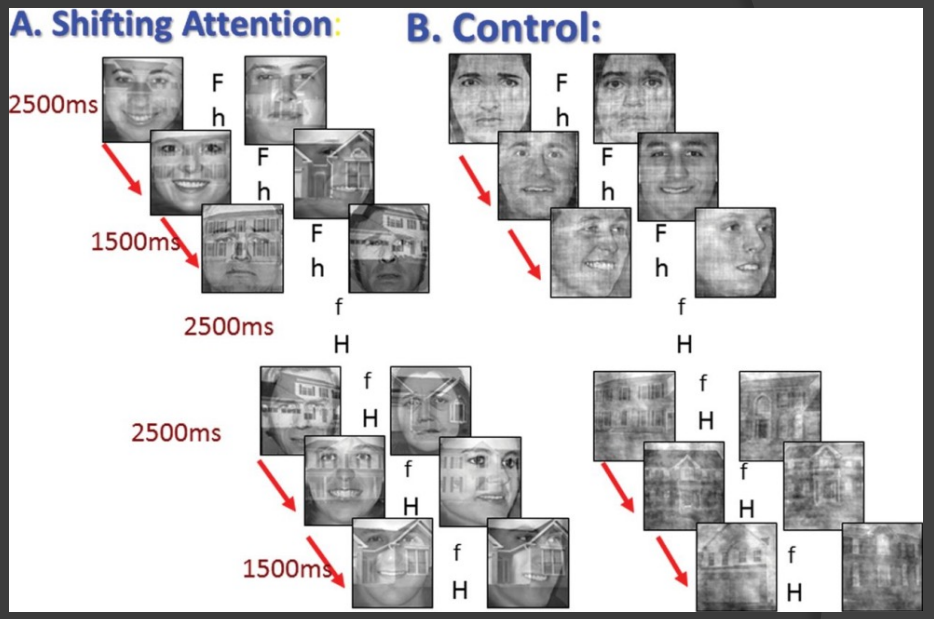
Right Fusiform
K=32
P<0.04

Jessica Ihne, et al.

Scopolamine:
Working Memory and Selective Attention



Explicit Face Processing
Implicit Emotion Processing
Explicit Emotion Processing

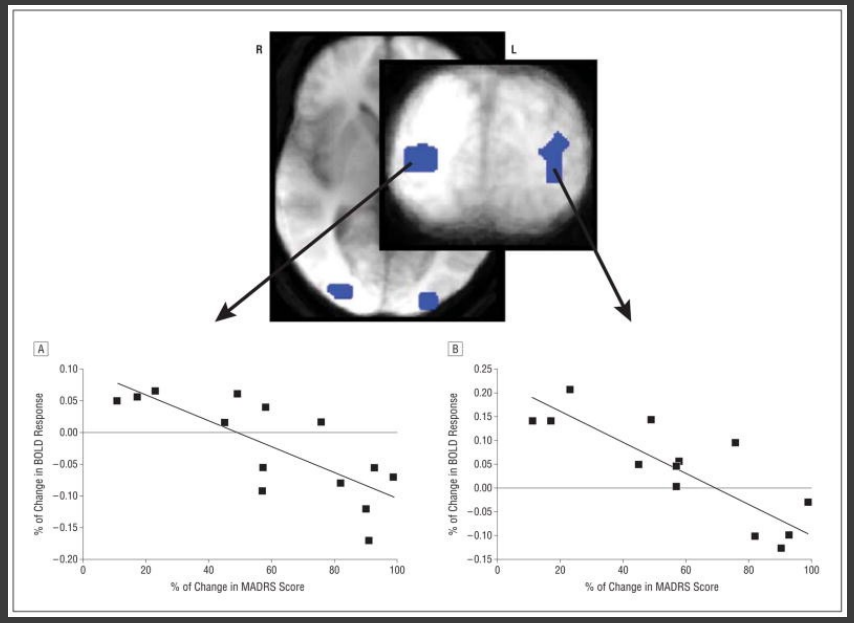


Implicit Face Processing
Explicit Face Processing
Implicit Emotion Processing

Furey, et al. JAMA Psychiatry (2013), 70(3):280-90

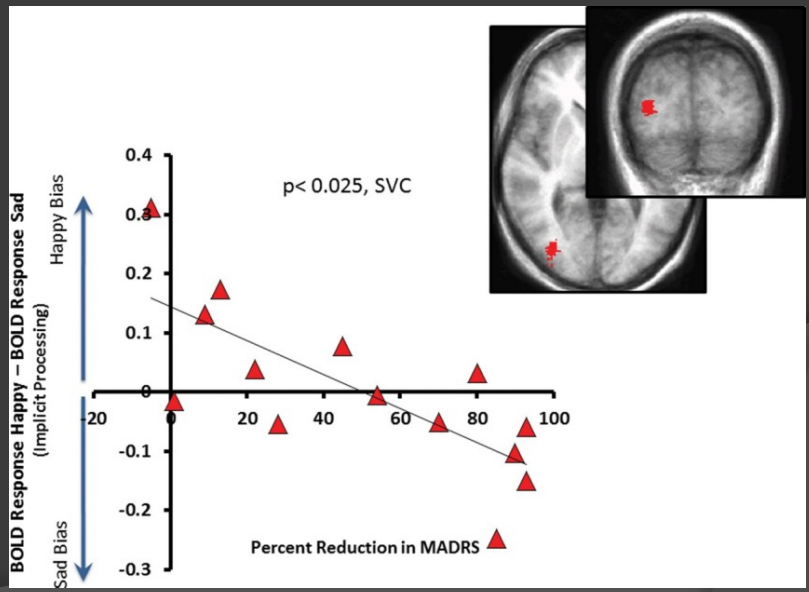
Furey, et al. Int J Neuropsychopharmacol (2015), 18(8)

Scopolamine: Working Memory and Selective Attention



Patients showing the greatest antidepressant response showed little change or slight reductions in BOLD activity while attending to emotion in both the encoding and test components of the working memory task

Patients showing the greatest antidepressant response showed a negative bias, such that the response to negative stimuli was less than the response to positive stimuli during implicit processing in the selective attention task



Furey, et al. JAMA Psychiatry (2013), 70(3):280-90

Furey, et al. Int J Neuropsychopharmacol (2015), 18(8)

Emotional Evaluation Task: Ketamine

Emotion Block:
Positive or Negative?

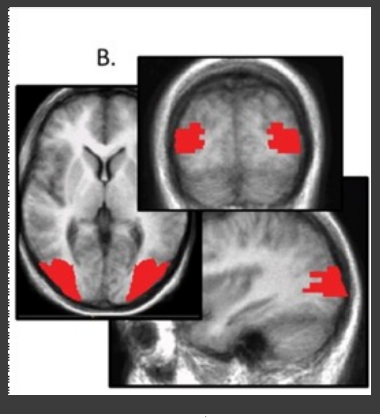
+

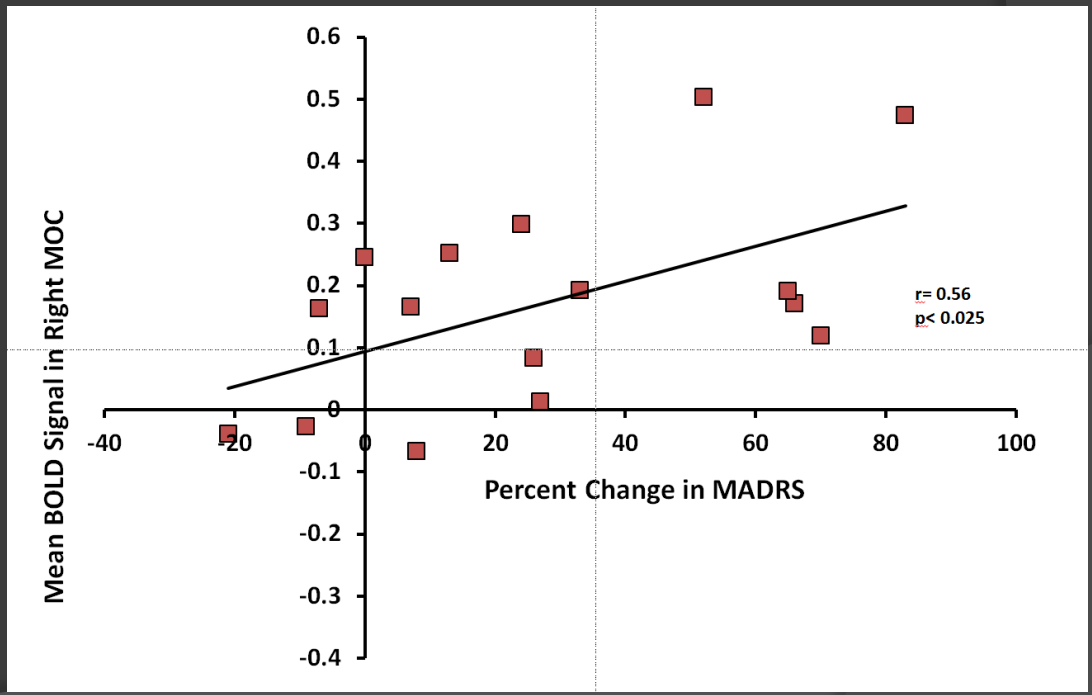
+

Gender Block:
Male or Female?

+

+



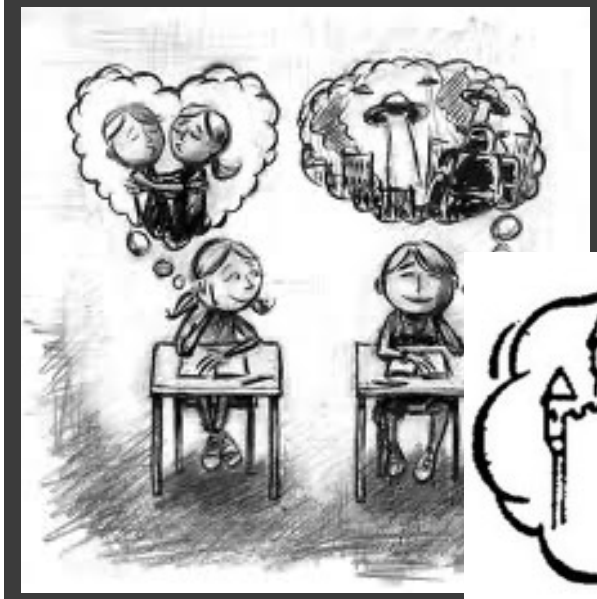


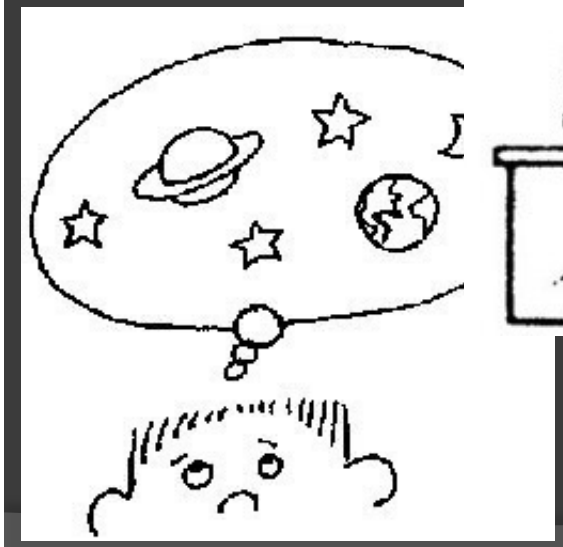
Furey, et al., under review

What do these results tell us?

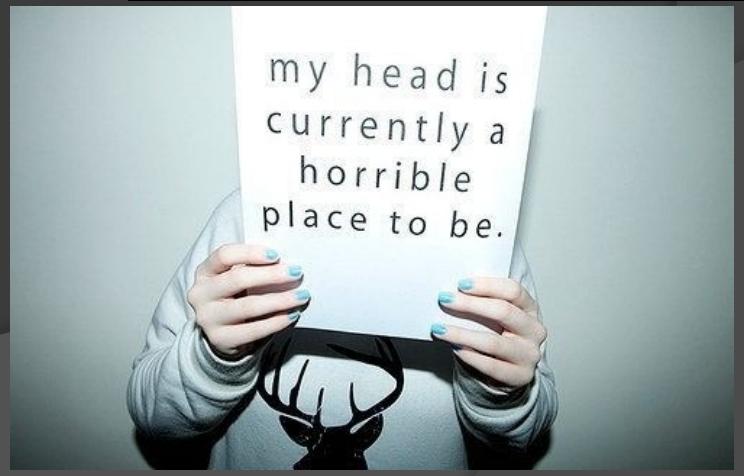
- Hyperactivity to negative stimuli
  - Amygdala
  - Dorsal cingulate
  - Insula/superior temporal
- Hypoactivity to negative stimuli
  - DLPFC
  - Striatum
- Associations with treatment
  - Middle occipital / visual
  - Posterior Cingulate / cuneus

MDD and the Resting State





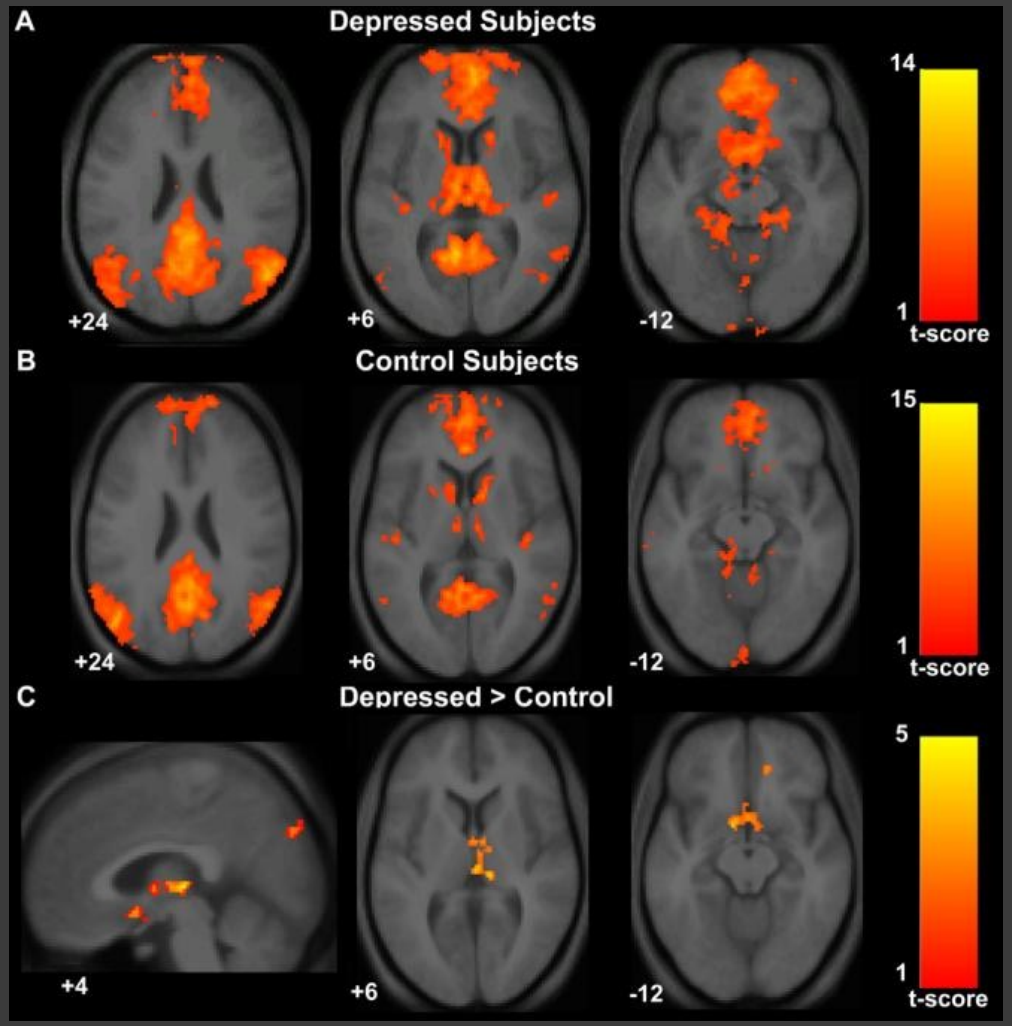
VS.



Resting State Networks

- Default Mode Network
- Salience Network
- Executive Control Network

MDD and the Resting State



- Hyperconnectivity in the sgACC and thalamus compared to healthy subjects
- These are areas of hyperactivity as shown by PET and MRI meta-analyses
- Increased resting state connectivity in sgACC has been replicated in meta-analyses.

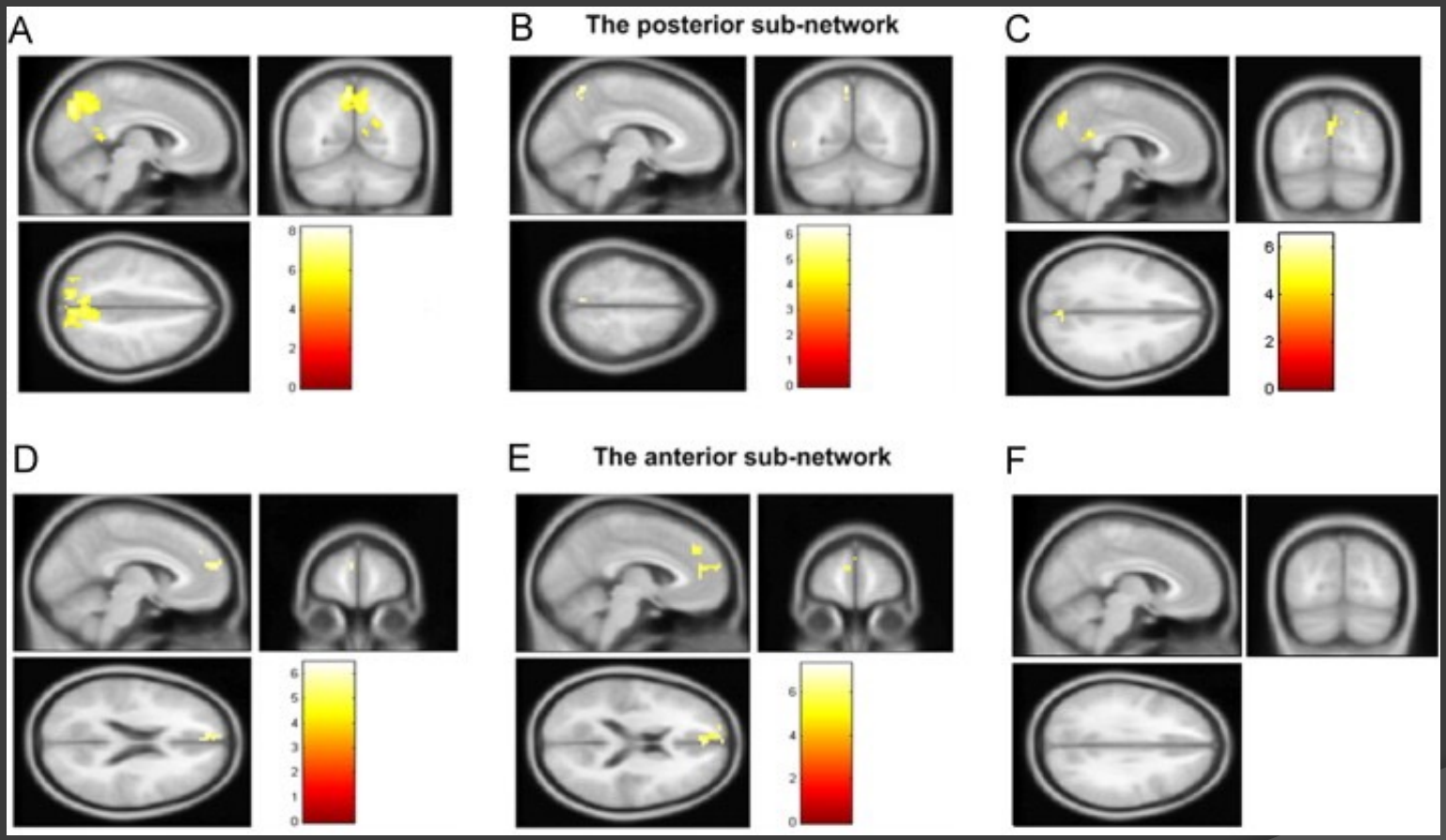
Greicius, et al. (2007) Biological Psychiatry 62(5):429-37

Resting State

Pre-treatment MDD vs. HC

Post-treatment MDD vs. HC

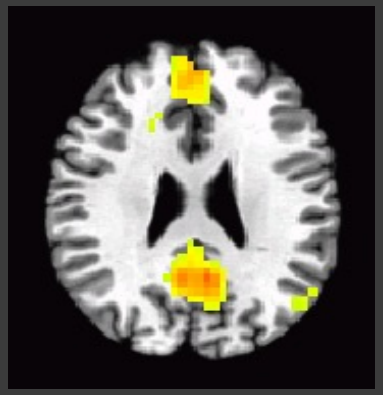
Pre-treatment MDD vs. Post-treatment MDD

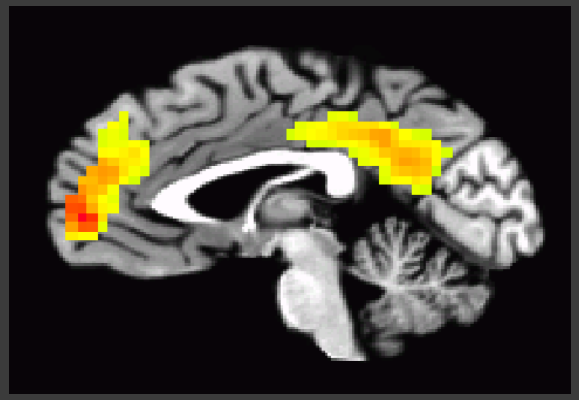


While posterior default mode network responds to antidepressant treatment, dysfunction in the anterior default mode network is unchanged

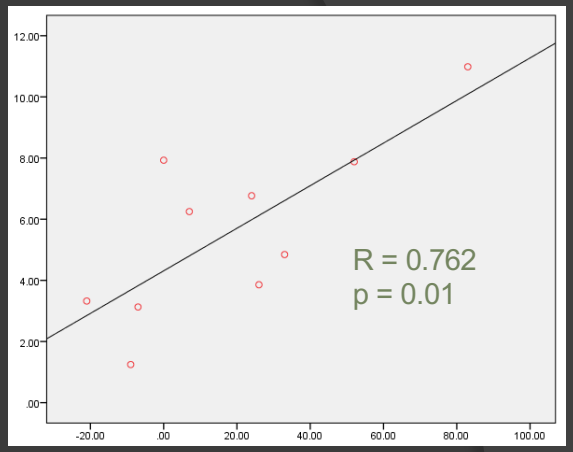
Baojuan, et al. (2012) Biological Psychiatry 74(1):48-54

Default Mode Connectivity Associated with Response to Ketamine:





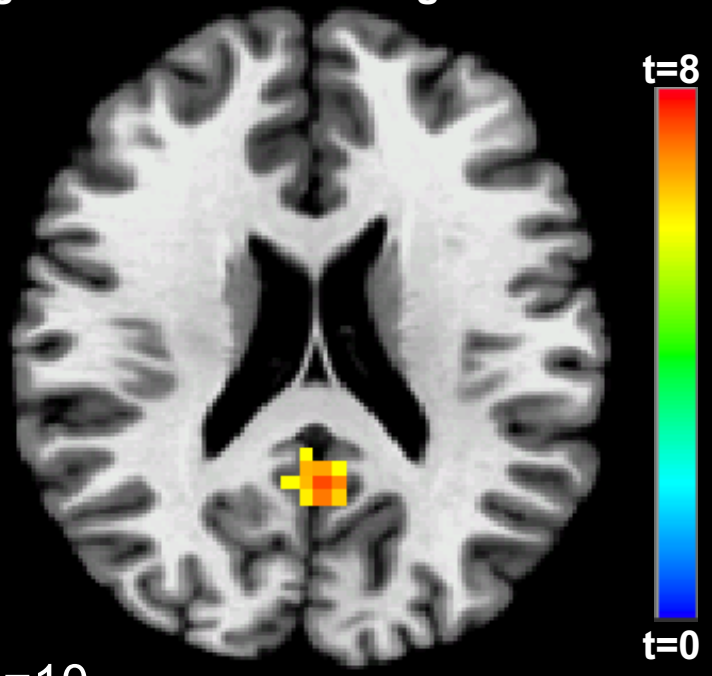
Average beta weight within an anatomical Posterior Cingulate ROI



% Change in MADRS score
Pre- vs. post-infusion

Significant Posterior Cingulate Cluster

Peak Coordinate = (1.8, 50, 26.5), t = 6.98, extent = 33

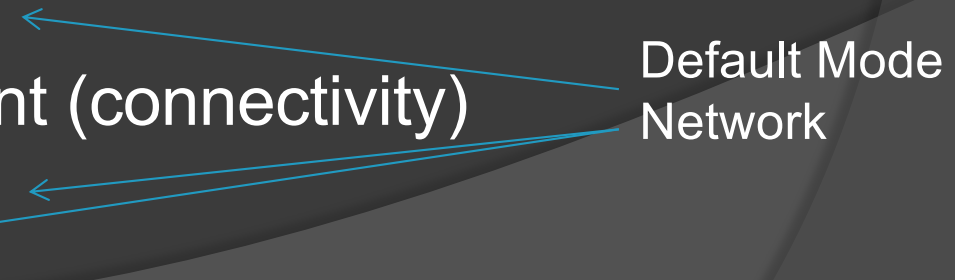


N=10

Nugent, et al., HBM 2013

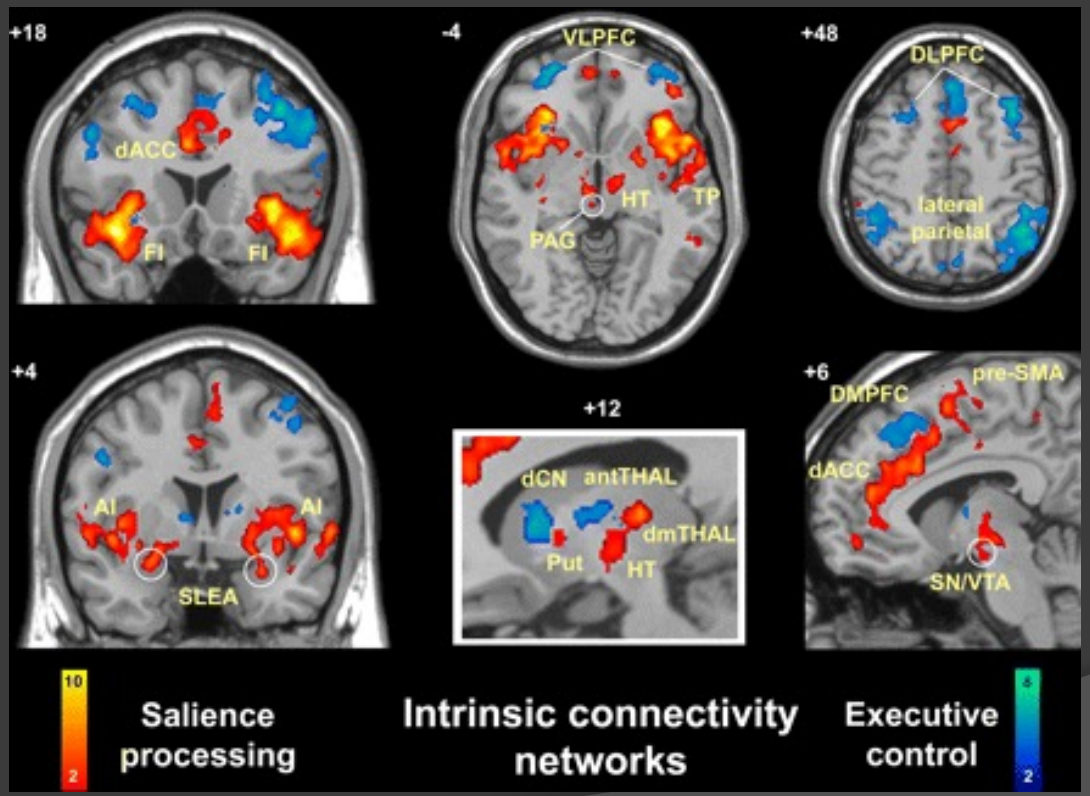
What do these results tell us?

- Hyperactivity to negative stimuli
  - Amygdala
  - Dorsal cingulate
  - Insula/superior temporal
- Hypoactivity to negative stimuli
  - DLPFC
  - Striatum
- Associations with treatment (activity)
  - Middle occipital / visual
  - Posterior Cingulate / cuneus
- Associations with treatment (connectivity)
  - Posterior Cingulate / cuneus
  - Medial PFC



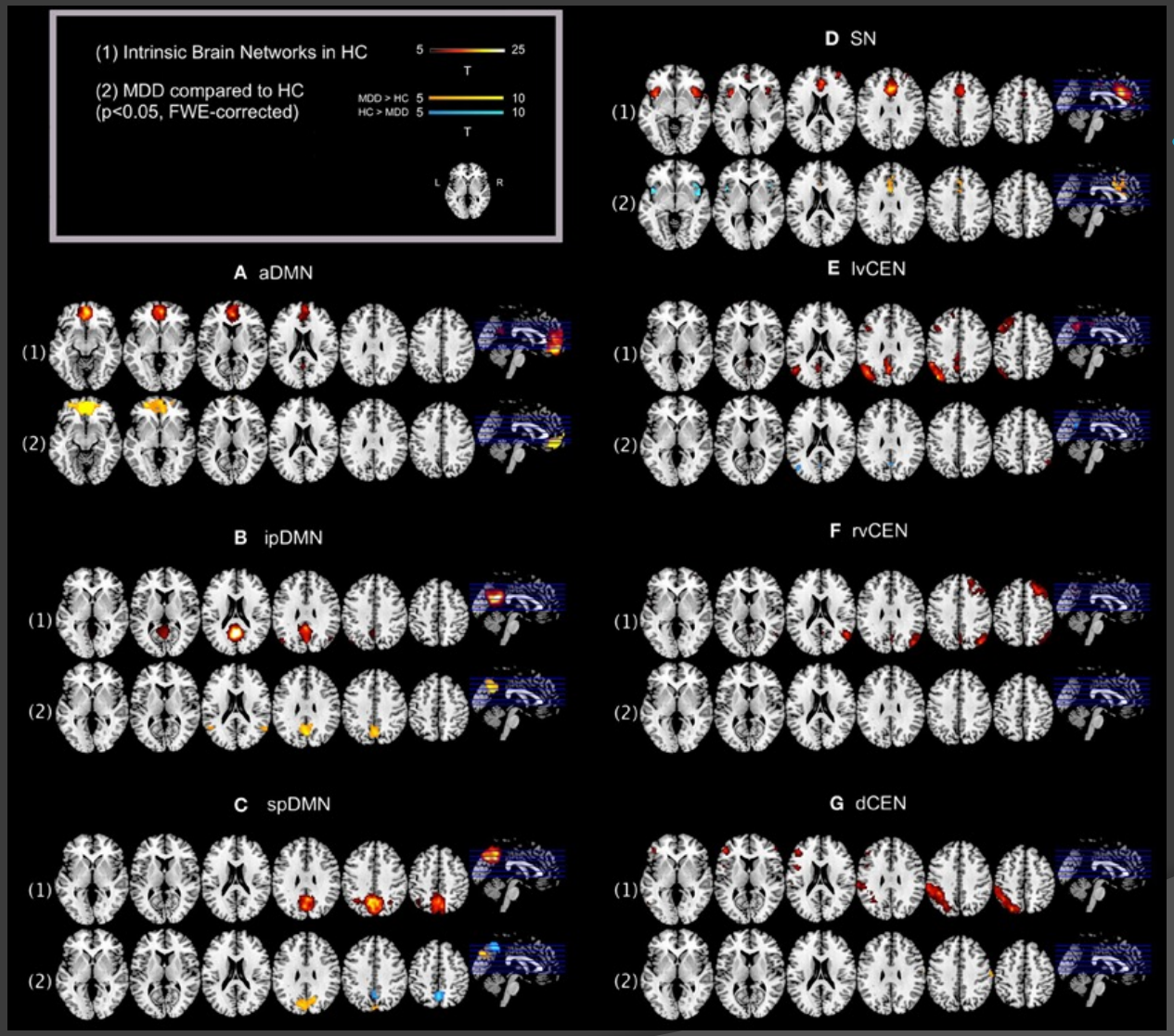
Resting State Networks

- Default Mode Network
- Salience Network
- Executive Control Network



Seeley, et al. (2007) J Neurosci 27(9):2349-2356

MDD and the Resting State



↑ ACC (DMN)

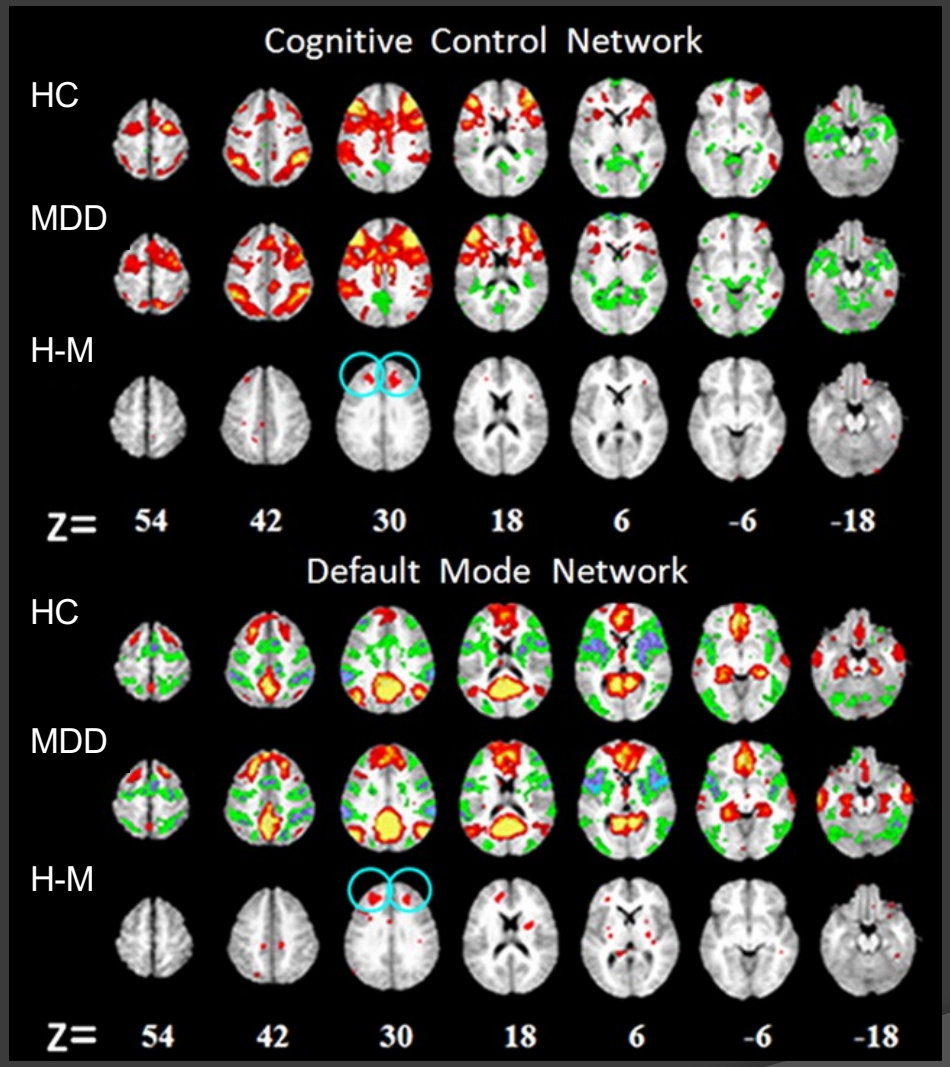
↑ PCC (DMN)

↑ PCC (DMN)

↓ Insula (SN)

Manoliu, et al. (2014) Frontiers in Human Neurosci vol 7

MDD and the Resting State

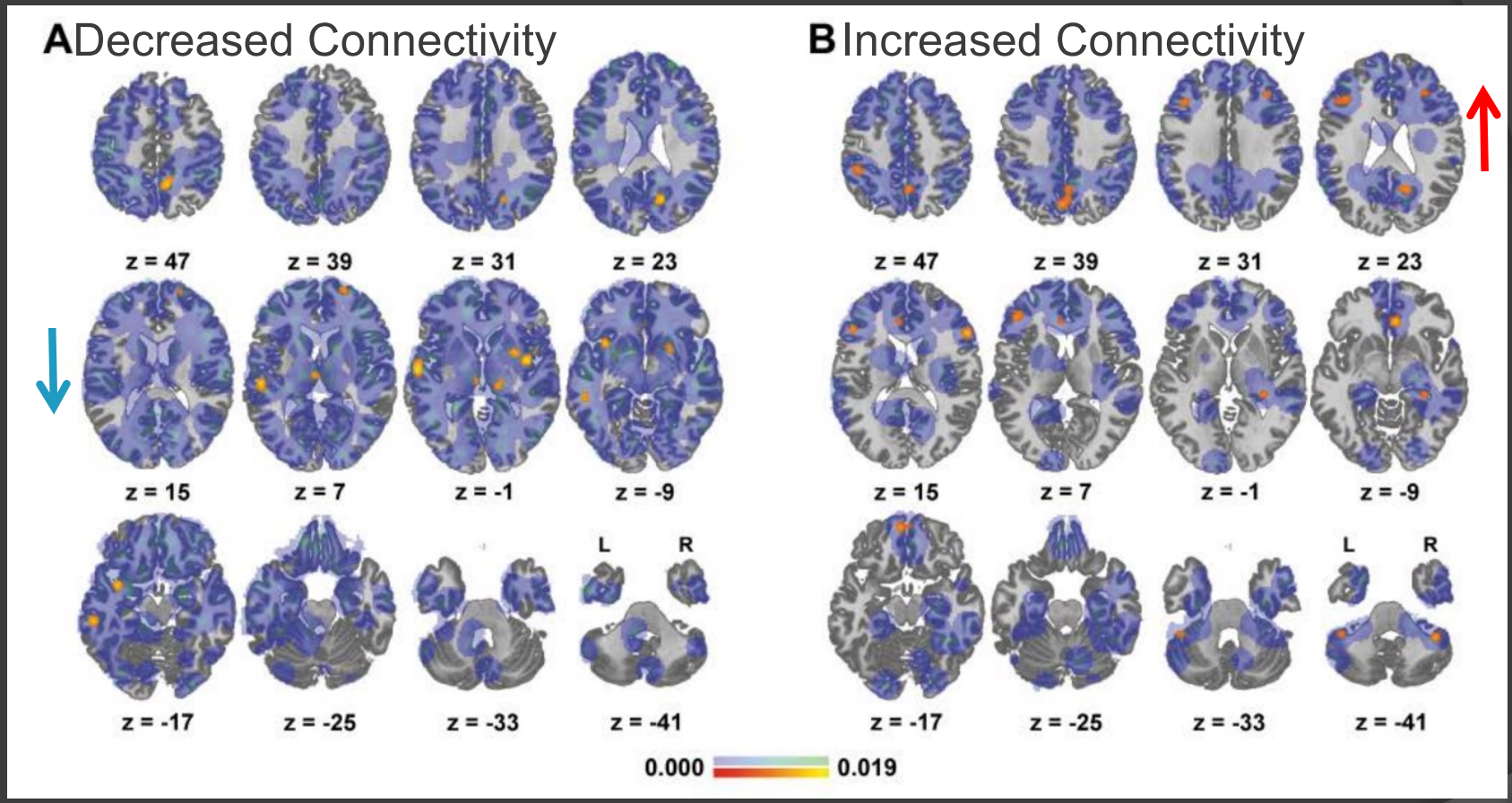


dmPFC (SN)

dmPFC (SN)

Sheline, et al. (2010) PNAS 107(24):11020-11025

MDD and the Resting State



Insula (SN)

DLPFC (CEN)

- Meta-analysis, 32 studies, separate analyses for results showing increased and decreased connectivity

Sundermann, et al. (2014) Front Hum Neurosci

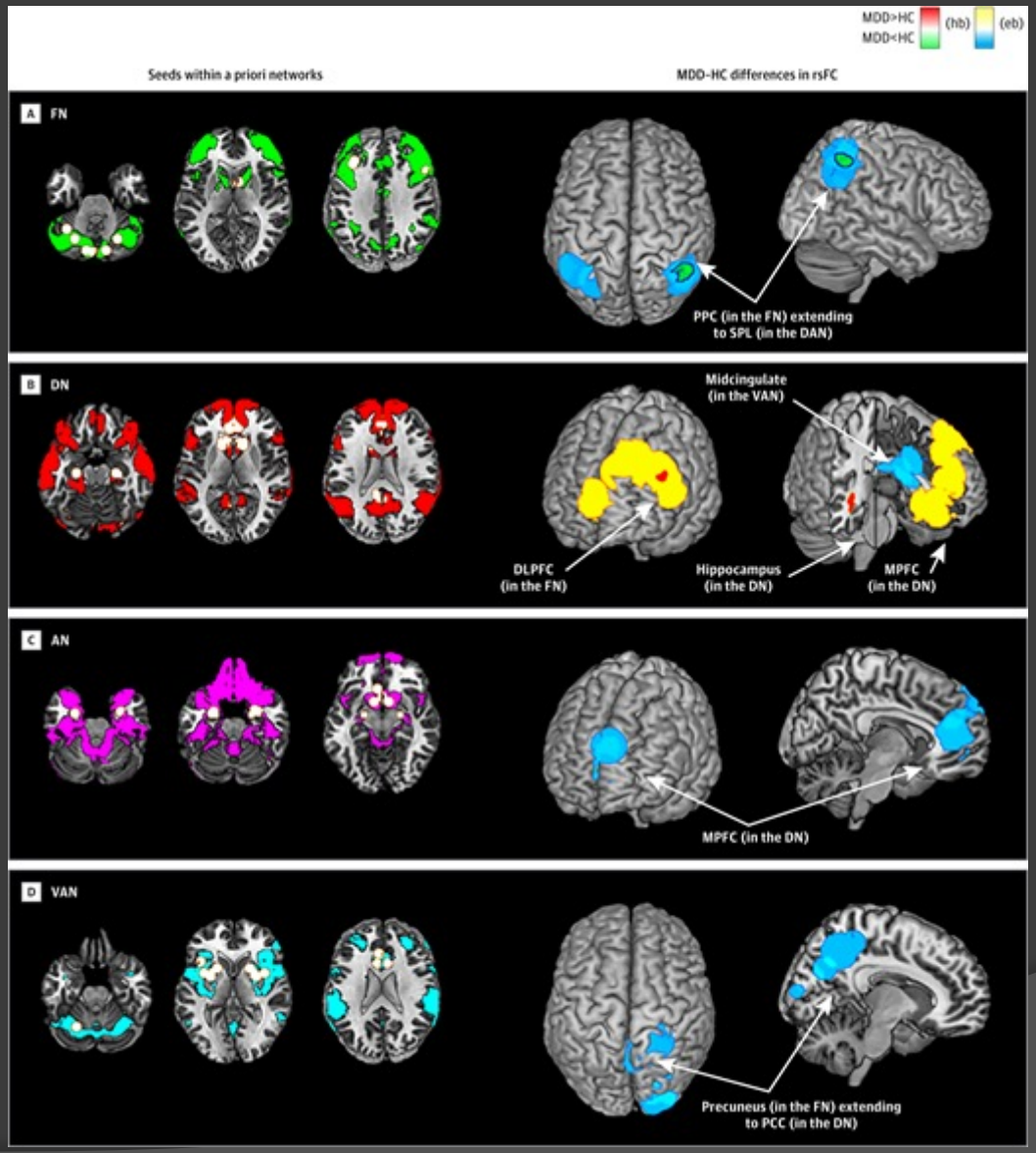
MDD and the Resting State: Meta-analysis, 25 studies

Central Executive

Default Mode

Affective

Salience



↓ Superior Parietal (SN)

↑ DLPFC (CEN)

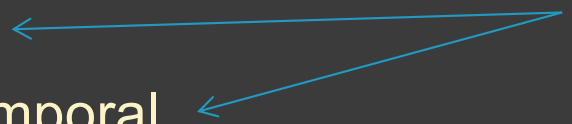
↓ dACC (SN)

↓ PCC

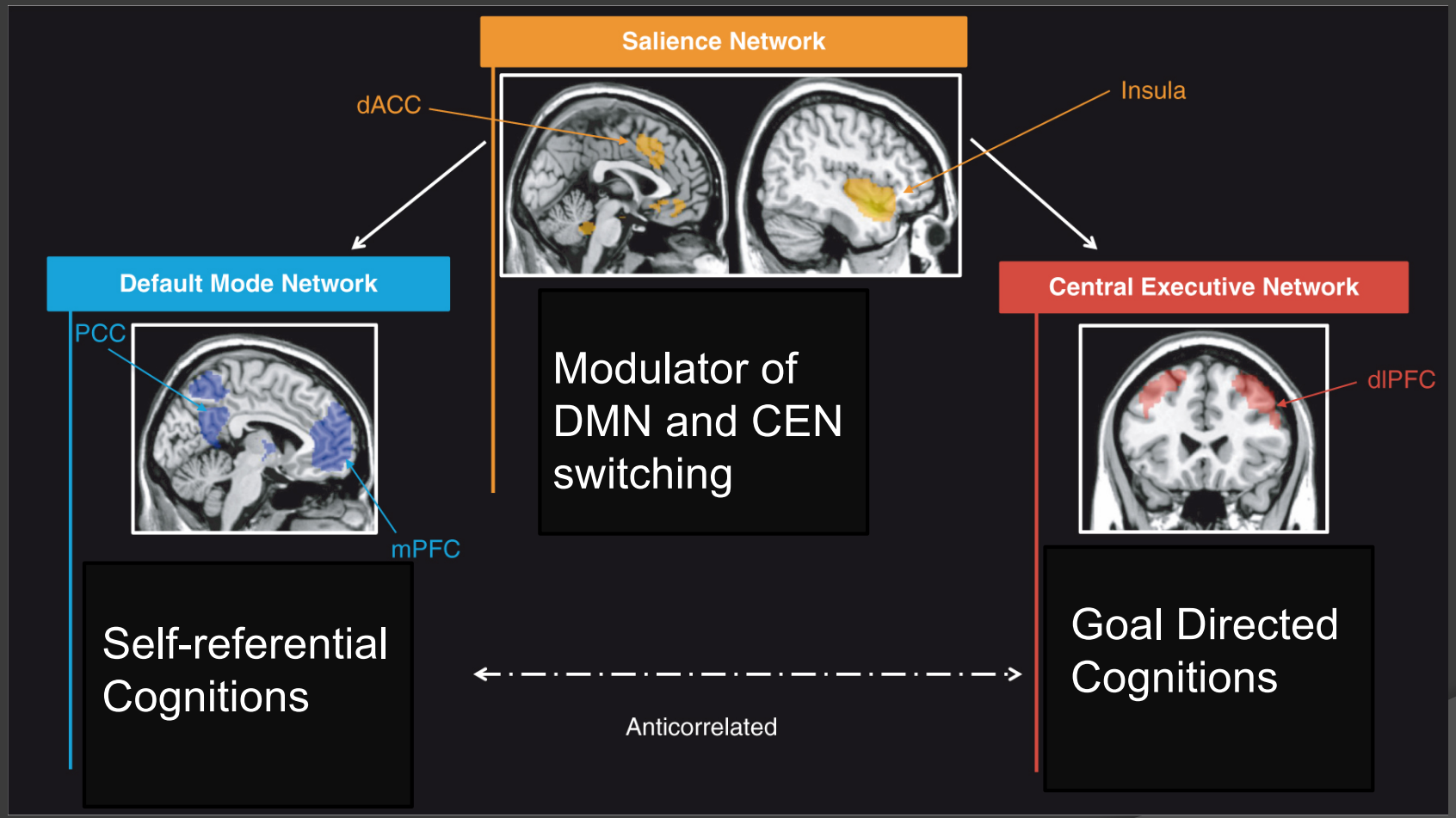
Kaiser, et al. (2015) JAMA Psychiatry 72(6):603-611

What do these results tell us?

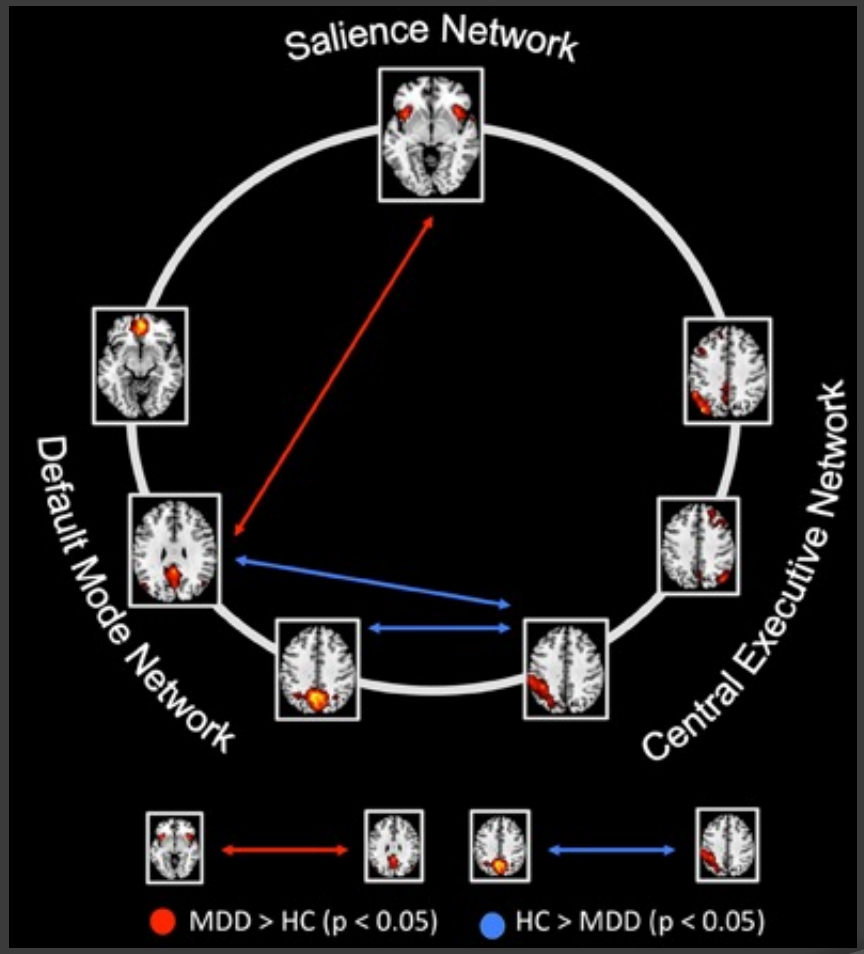
- Hyperactivity to negative stimuli
  - Amygdala
  - Dorsal cingulate
  - Insula/superior temporal
- Hypoactivity to negative stimuli
  - DLPFC
  - Striatum
- Hyperconnectivity
  - Executive control network
  - Default Mode network
  - Subgenual cingulate
- Hypoconnectivity
  - Salience network



Triple Network Model



Triple Network Model



Manoliu, et al. (2014) Frontiers in Human Neurosci vol 7

What isn’t known

- How does treatment affect the interplay between these networks?
- If there are dynamic changes in the relationship between these networks
- If there are fundamental differences in network function at a neuronal level

Conclusions

- Mood disorders are frequently disabling, but poorly understood and ineffectively treated
- New models are emerging, such as the triple network model, which may be significant in understanding brain function in mood disorders
- Translation of these models into new drug targets is not obvious
- Full understanding will likely involve multimodality approaches, integrating structure, function and other diverse modalities

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