Multimodal Imaging in Mood Disorders

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National Institute of Mental Health

Outline

- What are Mood Disorders?
- The Neurobiology of Depression and Treatment
- What can imaging teach us about Depression and its treatment?

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Mood Disorders

- Depressive Disorders
  - Major Depressive Disorder
  - Post-partum Depression and Premenstrual Dysphoric Disorder
  - Seasonal Affective Disorder
  - Etc.
- Bipolar Disorders
  - Bipolar Disorder Types I and II
  - Cyclothymia

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Mood Disorders

- Major Depressive Disorder
  - Either depressed mood or anhedonia
  - Changes in sleep, weight, activity; feelings of guilt or worthlessness; problems with concentration; suicidality
  - Treatment is empirical; many drugs, none are terribly effective
  - STAR*D study: 2 trials or 6 months for 50% remission

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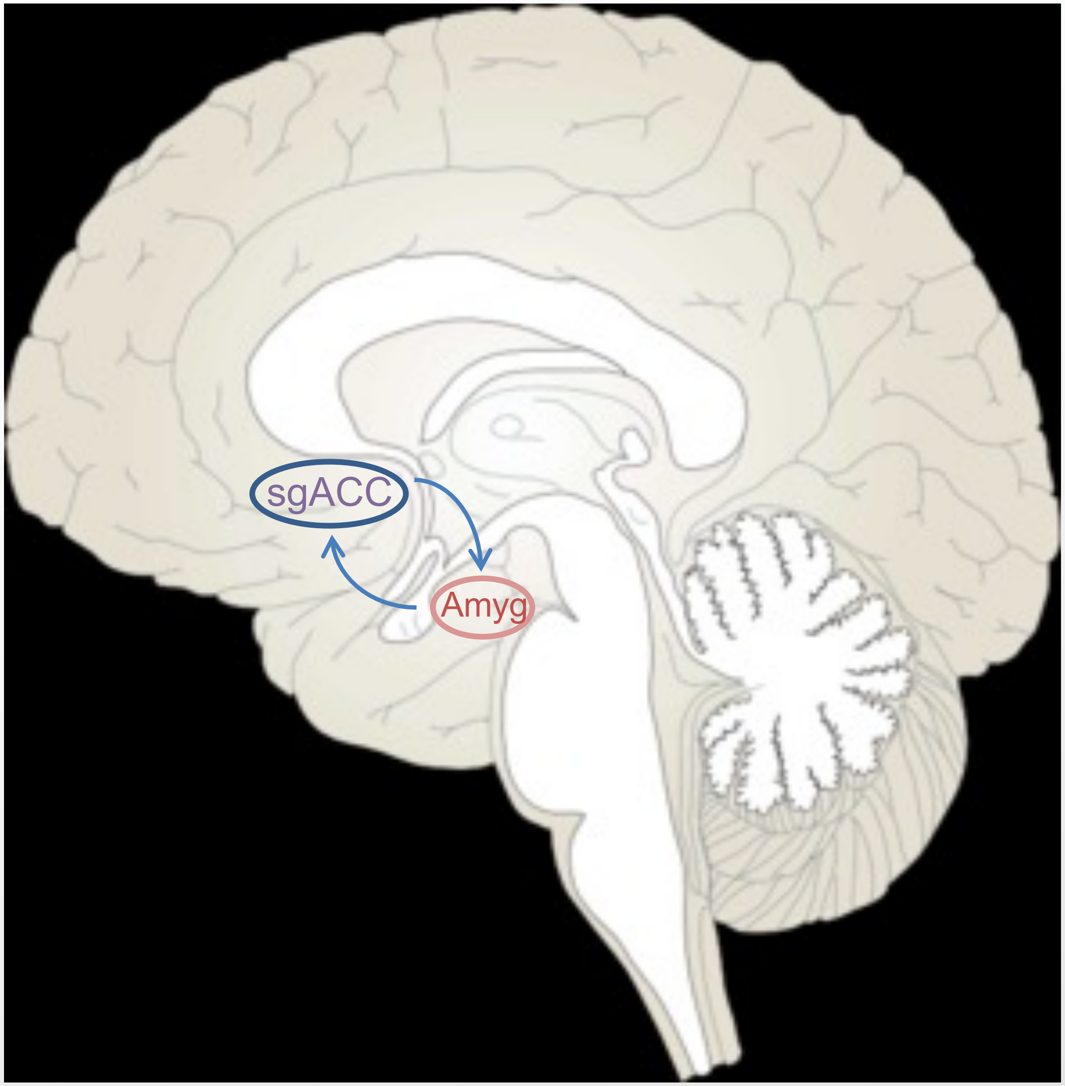
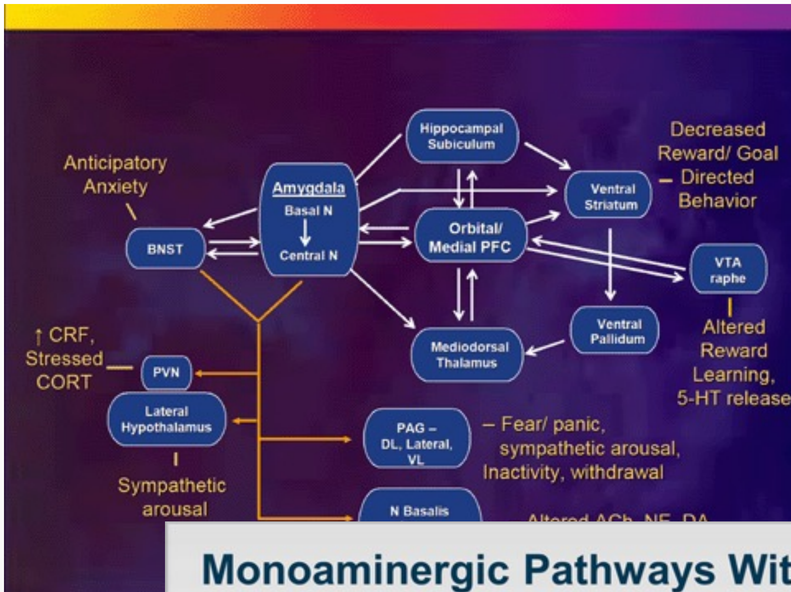
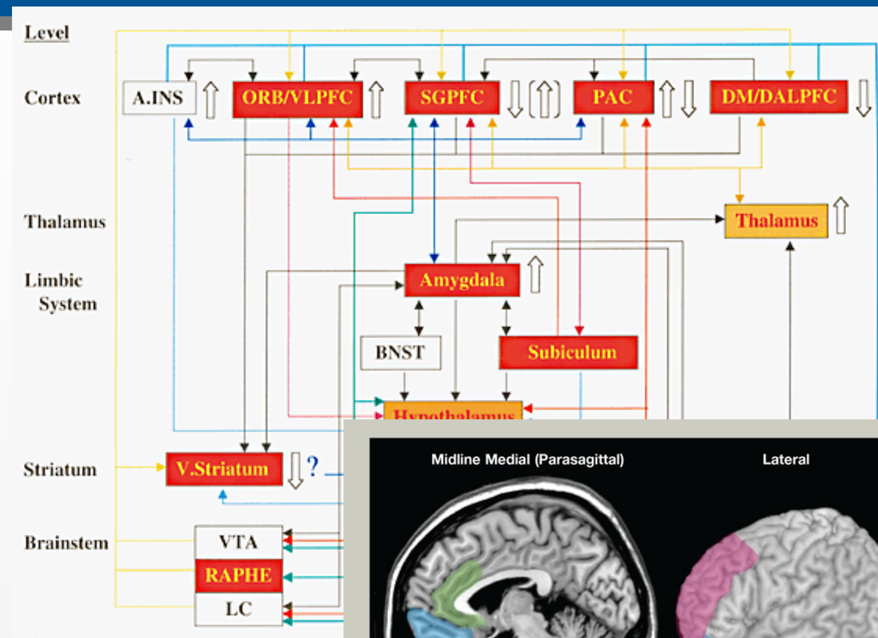
Neurobiology of Depression: Core Brain Regions

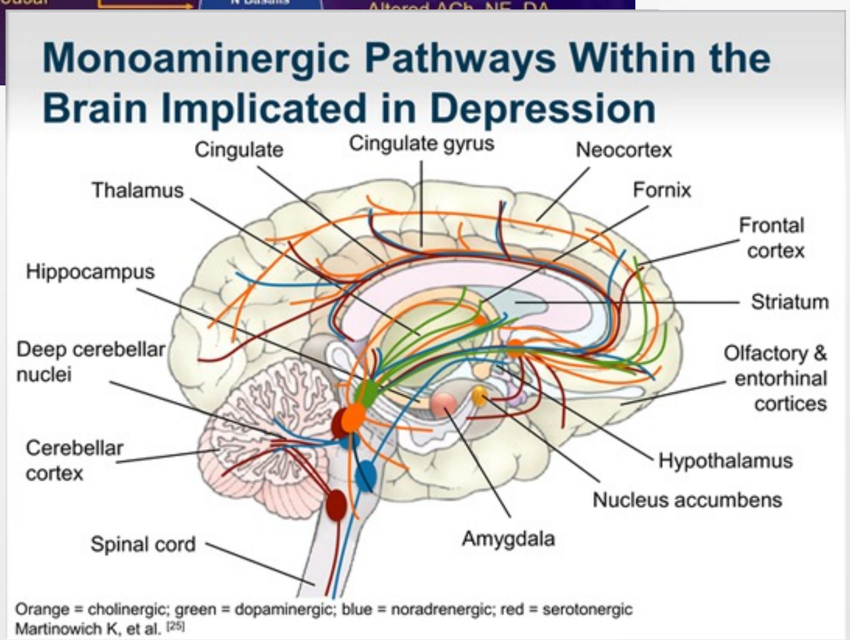


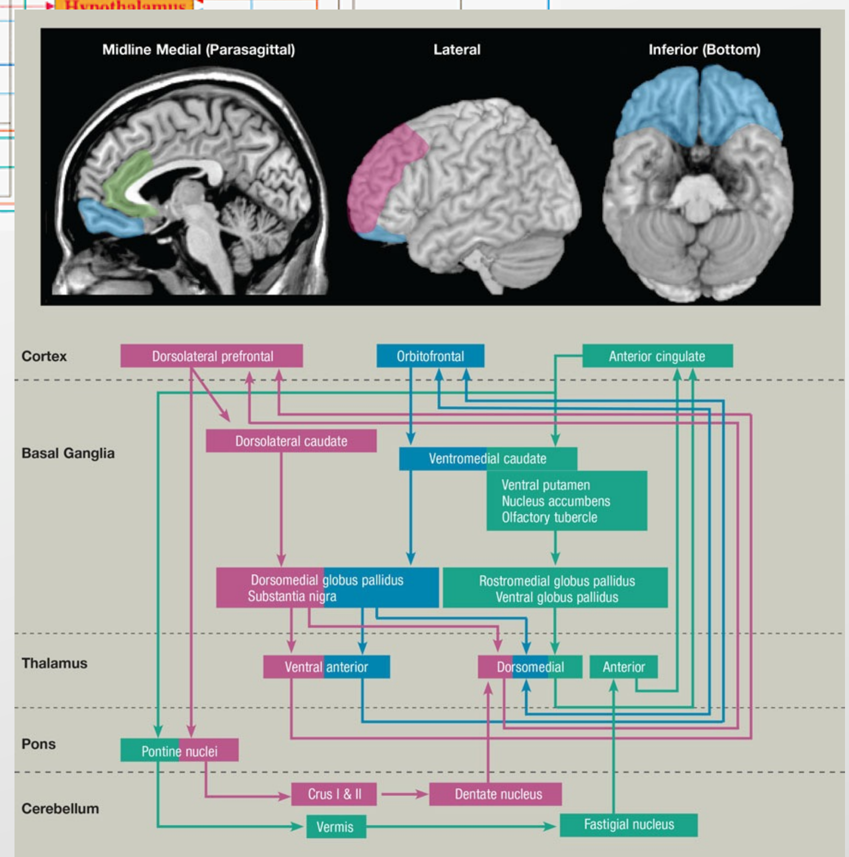
- Subgenual cingulate cortex, BA25
- Amygdala

Neurobiology of Depression: Less Simple

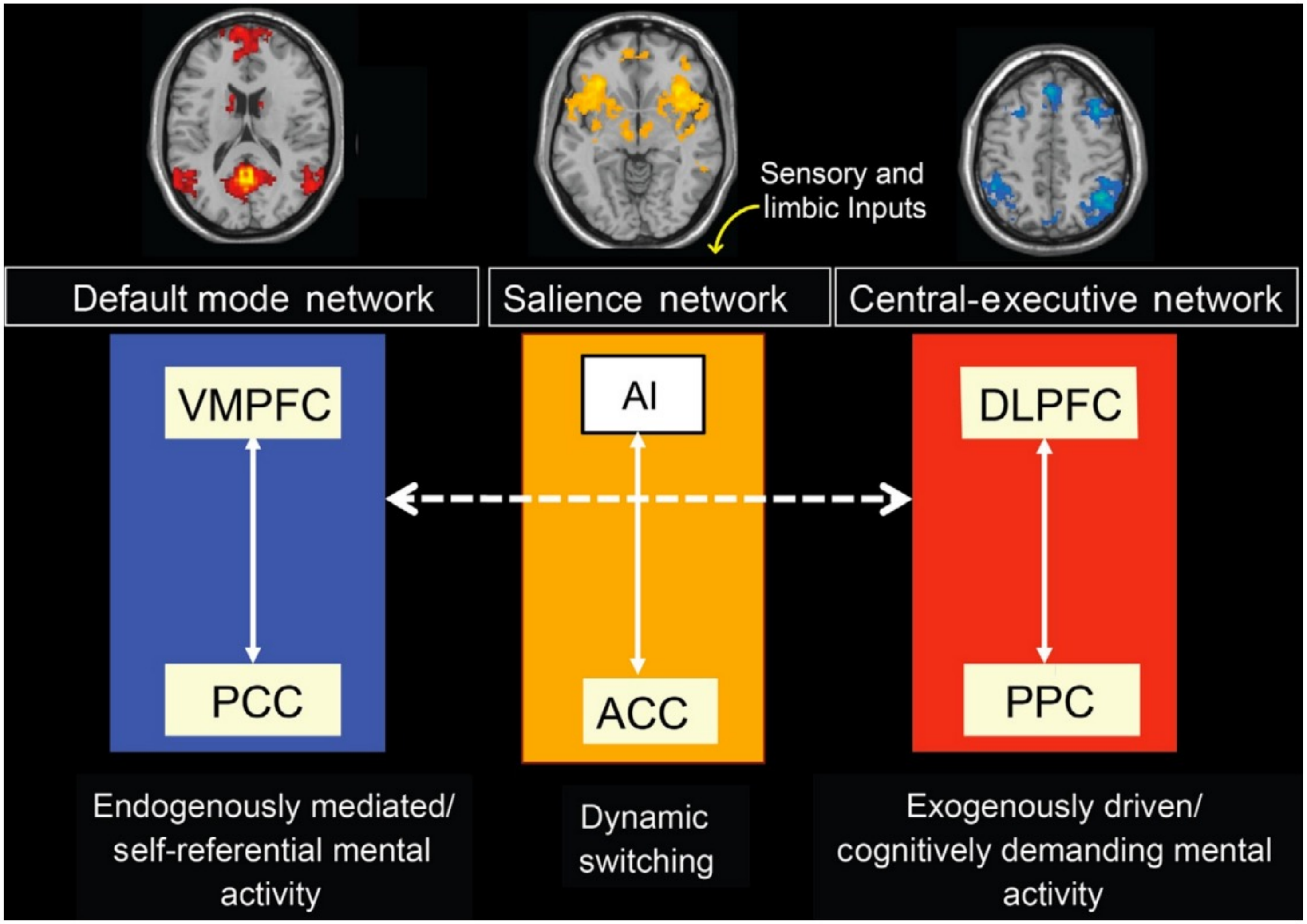








The Triple Network Model

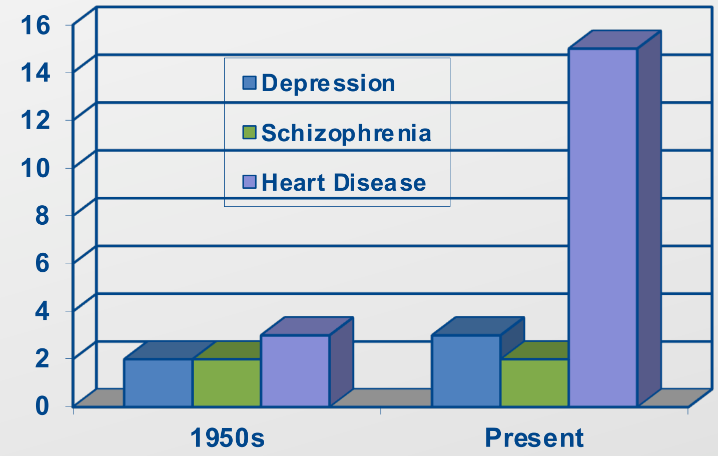


Menon V, Brain Mapping: An Encyclopedic Reference, (2015), vol. 2, pp. 597-611

MDD: Pathogenesis and Treatment

- Original Hypothesis : monoamine dysfunction
  - Norepinephrine
  - Serotonin
  - Dopamine
- All currently approved drugs target the monoaminergic system

# of Mechanistically Distinct Drugs



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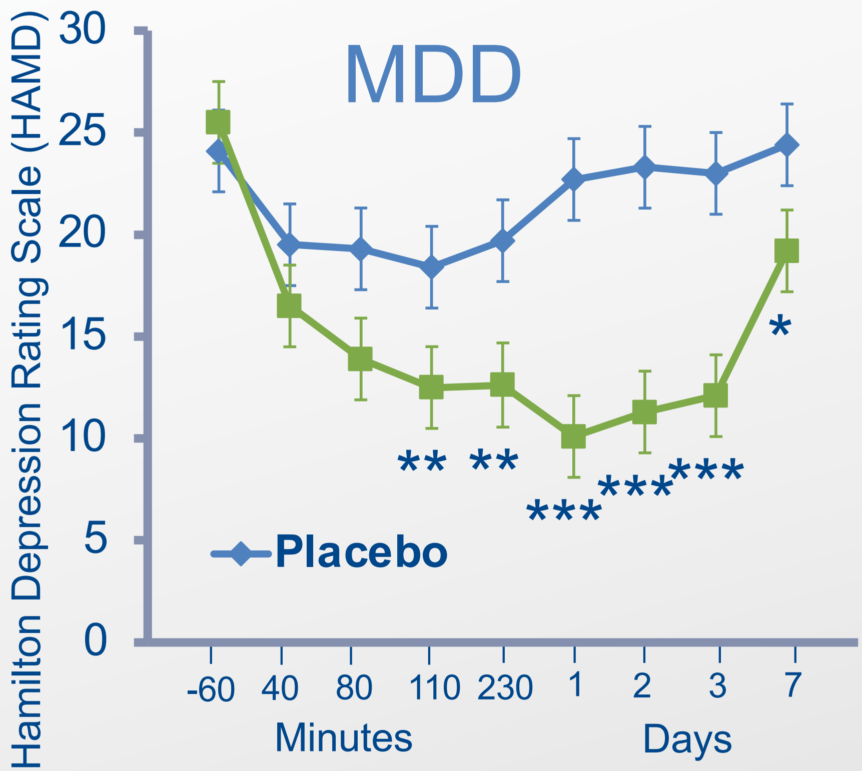
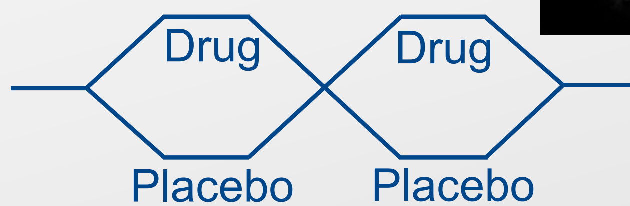
Ketamine

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





Ketamine: Investigative Tool to study Rapid Antidepressant Effects

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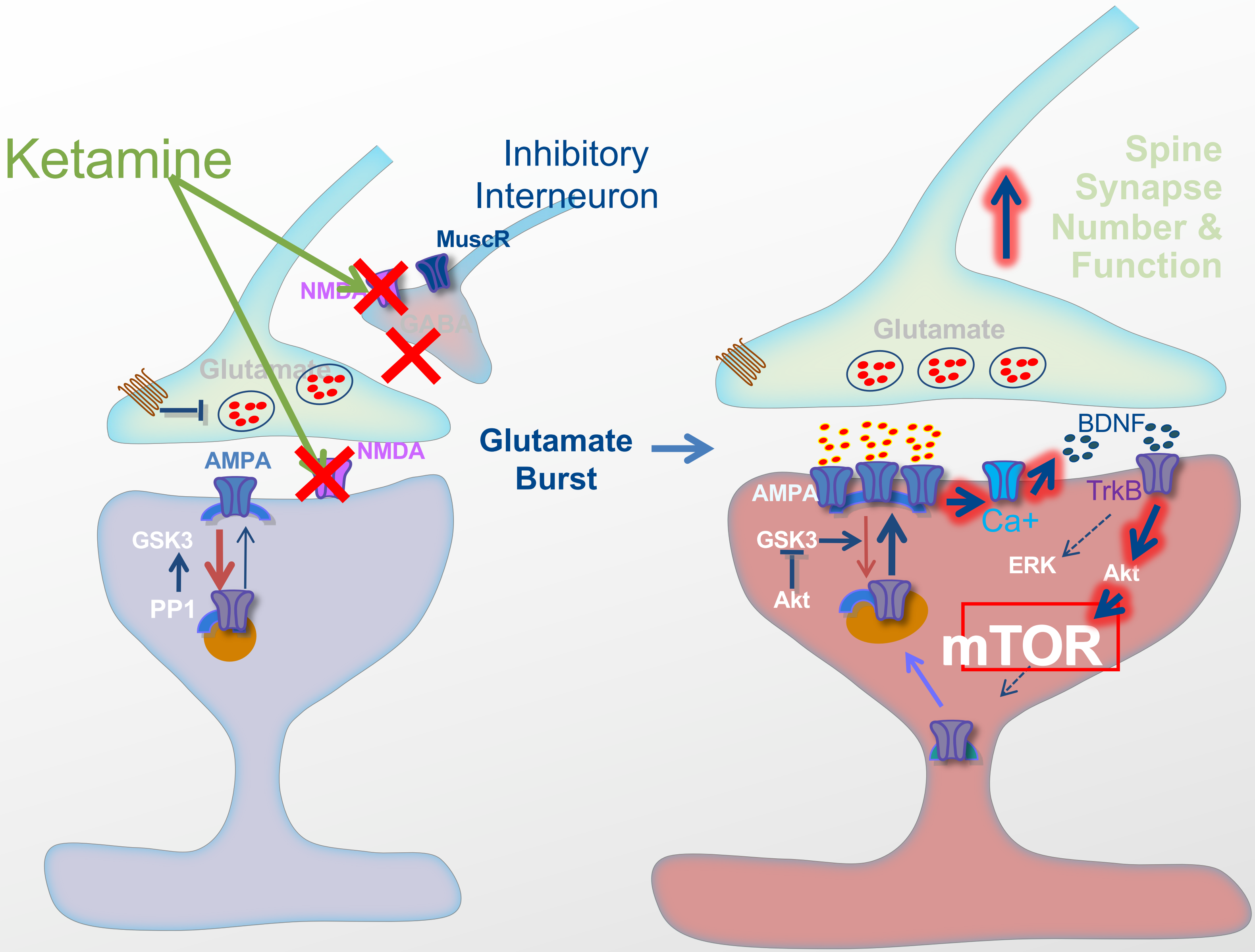
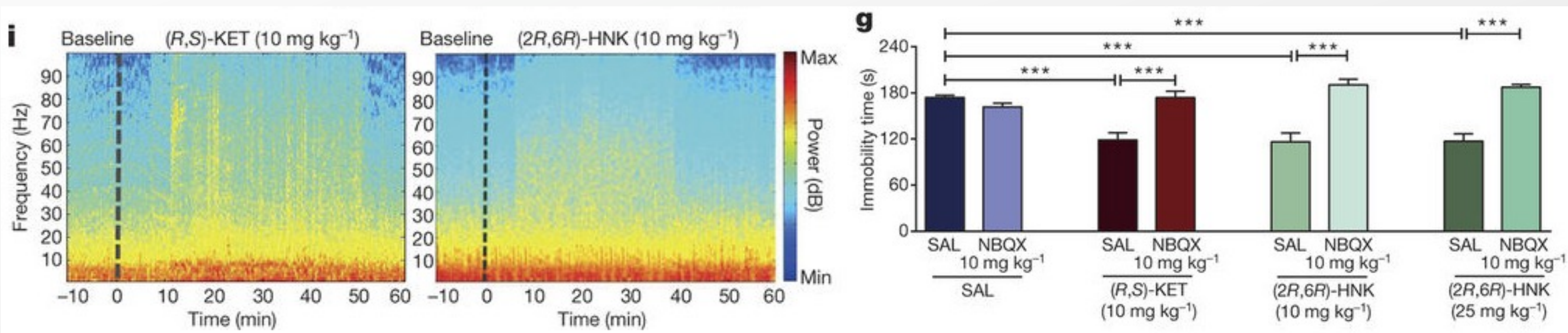
Rapid acting antidepressants: A common pathway of synaptogenesis?



Adapted from Duman, 2014

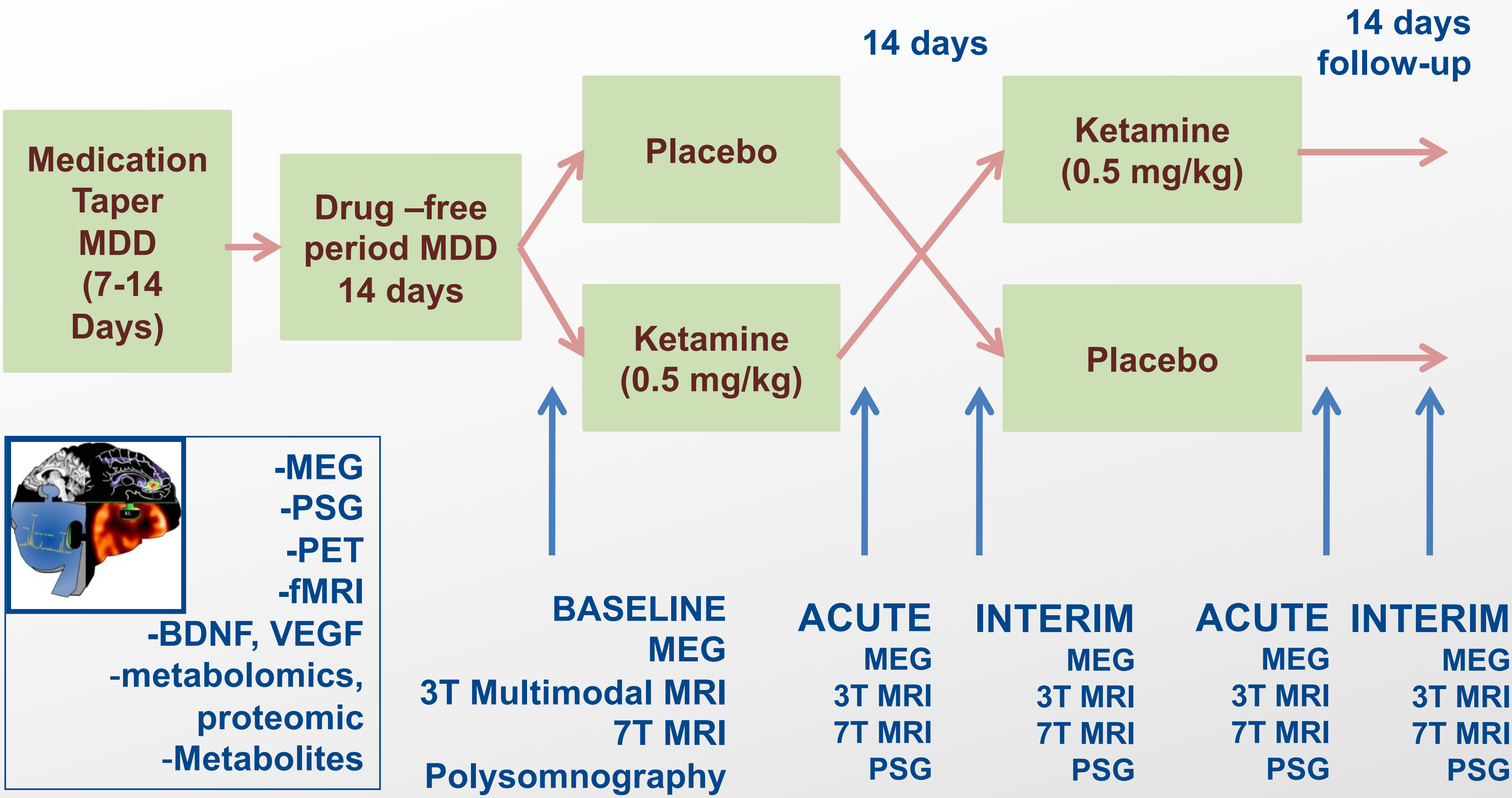
Ketamine: Active Metabolite

- Alternative NMDA antagonist MK-801 does not elicit an antidepressant response
- Metabolite (2R,6R)-HNK does elicit an antidepressant response, but is not an NMDA antagonist
- Both ketamine and (2R,6R)-HNK enhance AMPA throughput.



Zanos, et al., Nature, 2016

Ketamine MOA study



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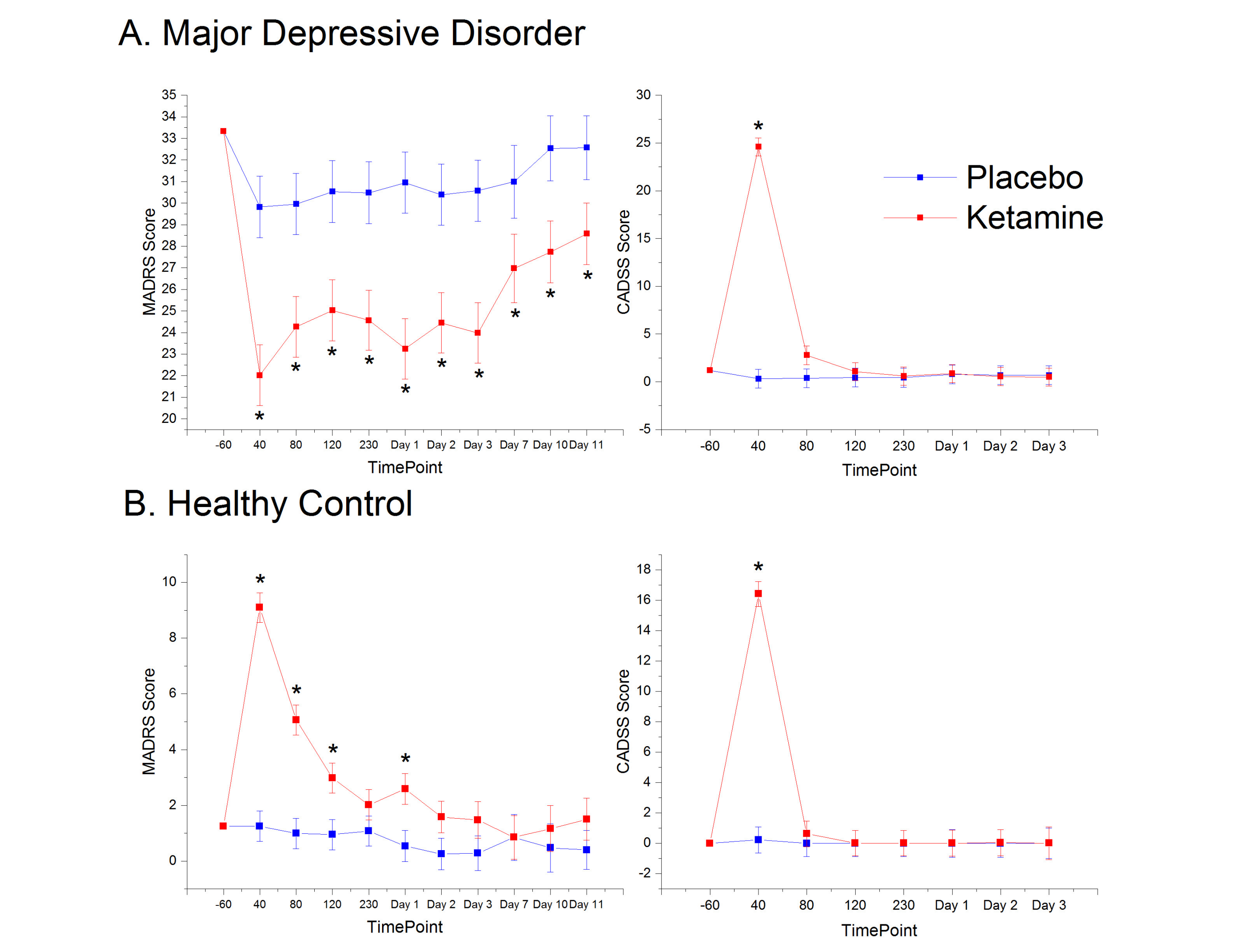
Ketamine MOA Study: Clinical Findings



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Outline

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How can we use imaging?

- Find brain "biomarkers" that can subdivide patients into distinct phenotypes
- Find brain "biomarkers" that can reliably predict who will respond to a given intervention
- Markers may change in response to treatment, and display a dose-response relationship

Potential Markers

- Structure
- Cognitive Function and Functional Imaging
- Intrinsic Connectivity
- Neurophysiology

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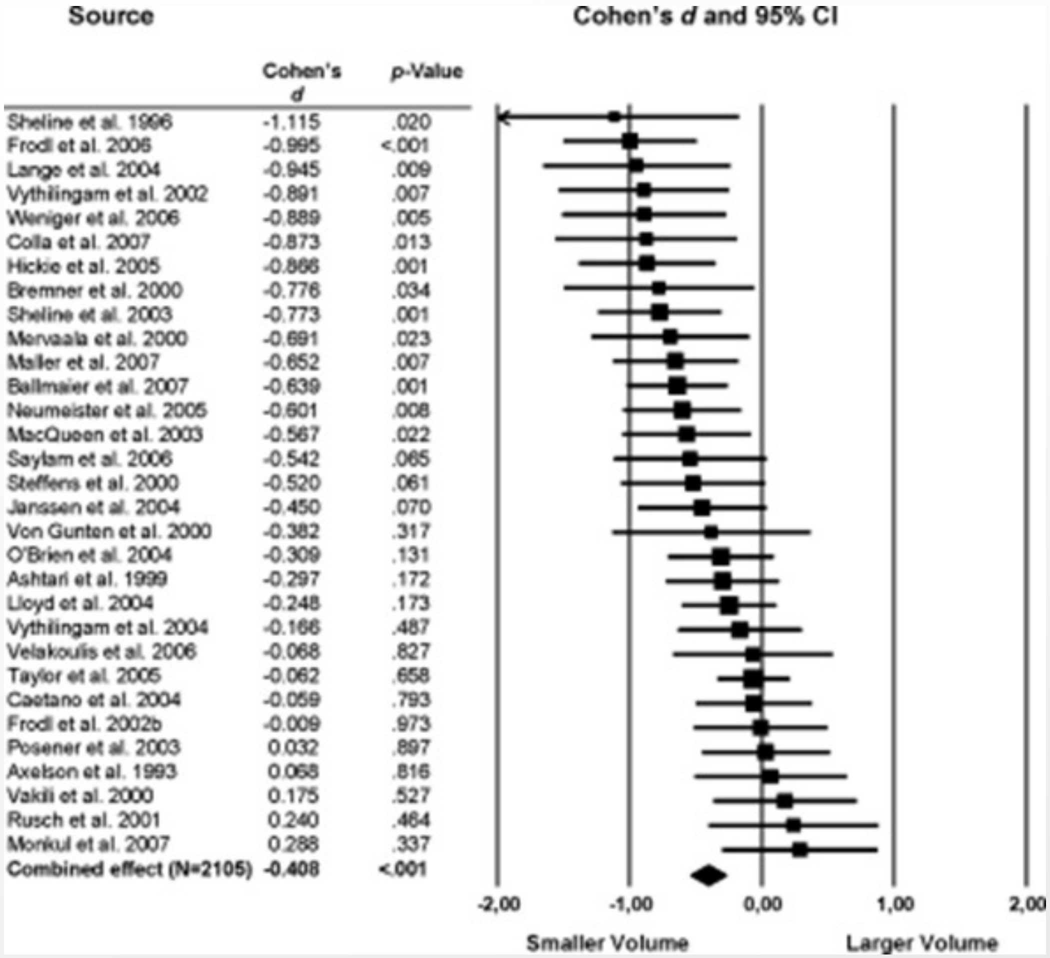
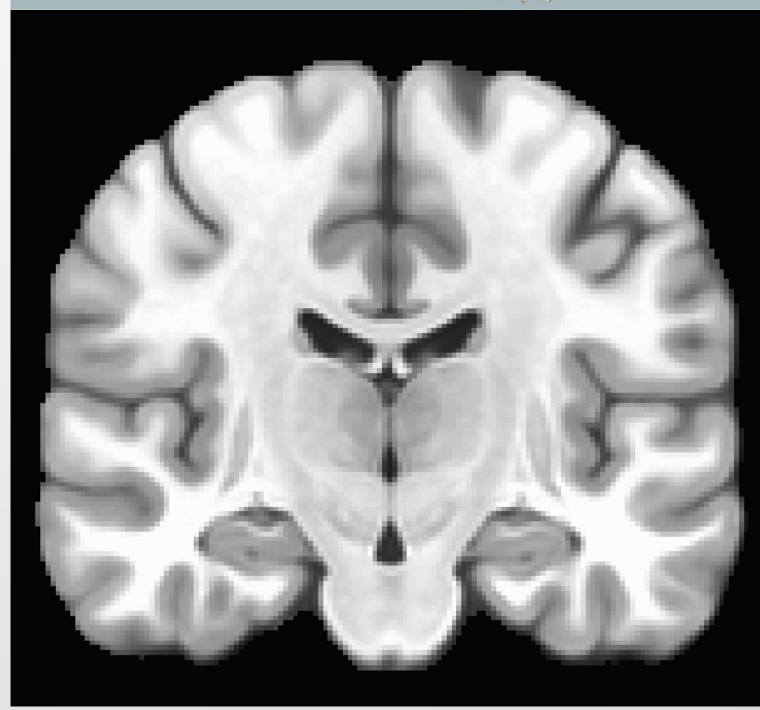
MDD and Brain Structure

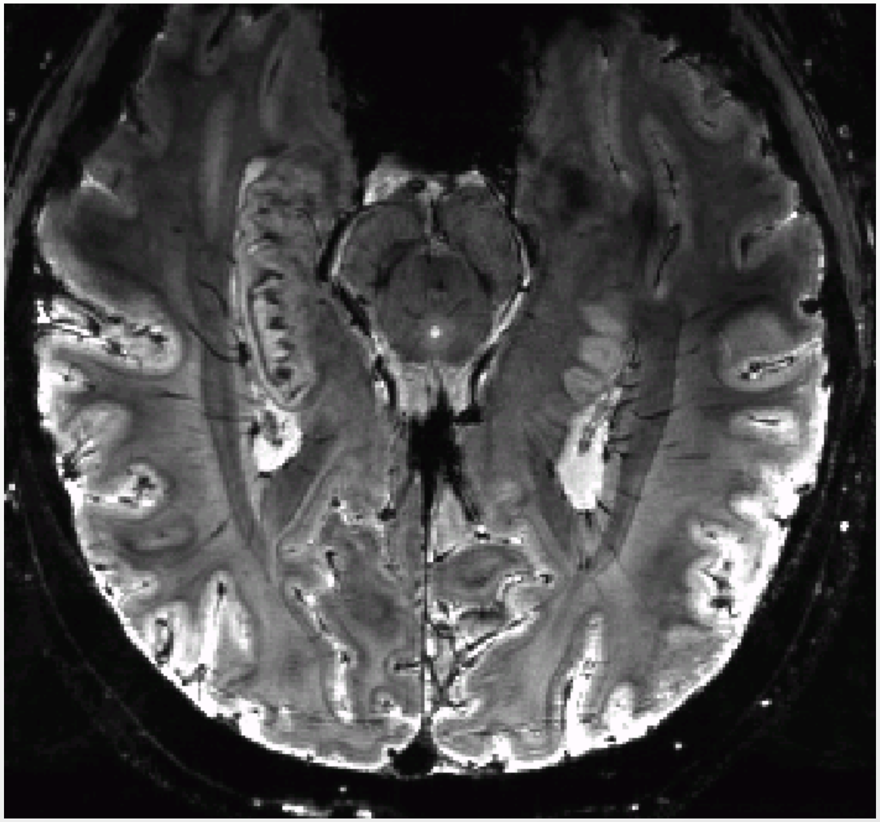


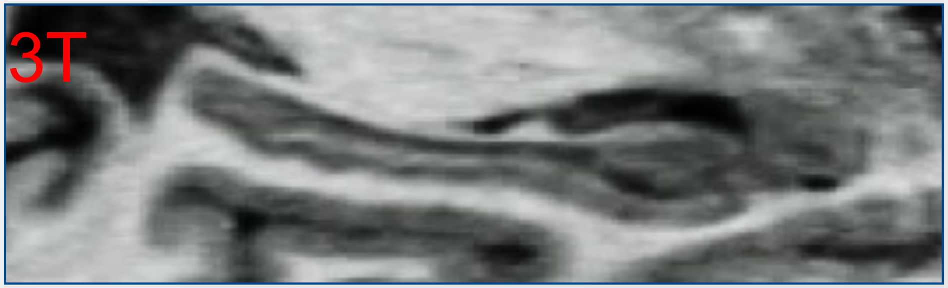
Koolschijn, et al.Human Brain Mapping (2009)

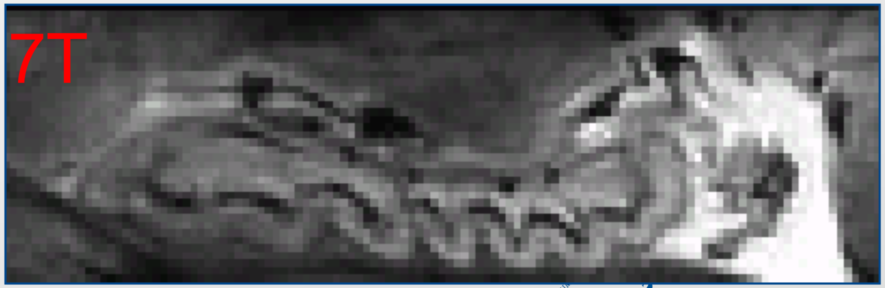


MDD and Brain Structure

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

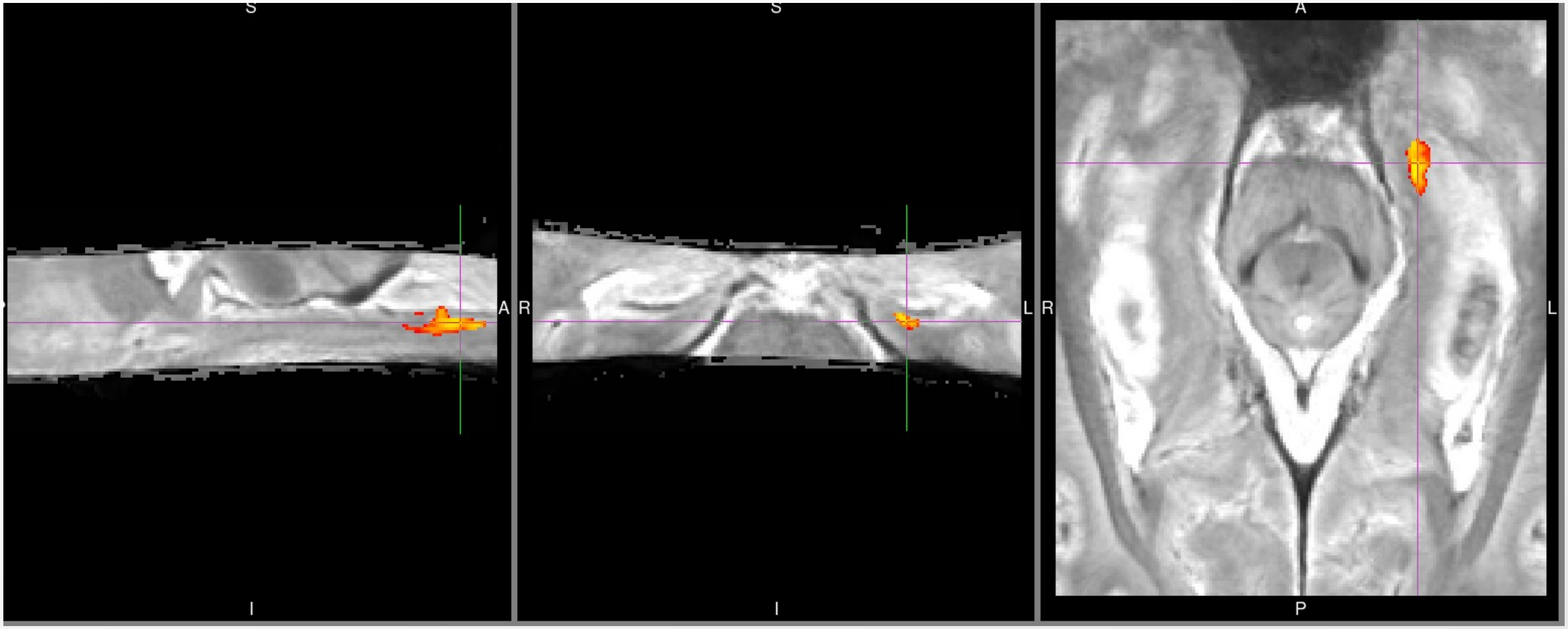






Thomas, Goodwin et al.

MDD and Brain Structure



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

Thomas, Goodwin, et al.

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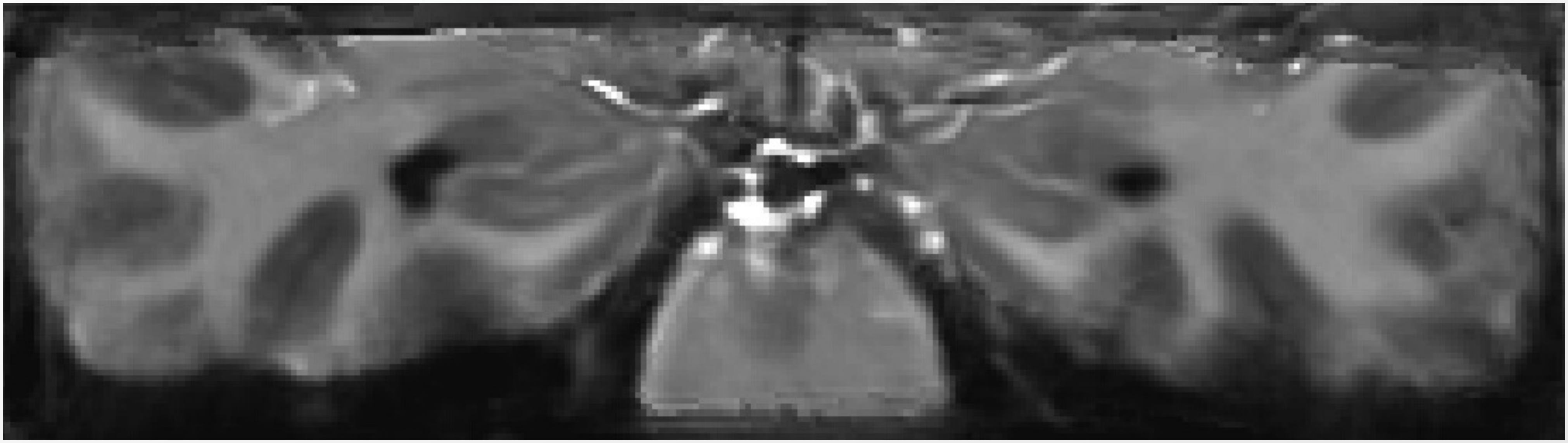
MDD and Brain Structure – Amygdala?



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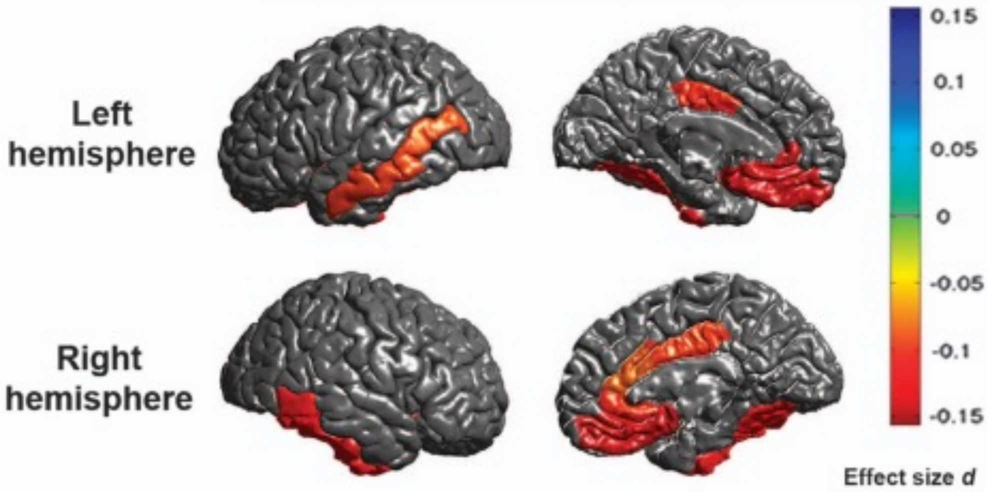
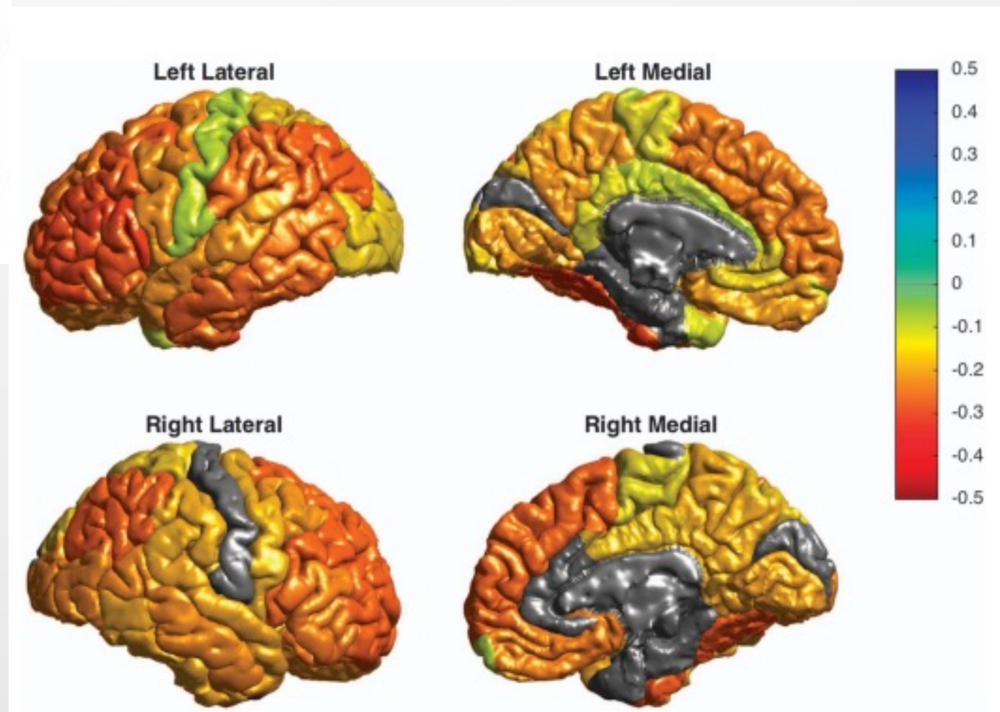
Mood Disorders and Brain Structure: Cortex

ENIGMA MDD Workgroup
N=2148 MDD, N=7957 HC



Schmaal, et al., 2016

ENIGMA BD Workgroup
N=2447 BD, N=4056 HC



Hibar, et al., 2017

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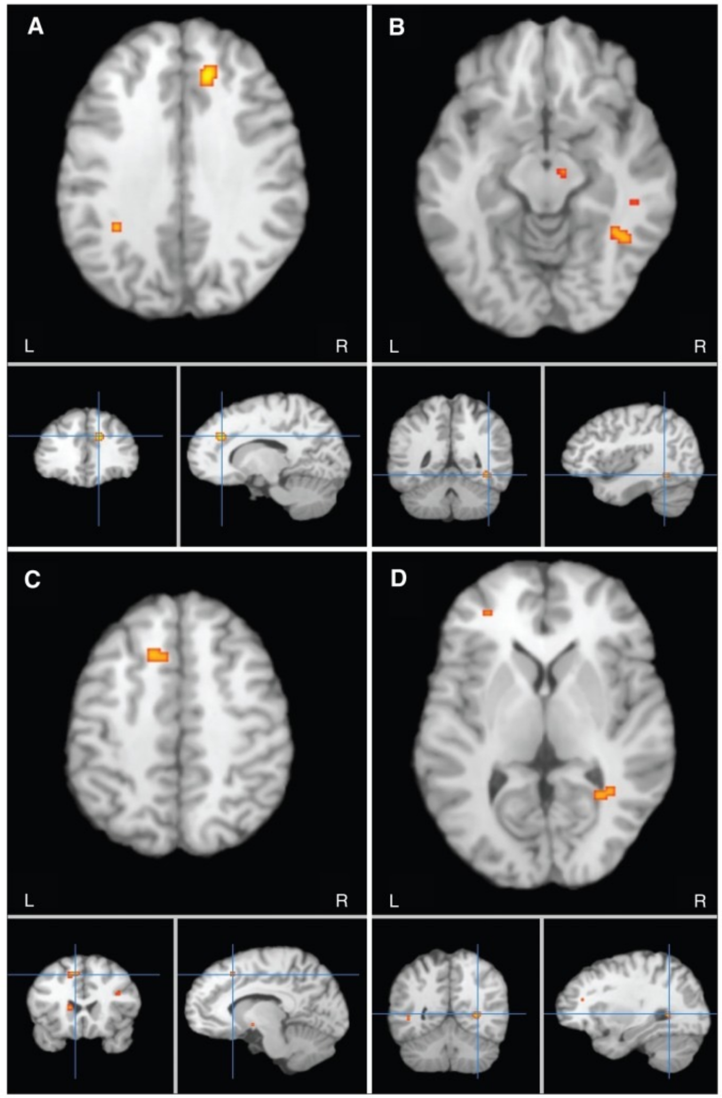
MDD and Brain Structure: DTI



Liao, et al. (2013)

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

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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

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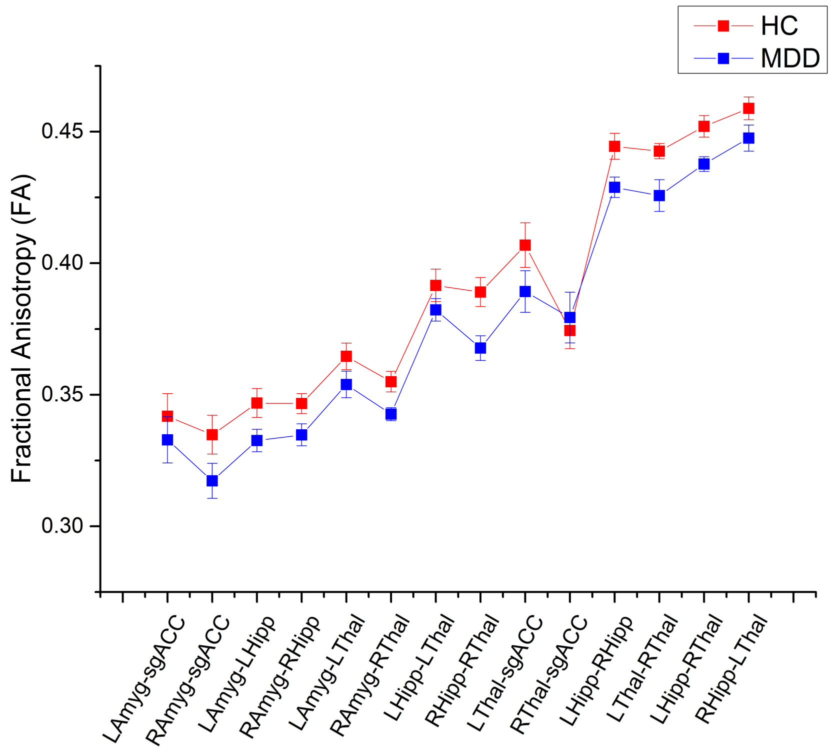
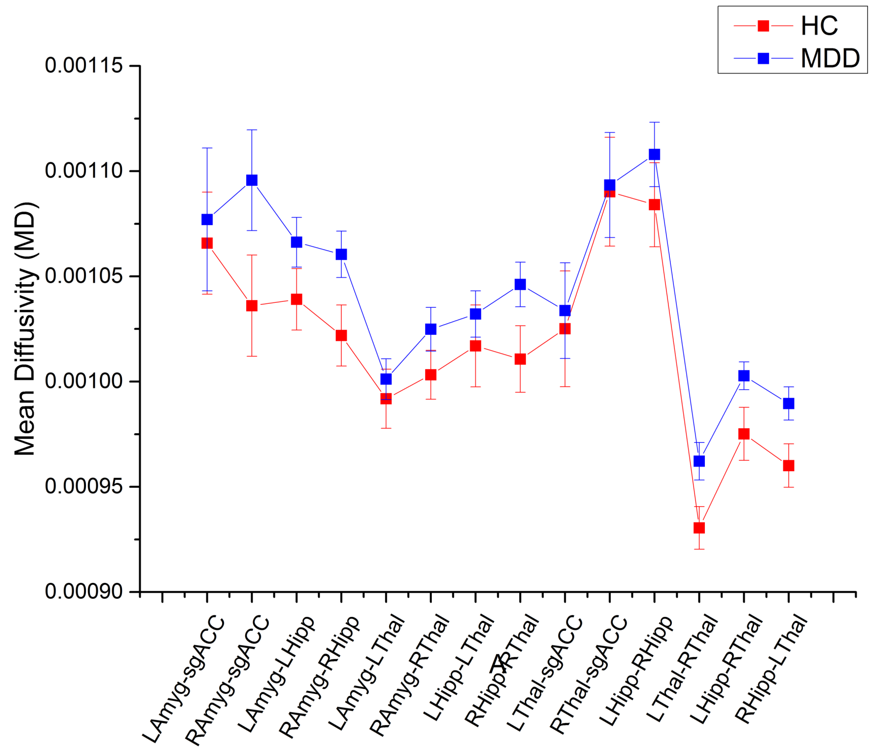
MDD: Focused Analysis

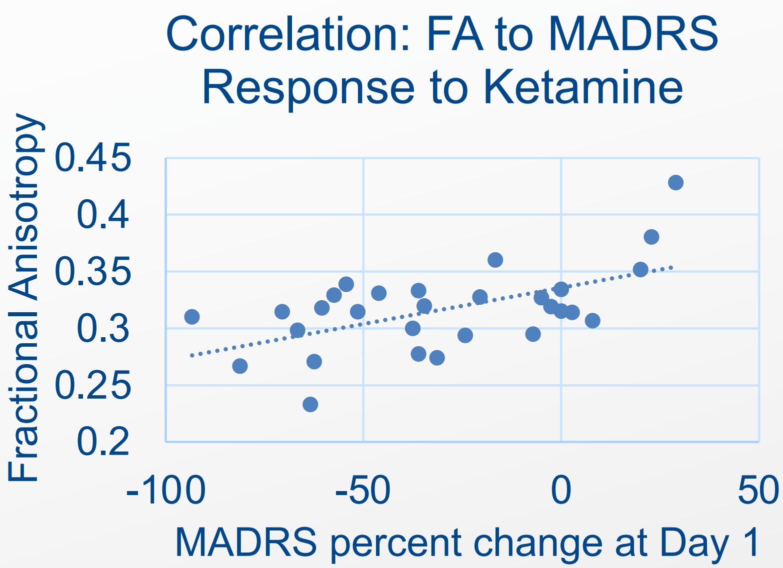
- Concentration on sgACC and Amygdala tracts, with additional hippocampus and thalamus regions of interest
- Baseline imaging in 31 MDD and 26 HC subjects before ketamine treatment



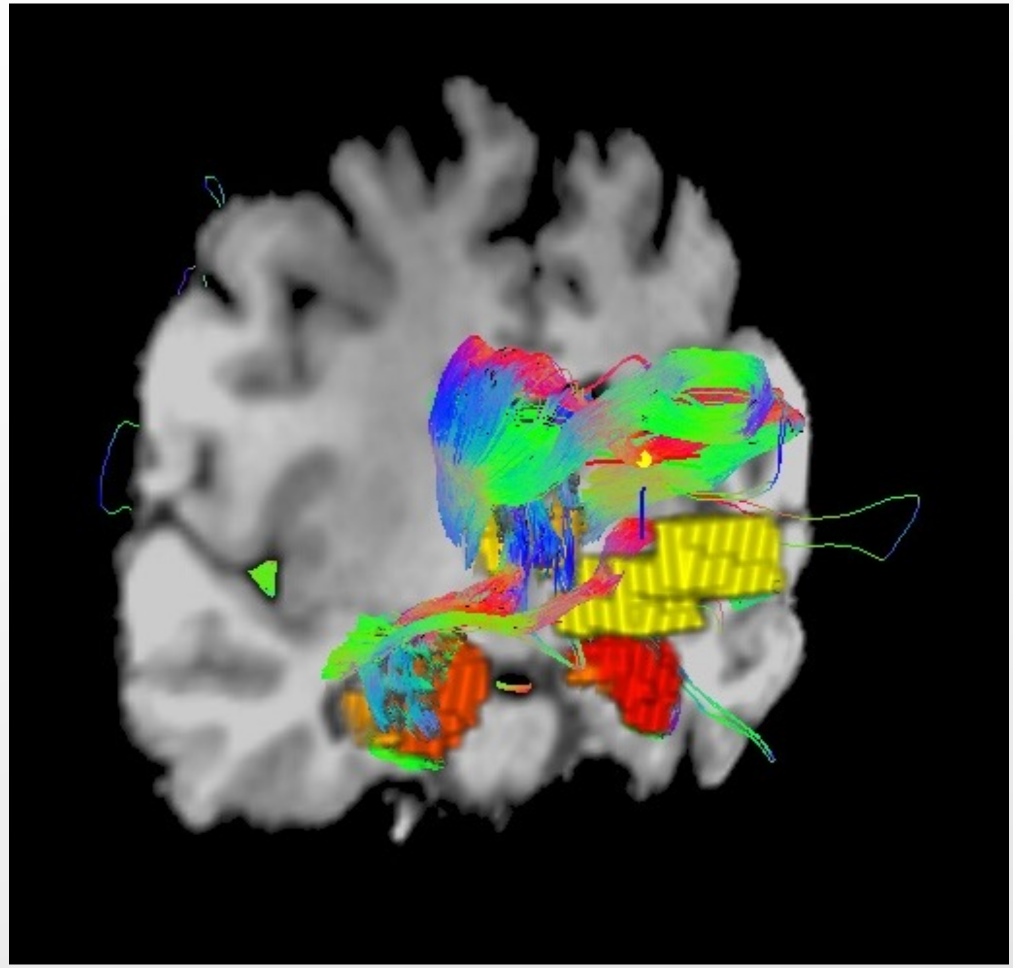


Nugent, et al., in preparation

DTI: MDD vs. HC, and response to ketamine



R=0.569, p=0.001



Nugent, et al., in preparation

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Recap!

- Structural Imaging
  - Volumetric alterations in limbic and ACC areas
  - Alterations in corticolimbic tracts

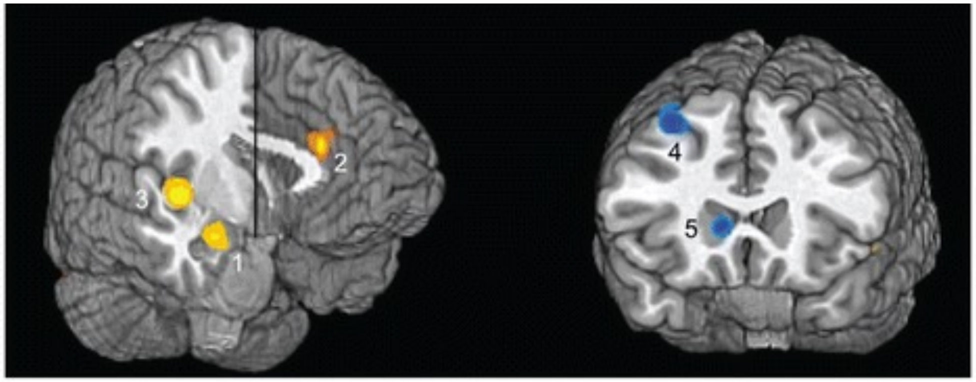
Potential Markers

- Structure
- Cognitive Function and Functional Imaging
- Intrinsic Connectivity
- Neurophysiology

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 (mm³)	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 dorsal cingulate and amygdala in response to negative stimulus vs. positive or neutral stimulus
- Hypo-reactivity in DLPFC and caudate

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

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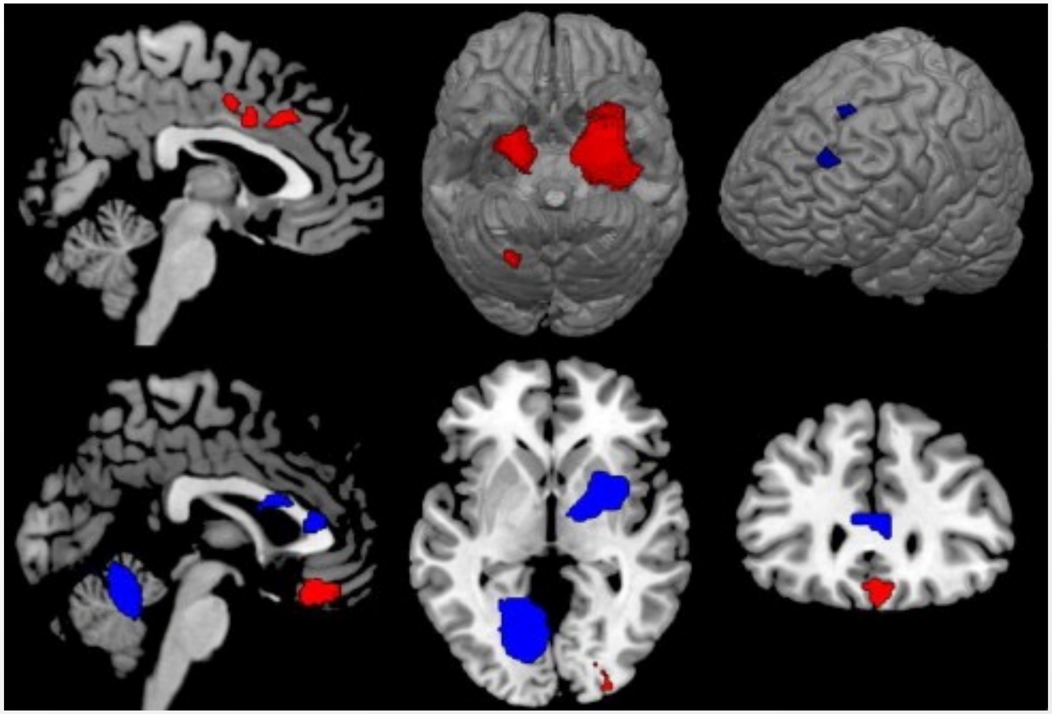
Emotion Processing: Depression

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

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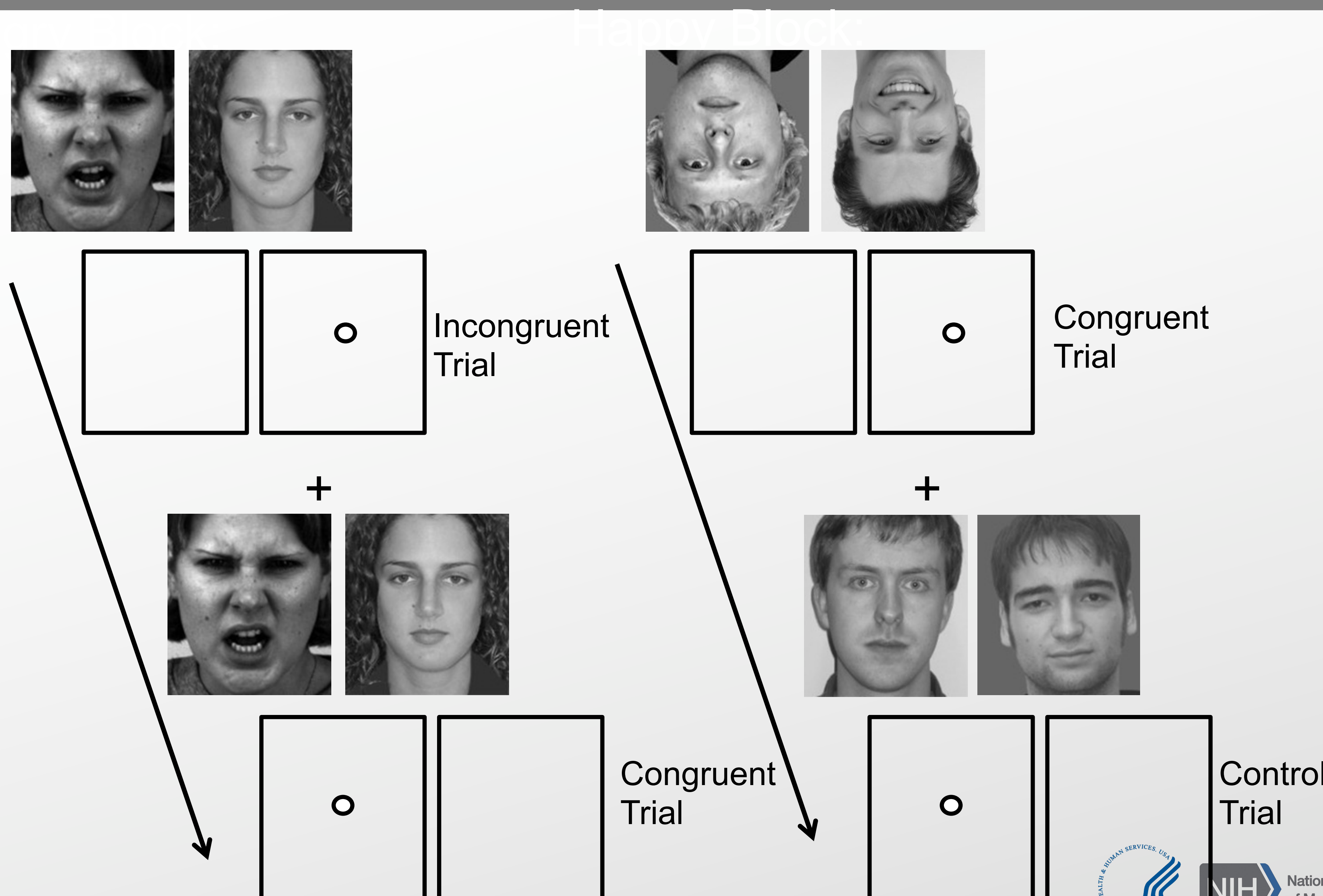
Dot Probe Task



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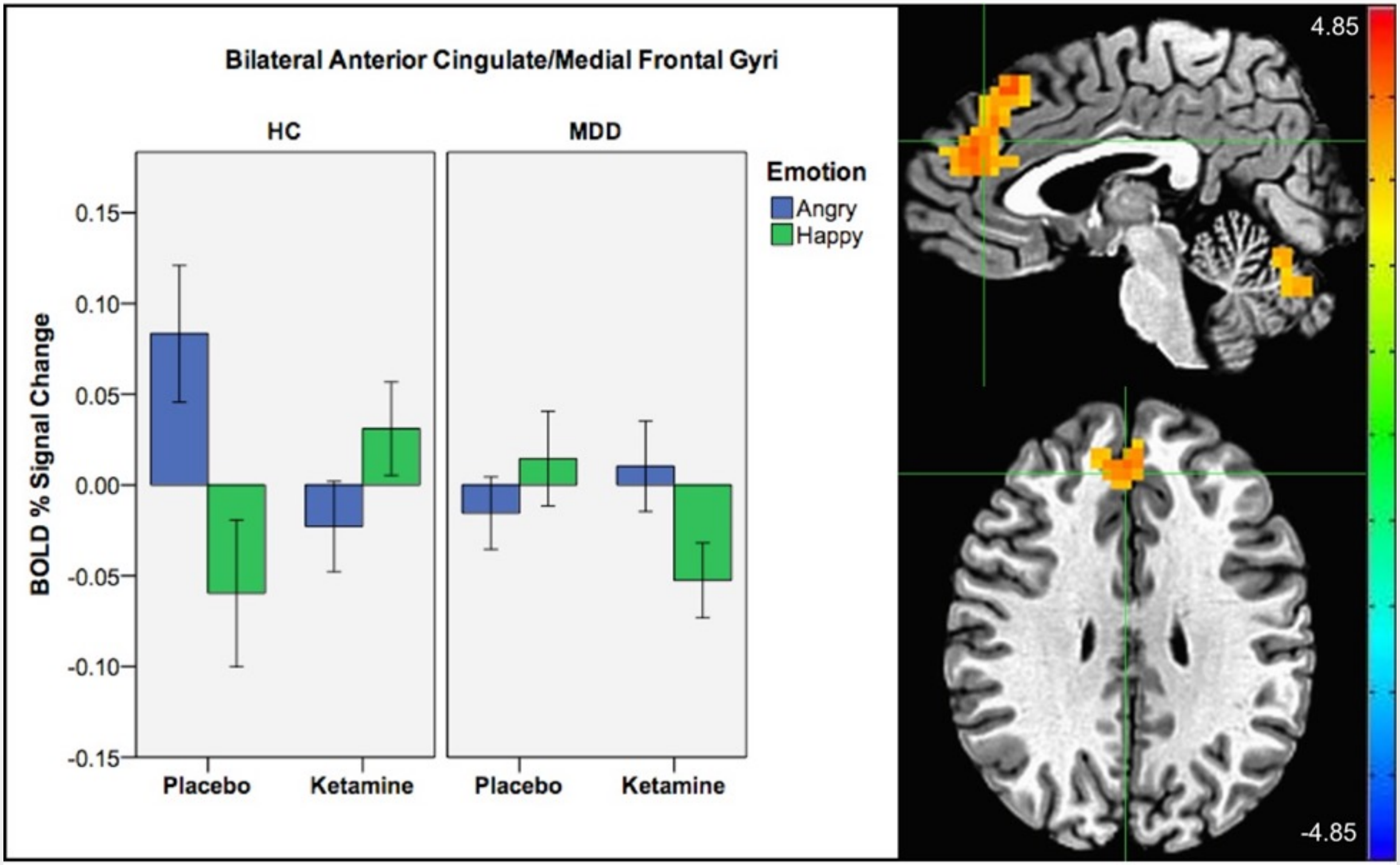
Dot Probe: Group * Emotion * Drug Interaction



 Reed, et al.

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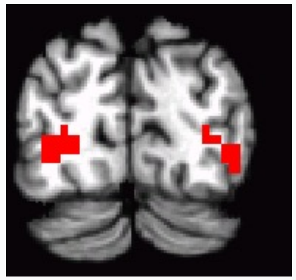
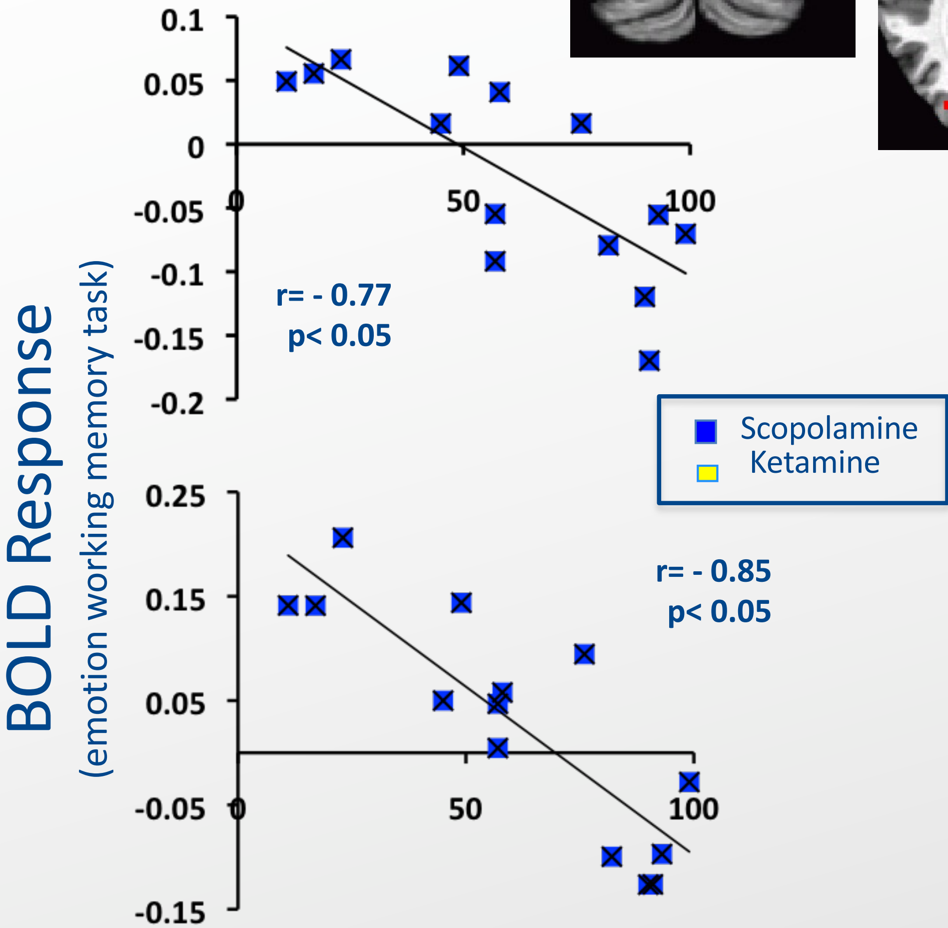
Dot Probe Task:
Baseline Associations with Subsequent Response to Ketamine

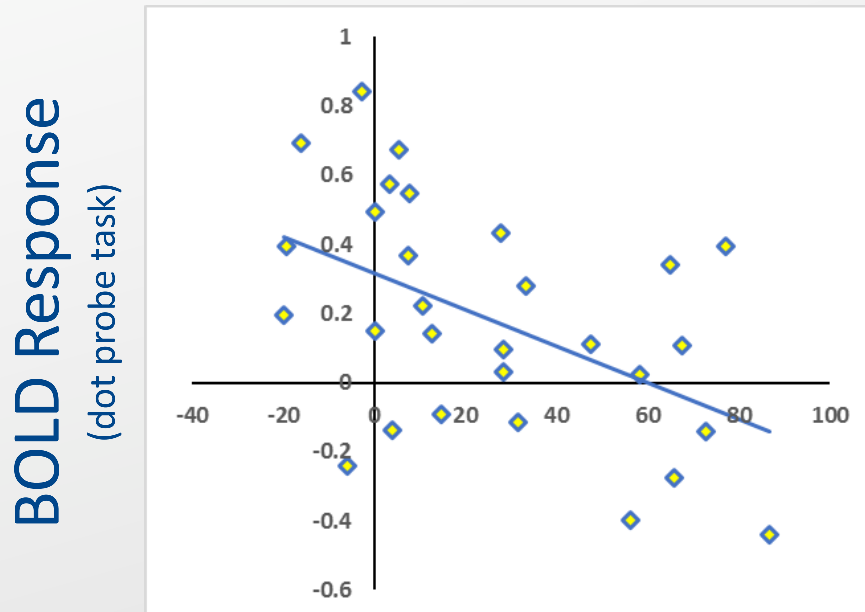


Scopolamine



Ketamine

r= - 0.50
p= 0.005



Furey et al., *JAMA Psychiatry*, 2013.

Szczepanik, Reed, Chung et al.

Activity Rating Task

LL L T R RR

Can't stand____Like a lot

+

+

Szczepanik, et al.

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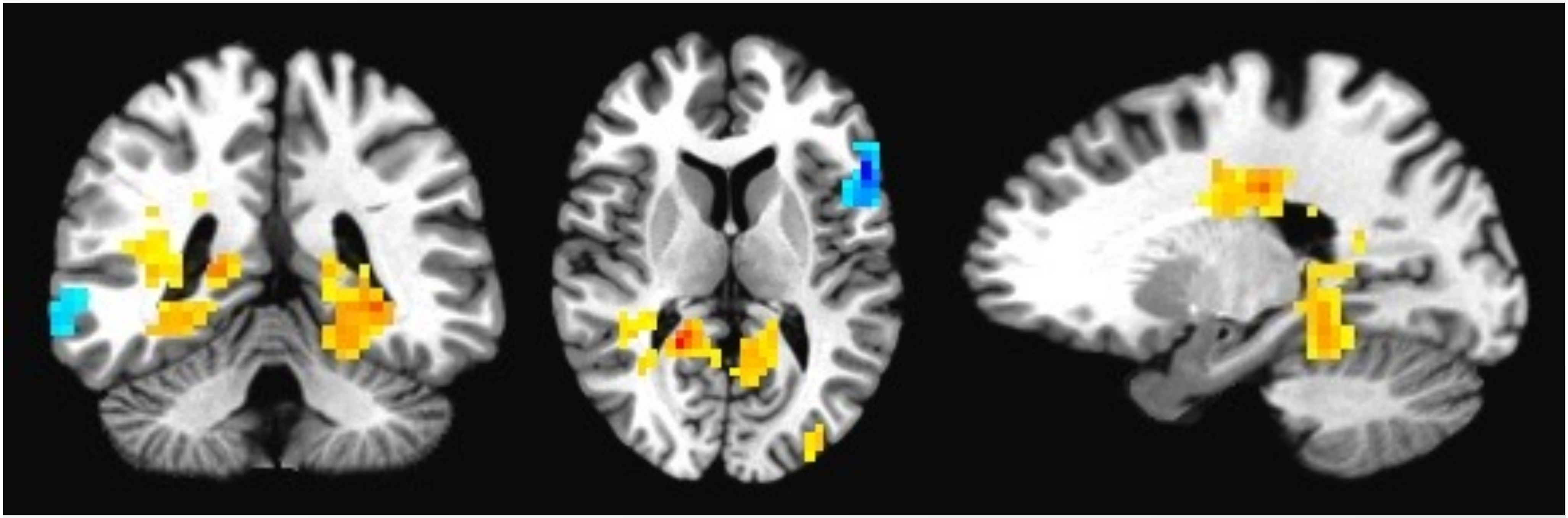
Activity Rating Task

Brain activation varying parametrically from most disliked to most liked



Szczepanik, et al.

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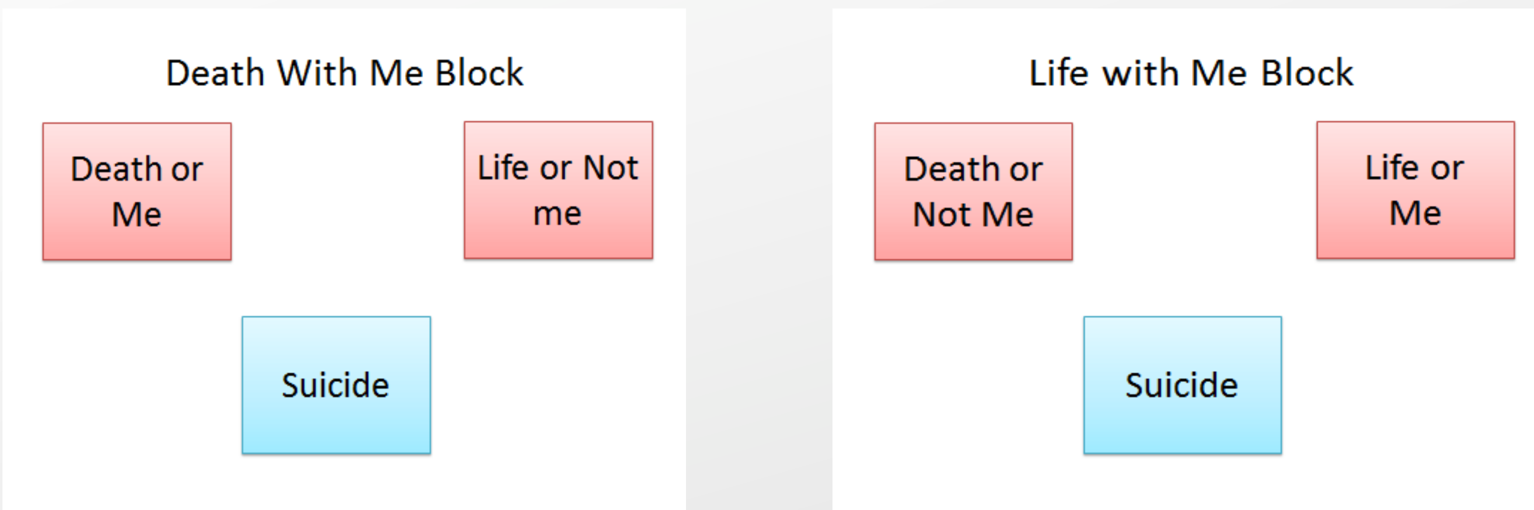
Suicide IAT task

- Predicts repeated suicide attempt at six month follow-up
- Individuals who go onto attempt suicide have a stronger implicit association between themselves and death

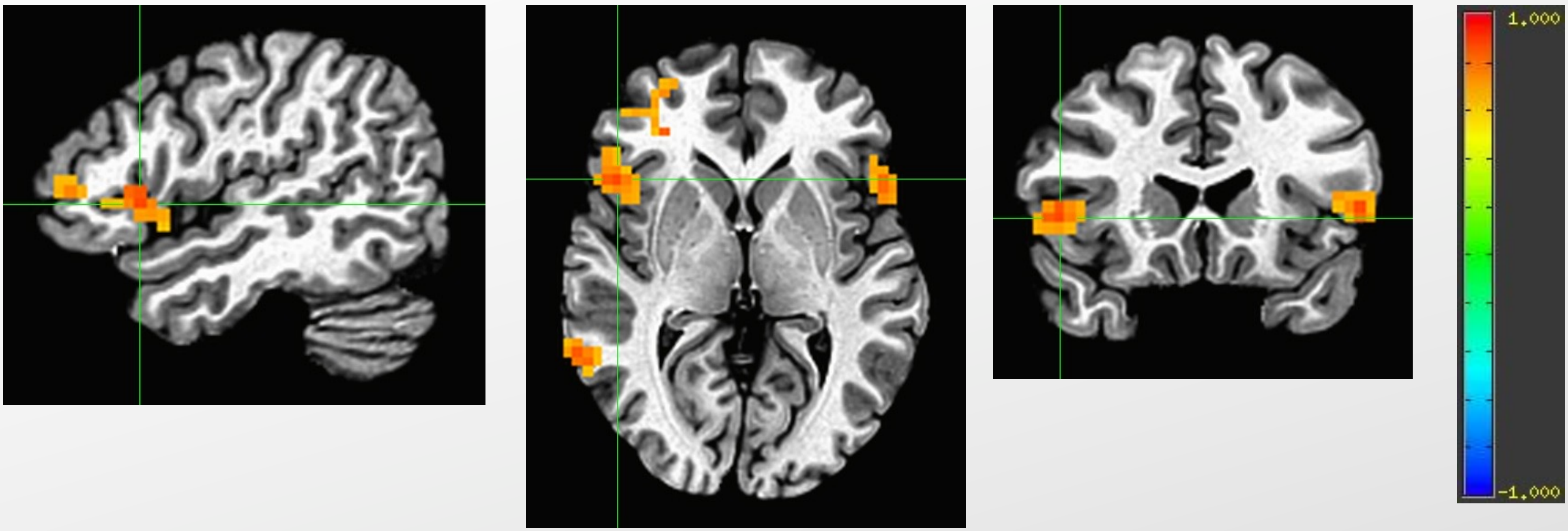


Nock, 2010; Price, 2009

Suicide IAT task

"Death" with "me" block vs. "Life" with Me"

Healthy controls potentially showing greater cognitive load when associating death with themselves.



Cluster-defining threshold $p<0.01$, cluster FWE corrected at $p<0.05$

Reed, Ballard, Szczepanik, et al.

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Recap!

- Structural Imaging
  - Volumetric alterations in limbic and ACC areas
  - Alterations in corticolimbic tracts
- Cognitive Function and Functional Imaging
  - Differential responses to negative and positive emotional stimuli differ in limbic regions and cortical regions in the three core networks
  - Ketamine treatment appears to reverse some neural biases
  - Novel tasks may uniquely assess new symptom domains

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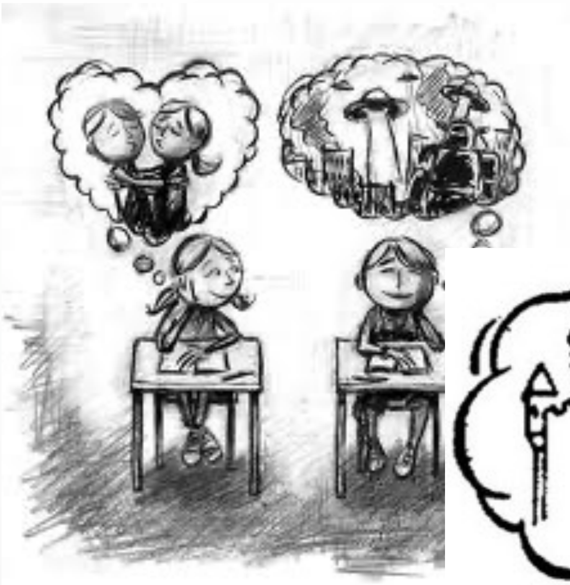
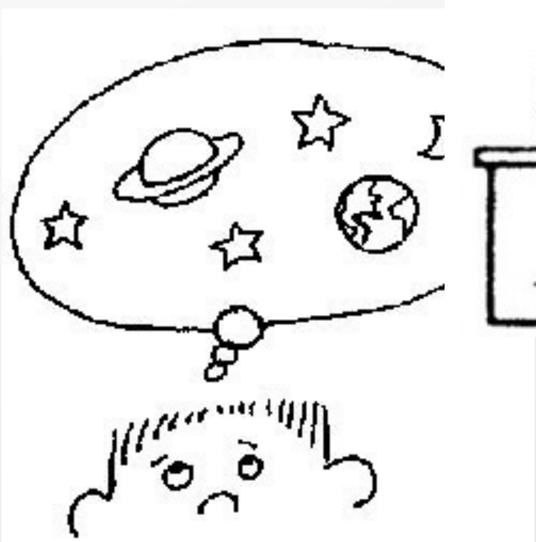
Potential Markers

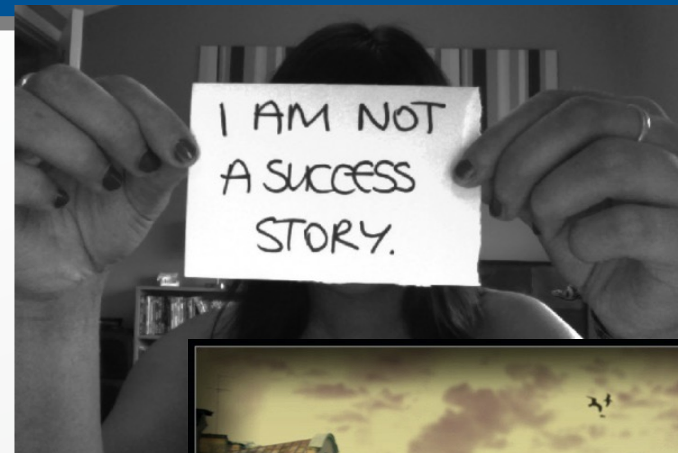
- Structure
- Cognitive Function
- Intrinsic Connectivity
- Neurophysiology

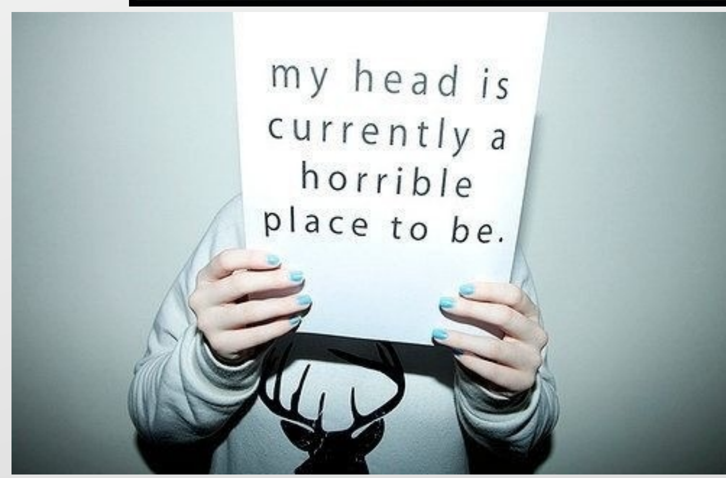
Why Study the Resting State in MDD and BD?



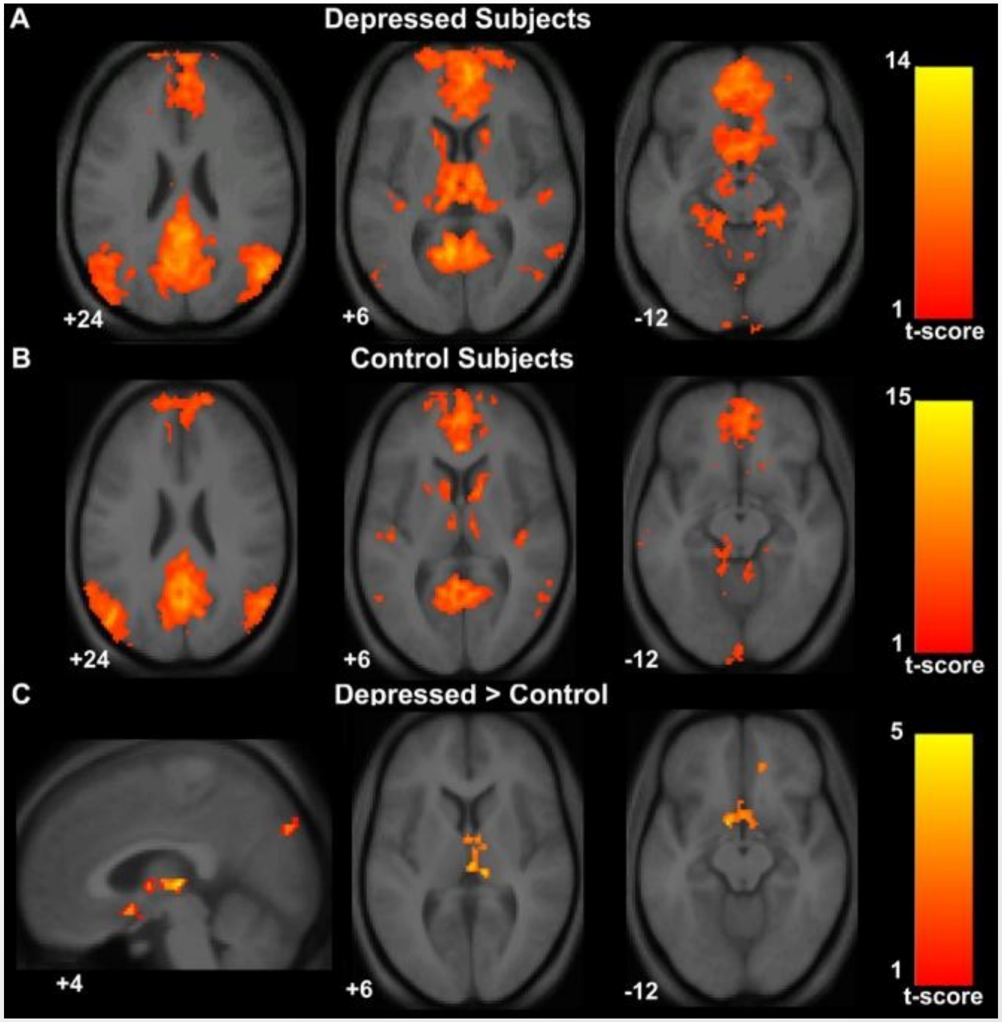


VS.





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

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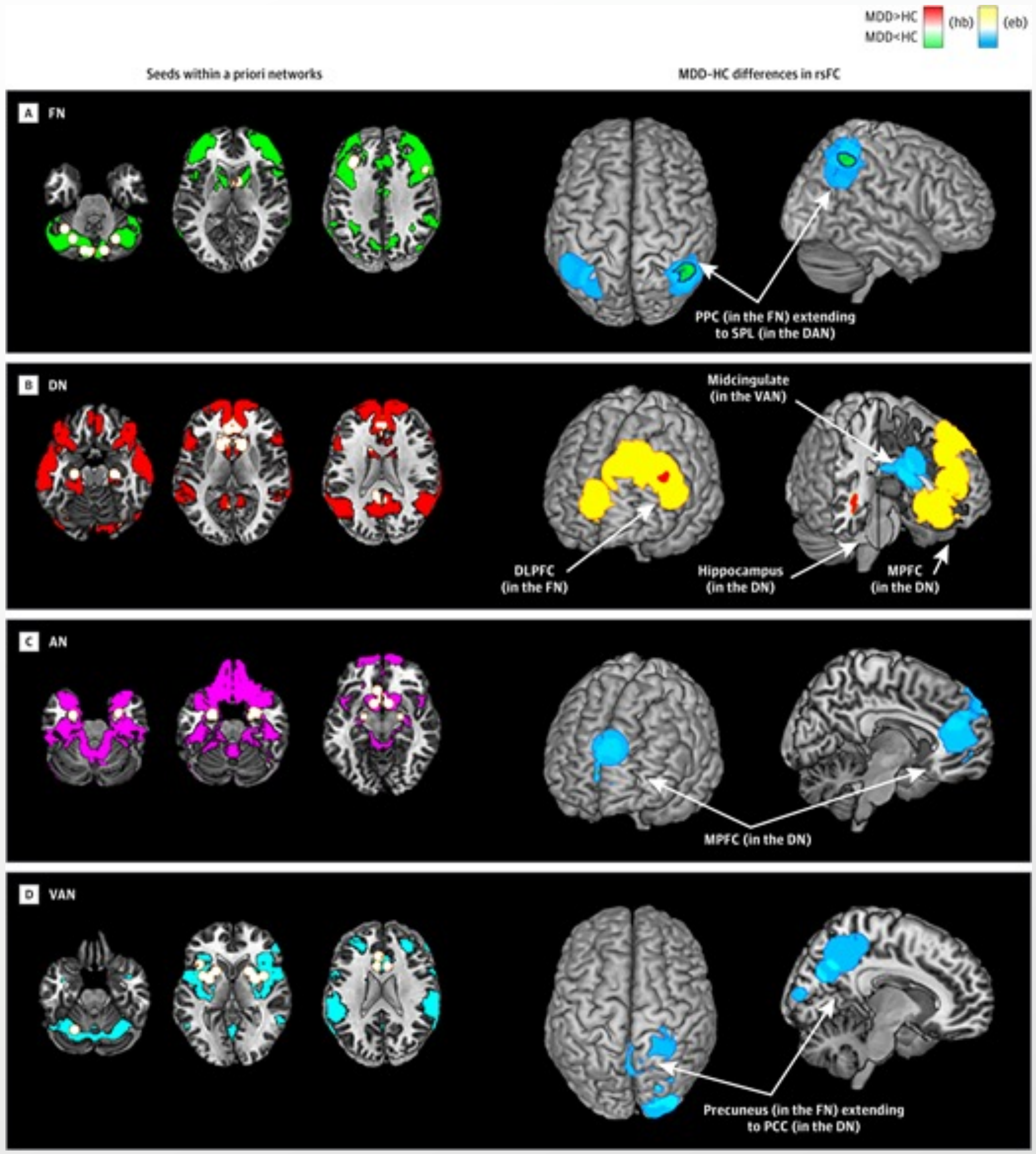
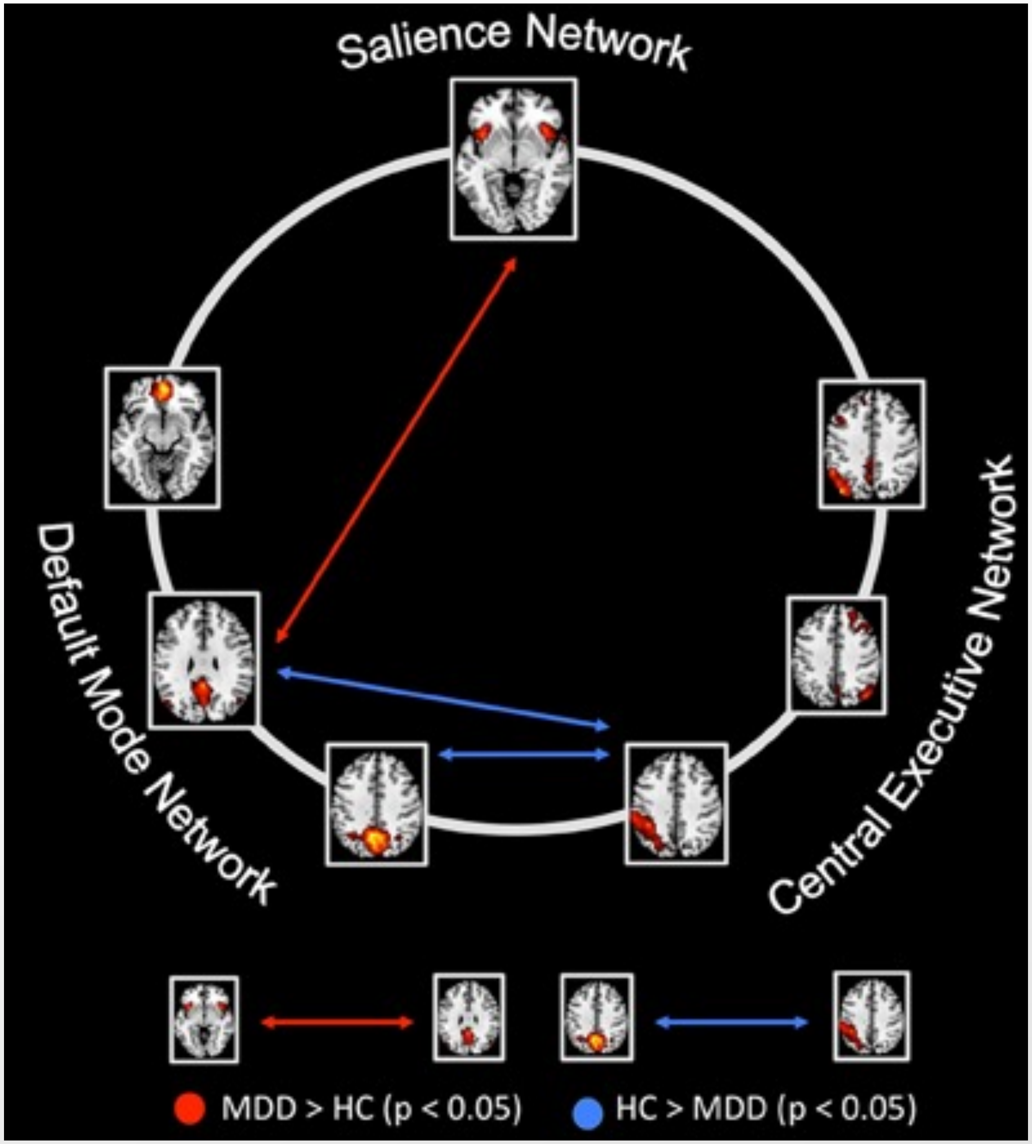
MDD and the Resting State: Meta-analysis, 25 studies

Central Executive		↓ Superior Parietal (SN)
Default Mode		↑ DLPFC (CEN)
Affective		↓ dACC (SN)
Salience		↓ PCC (DMN)

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

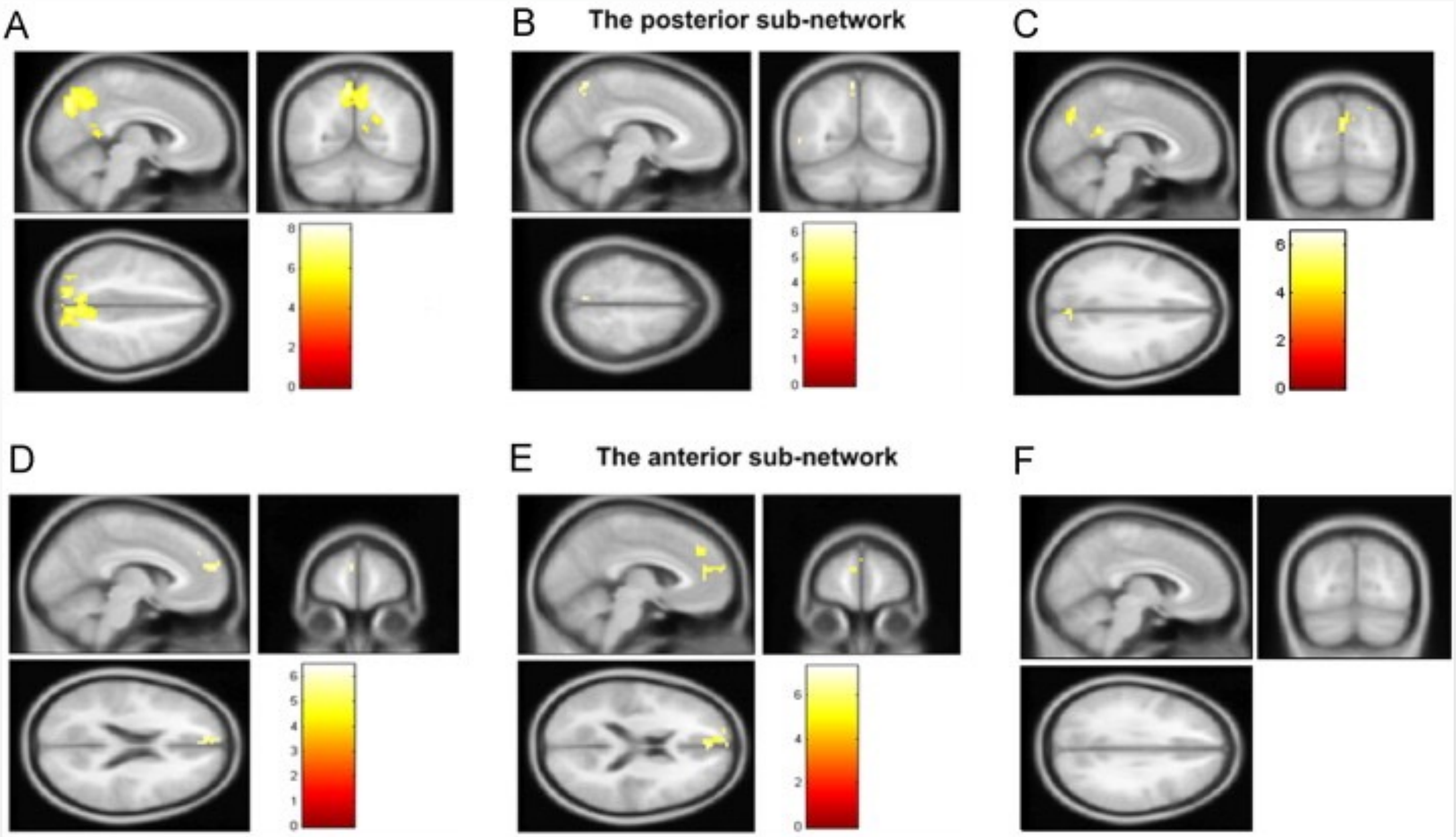
Triple Network Model



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

Resting State: Treatment

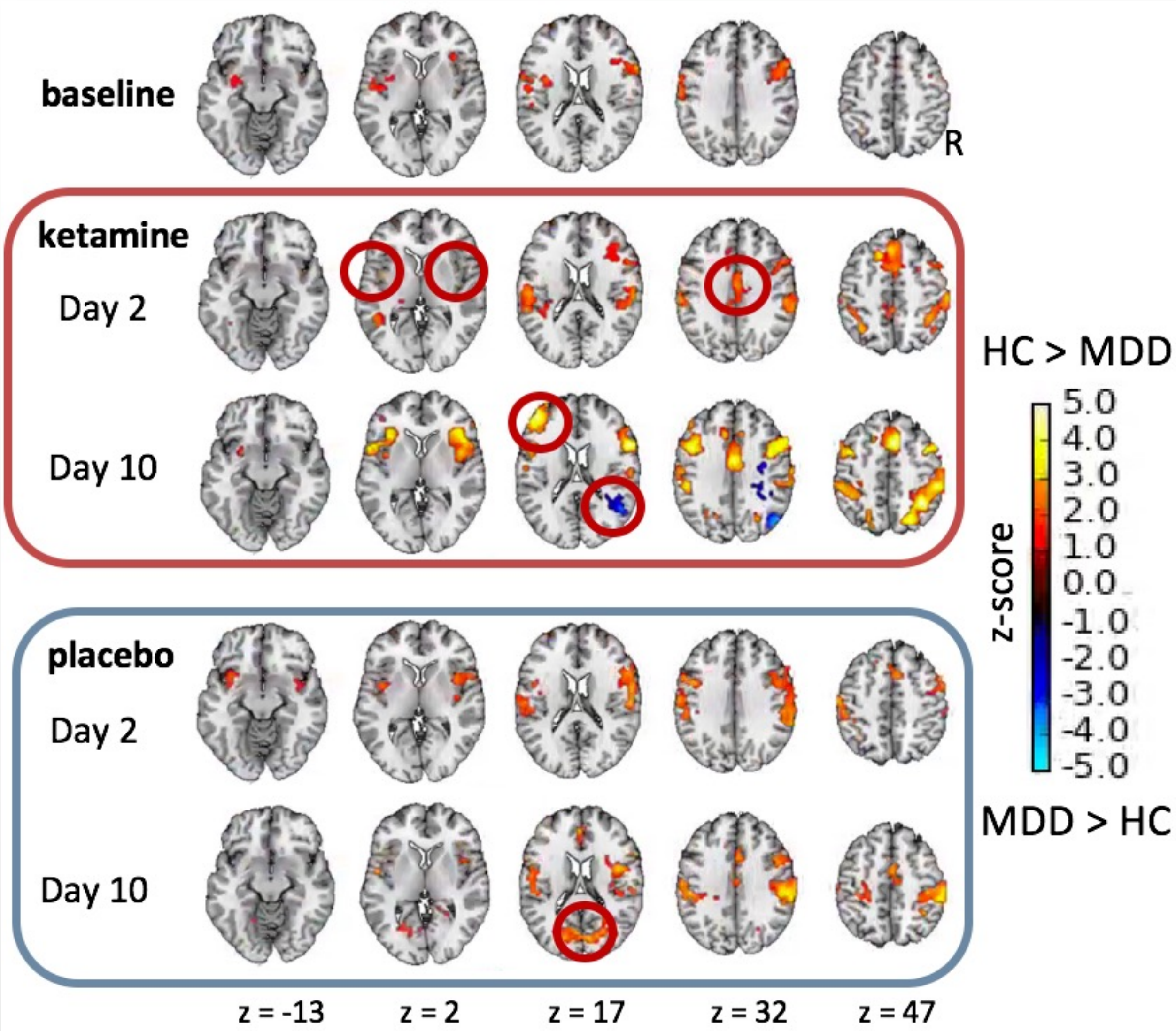
Pre-treatment MDD vs. HC | Post-treatment MDD vs. HC | Pre-treatment MDD vs. Post-treatment MDD



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
Group Differences by Treatment Session



Evans, et al.

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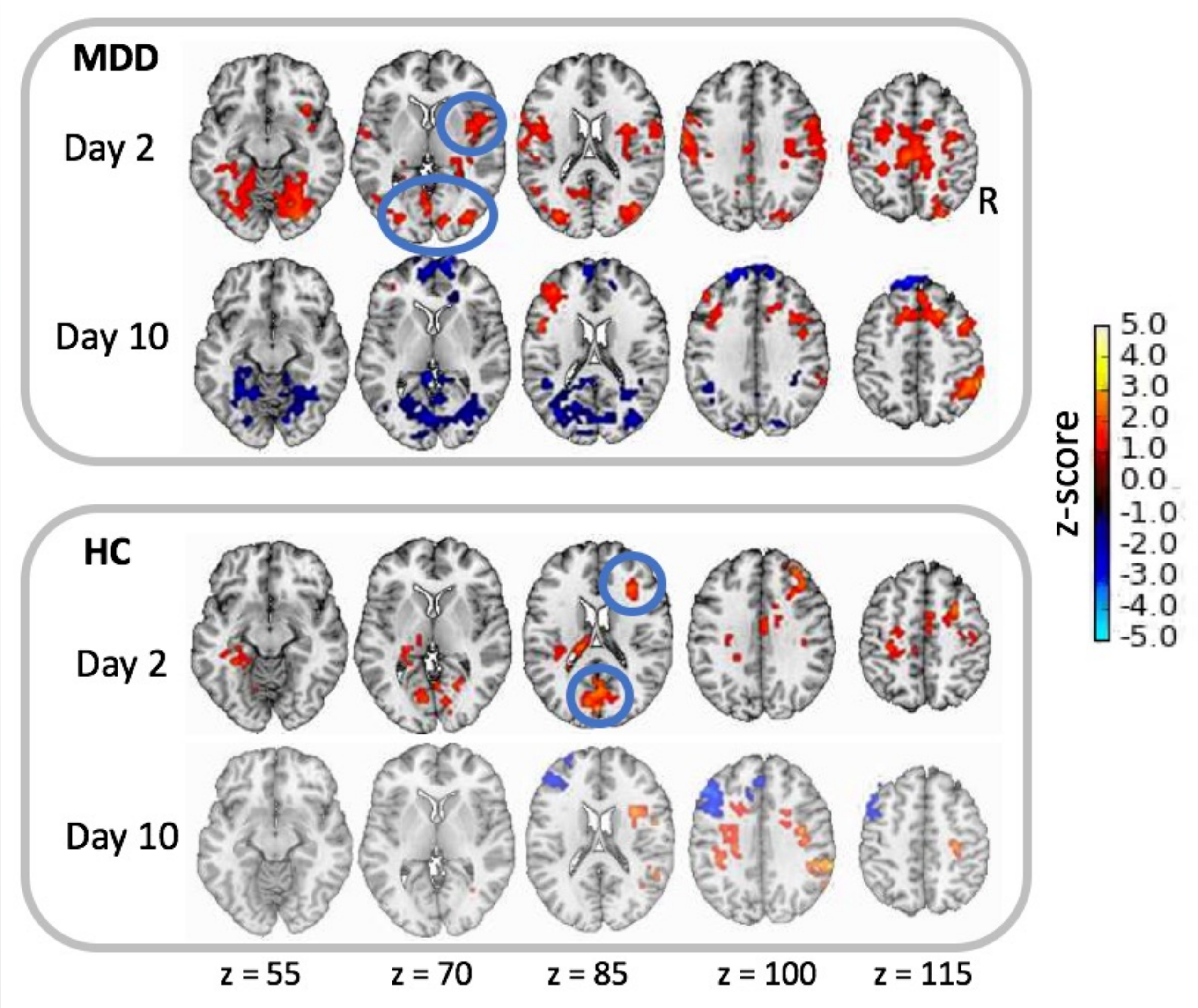
Default Mode Network Connectivity Treatment Effects



Evans, et al.

Recap!

- Structural Imaging
  - Volumetric alterations in limbic and ACC areas
  - Alterations in corticolimbic tracts
- Cognitive Function and Functional Imaging
  - Differential responses to negative and positive emotional stimuli differ in limbic regions and cortical regions in the three core networks
  - Ketamine treatment appears to reverse some neural biases
  - Novel tasks may uniquely assess new symptom domains
- Intrinsic Connectivity
  - Complex alterations in triple network system connectivity

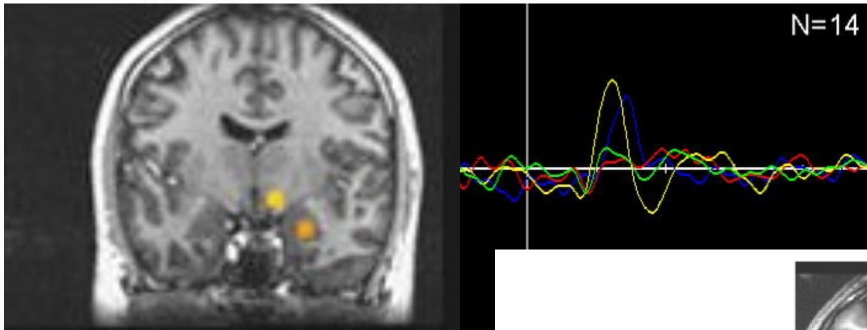
Potential Markers

- Structure
- Cognitive Function
- Intrinsic Connectivity
- Neurophysiology

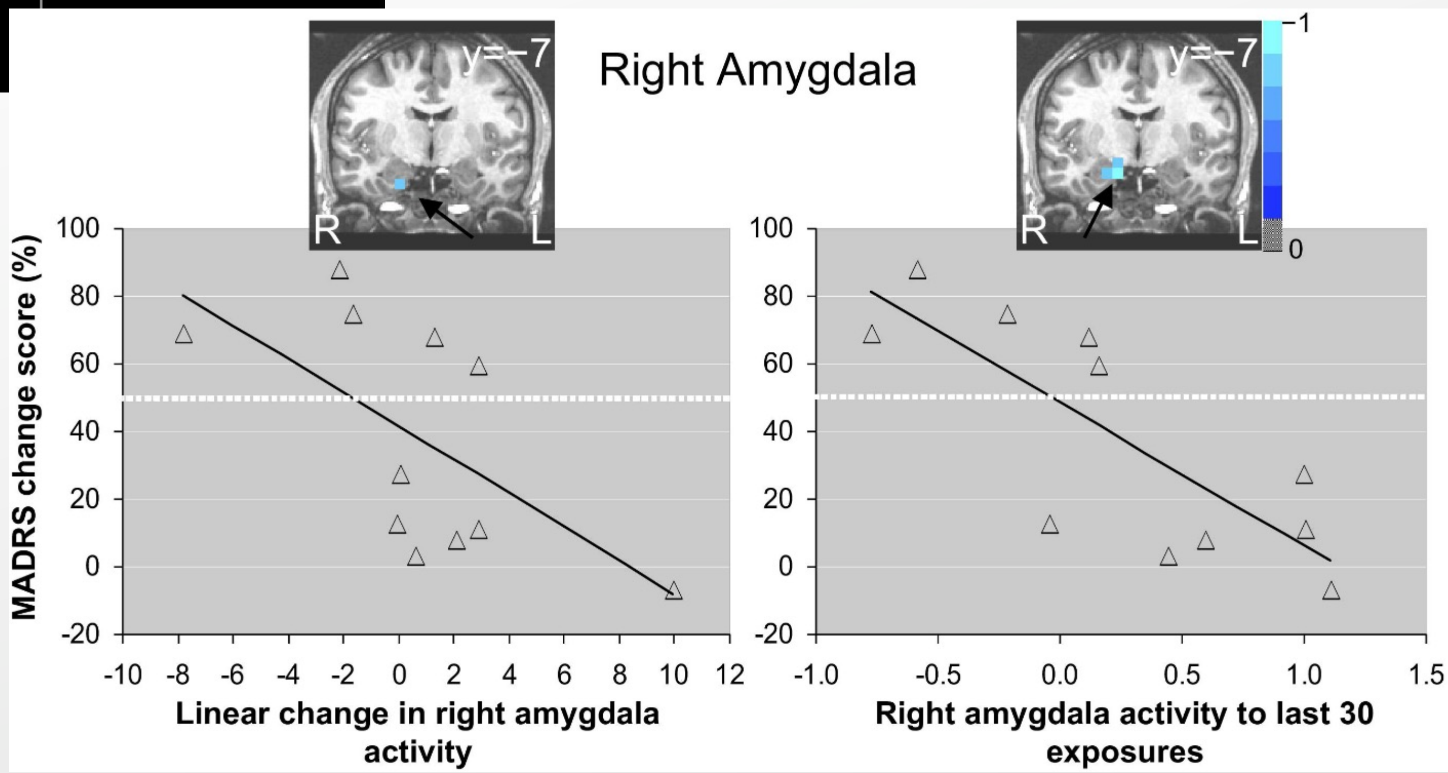
Electrophysiology in Depression

- Electroencephalography
  - Much of the literature is focused on frontal asymmetry, particularly in alpha bands
  - Some work in prediction of response to SSRI antidepressants
- Magnetoencephalography
  - Far fewer studies, not enough data for meta-analyses to show convergent results
  - Source localization allows the observation effects localized to anatomical structures

MEG: Emotional Face Perception

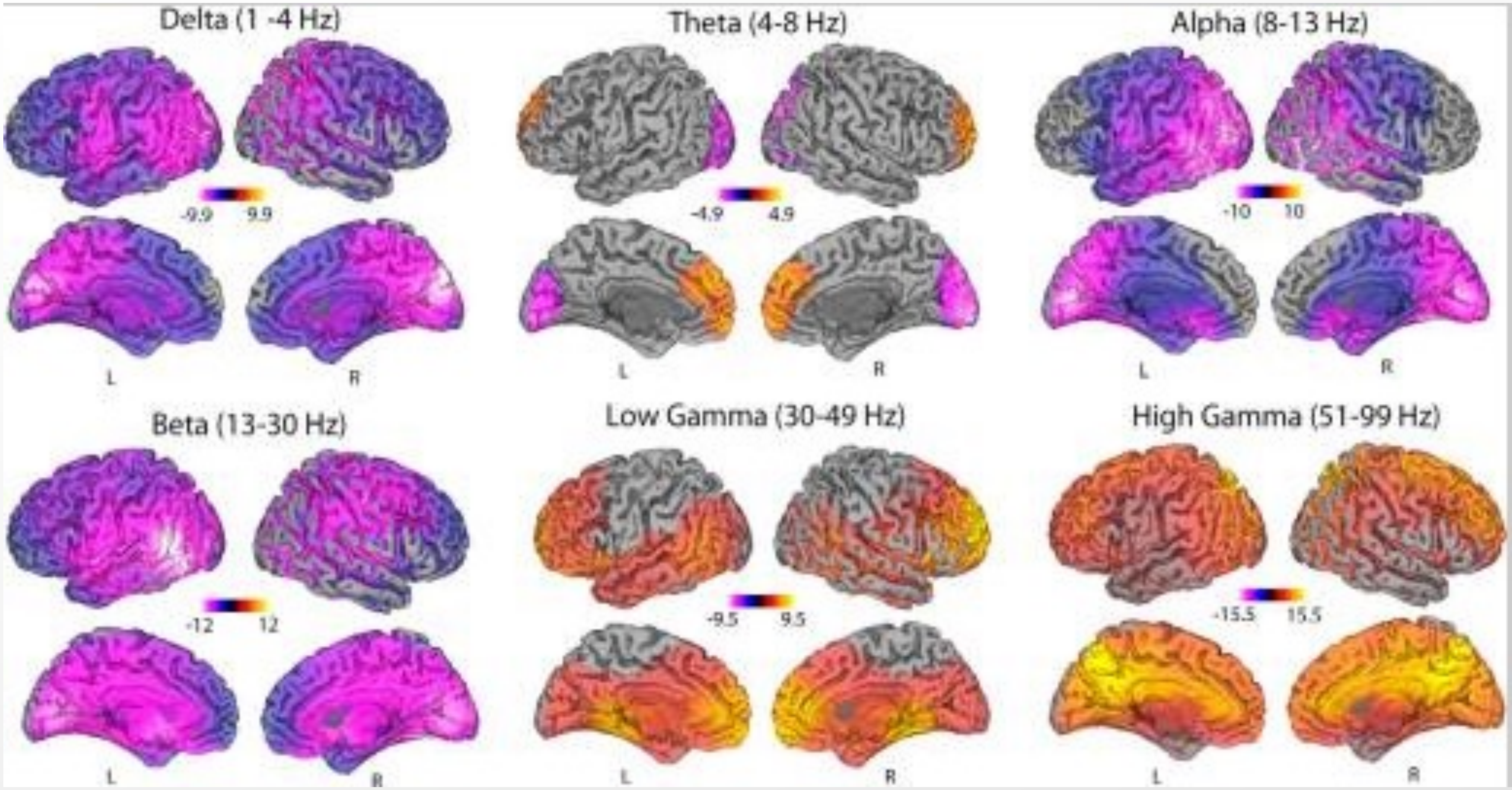


Cornwell, et al 2008.



Salvadore, et al 2009.

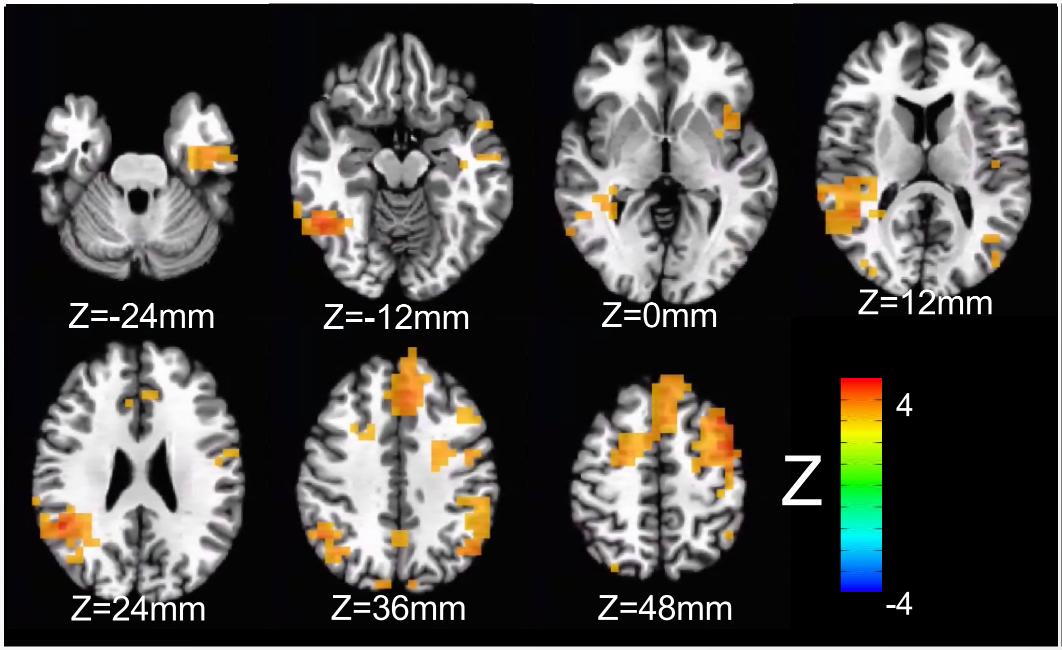
Acute Changes with Ketamine Infusion



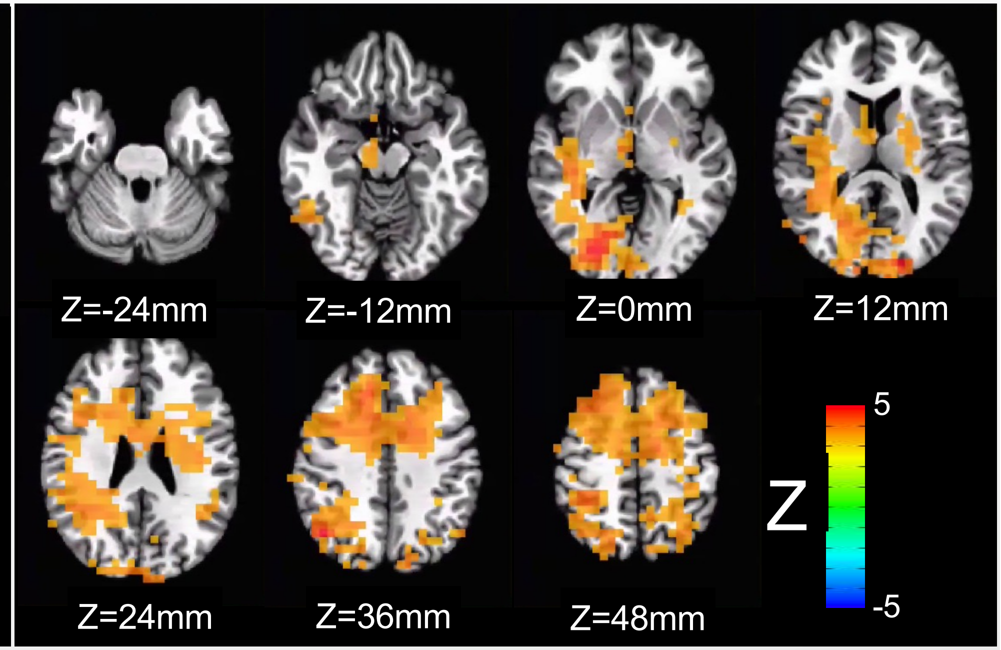
Muthukumaraswamy, 2015

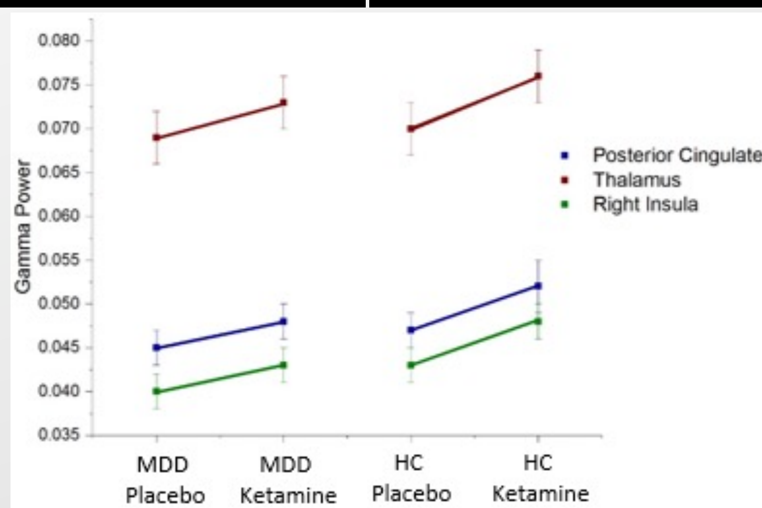
Gamma power changes in response to ketamine

A. MDD: Ketamine > Placebo



B. HC: Ketamine > Placebo





Nugent, et al. Under Review

National Institute of Mental Health

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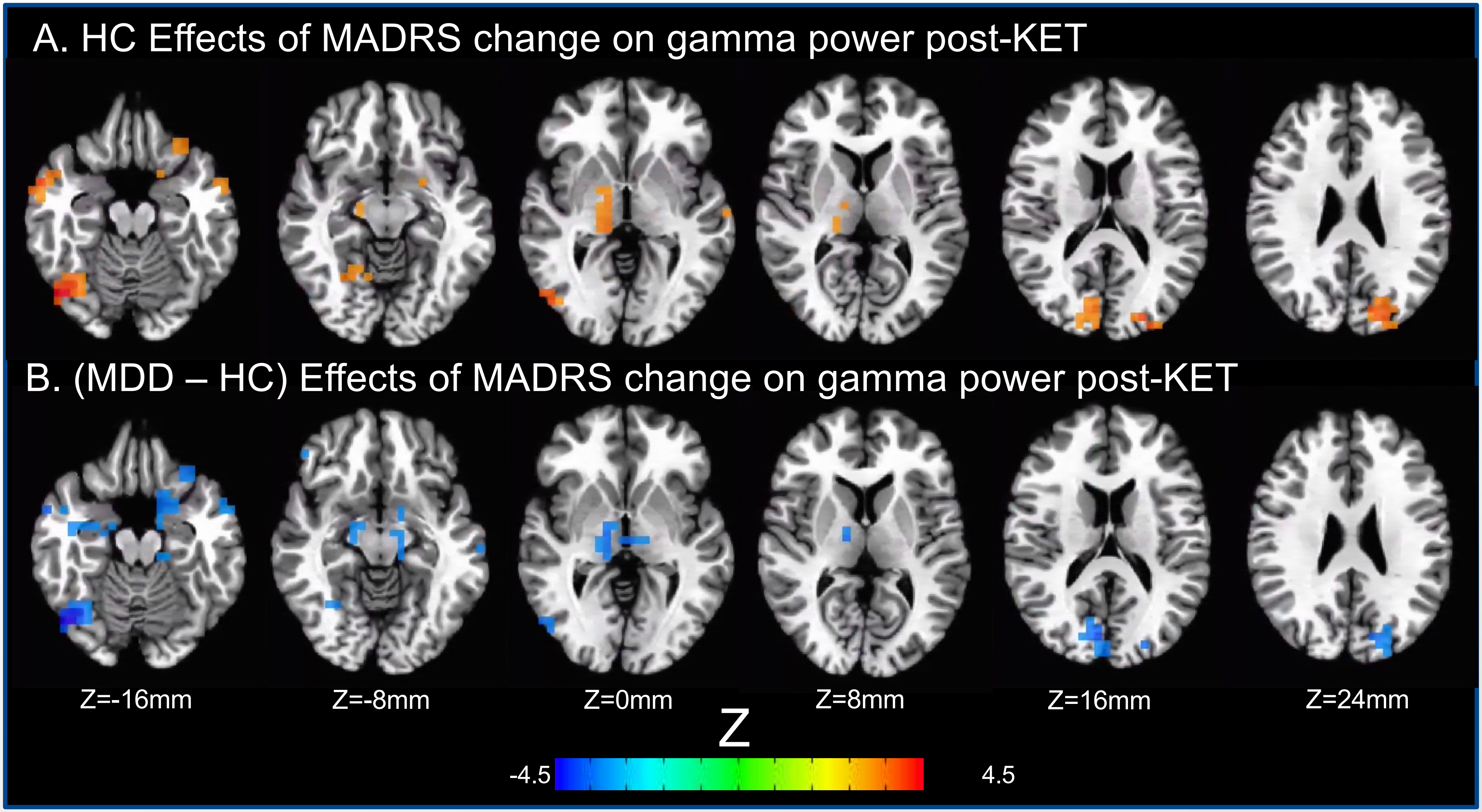

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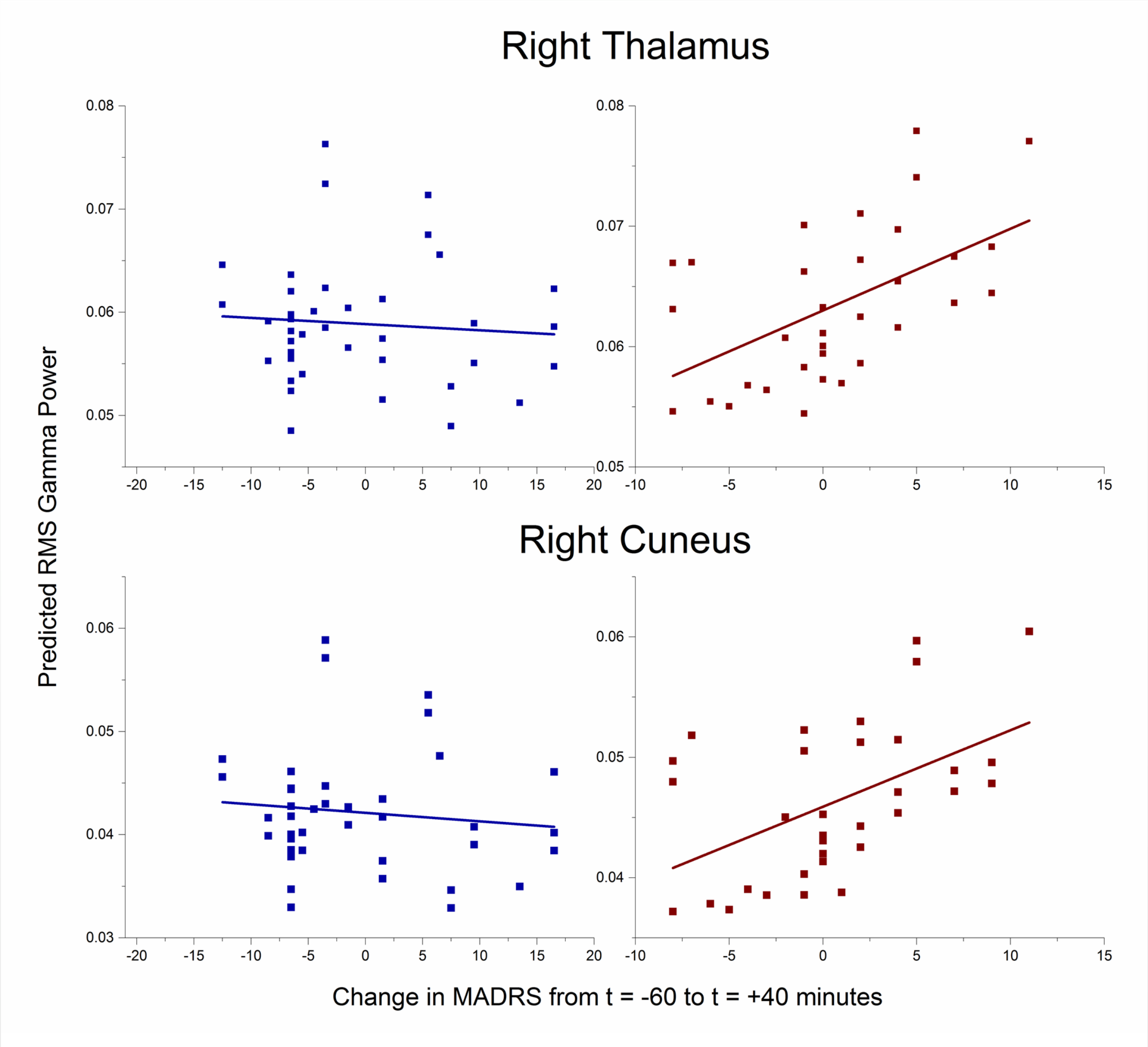
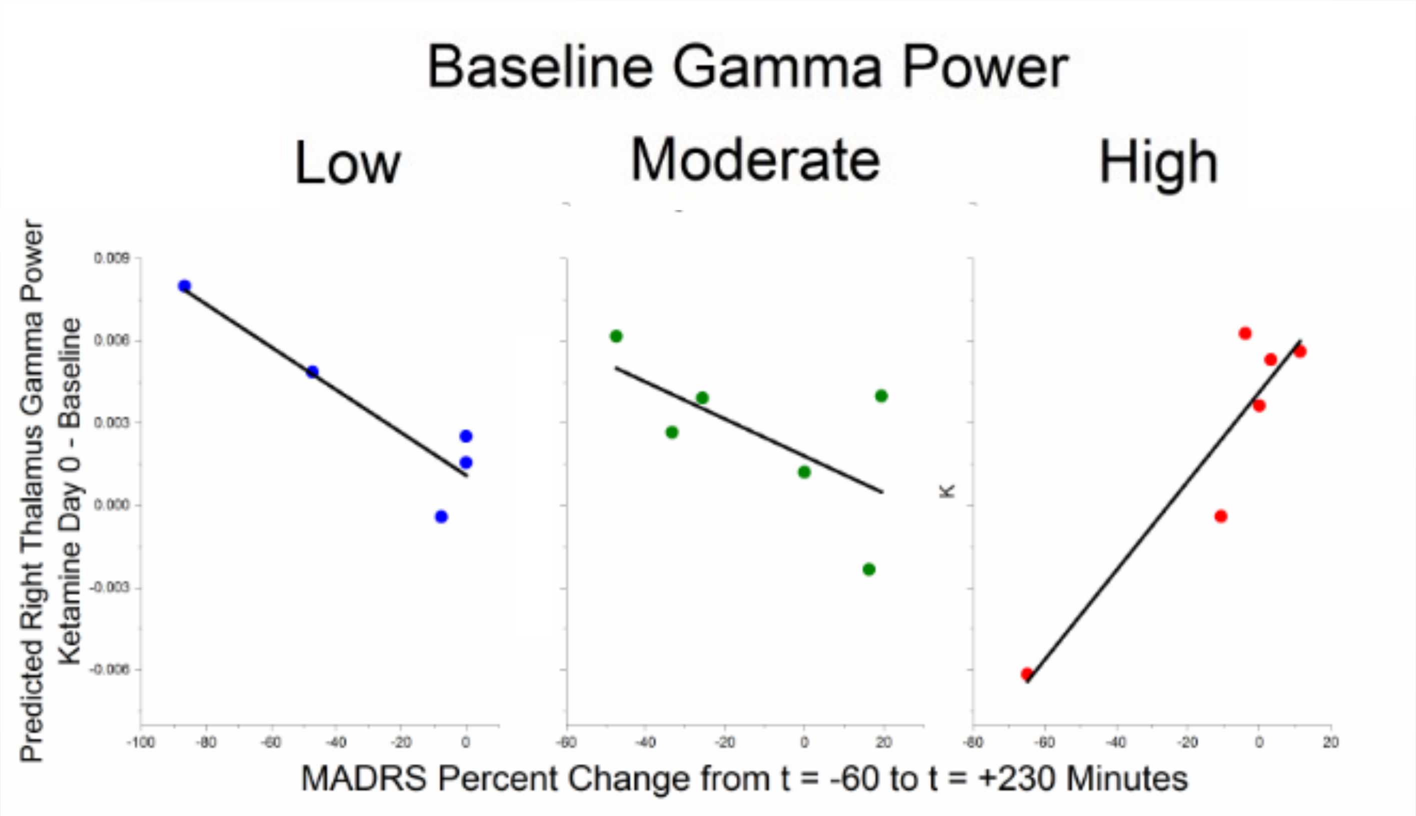


Gamma power changes in response to ketamine



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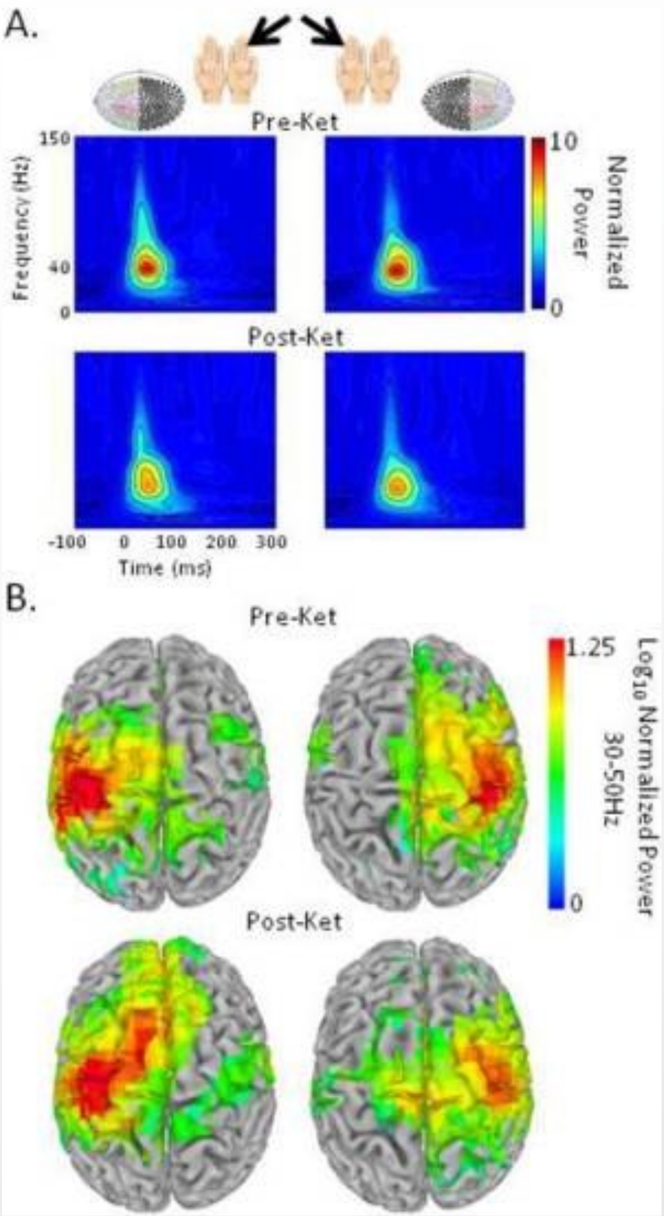
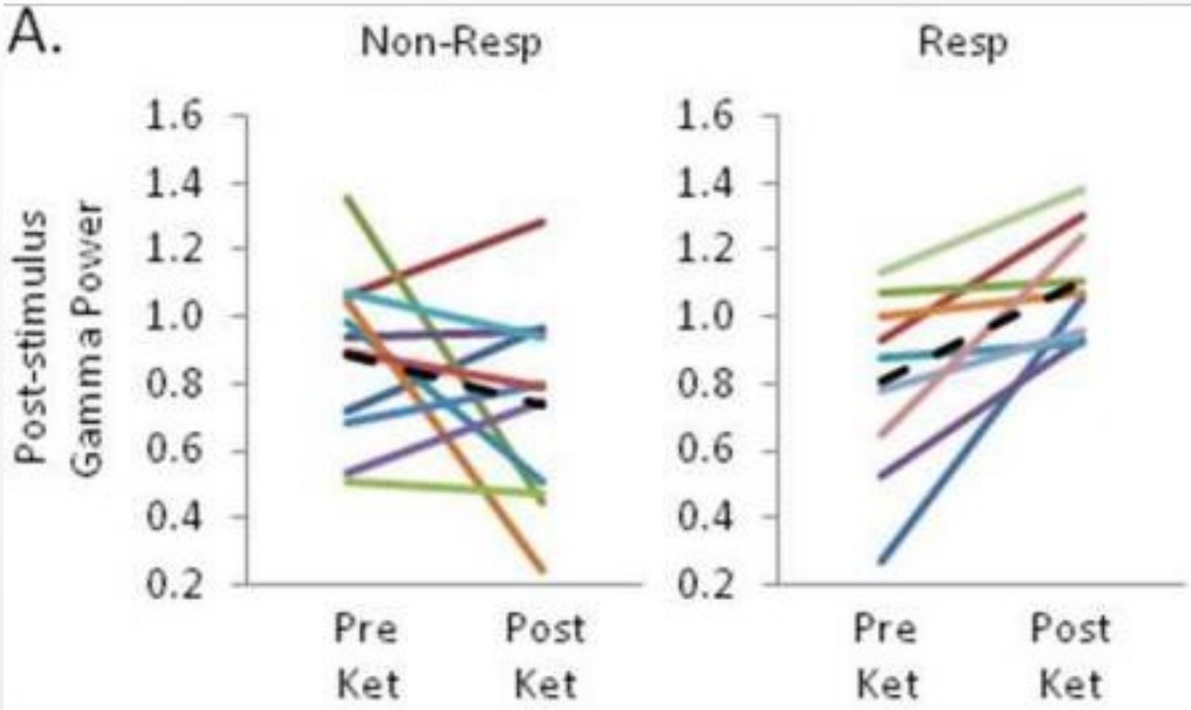
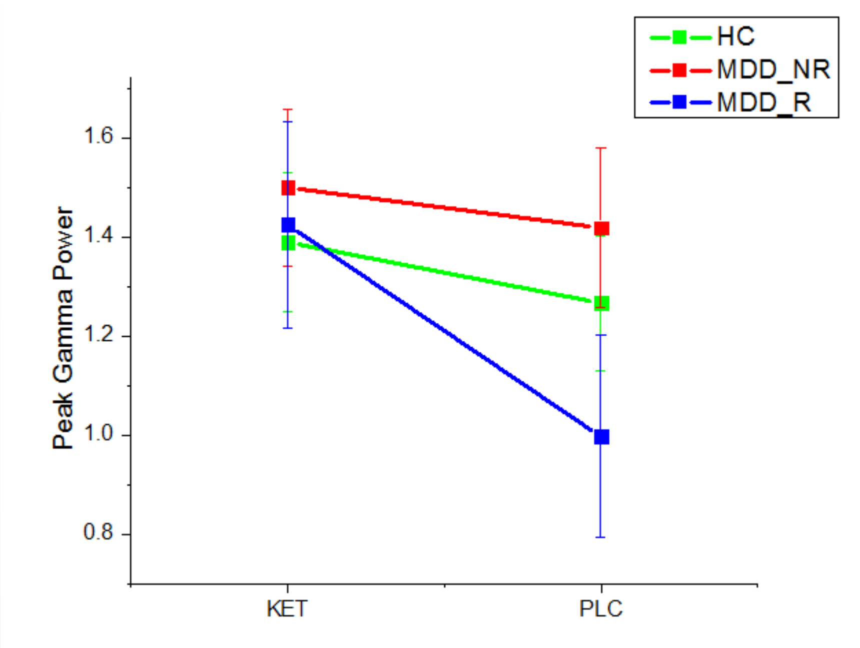
MEG in MDD: Somatosensory Task

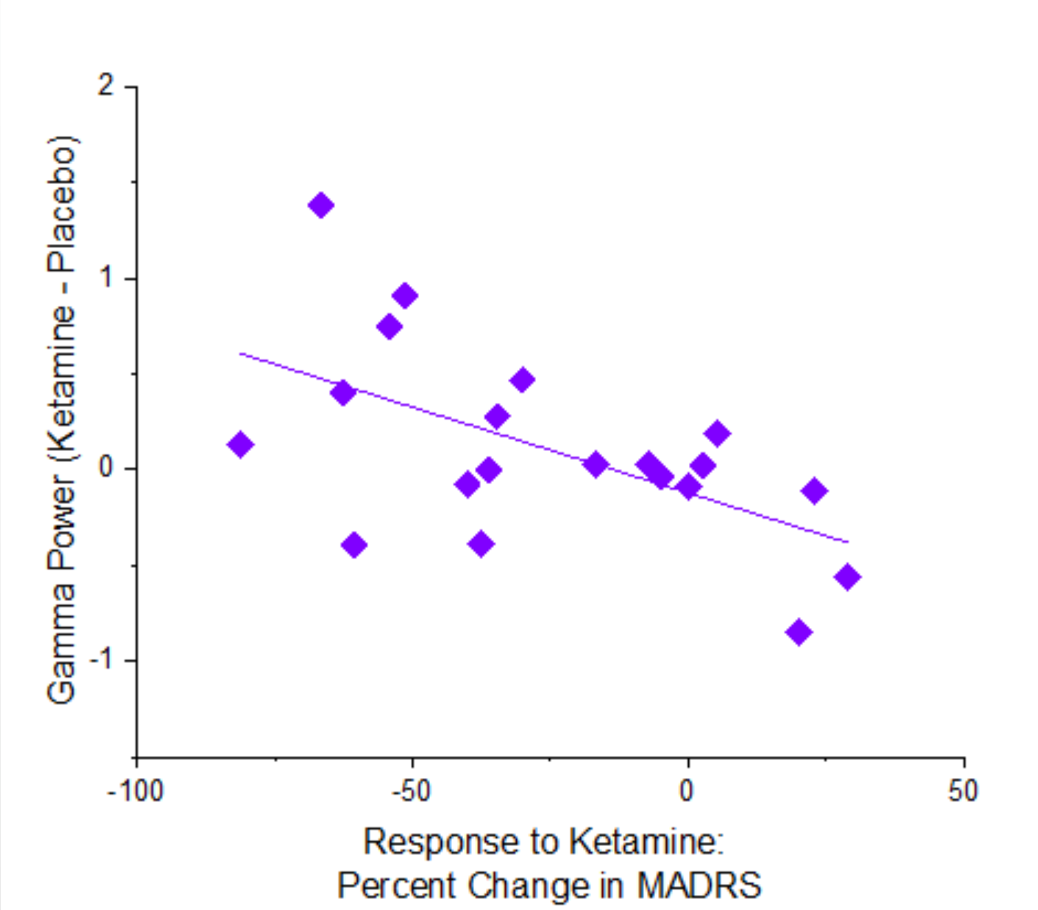




Cornwell, et al. 2012

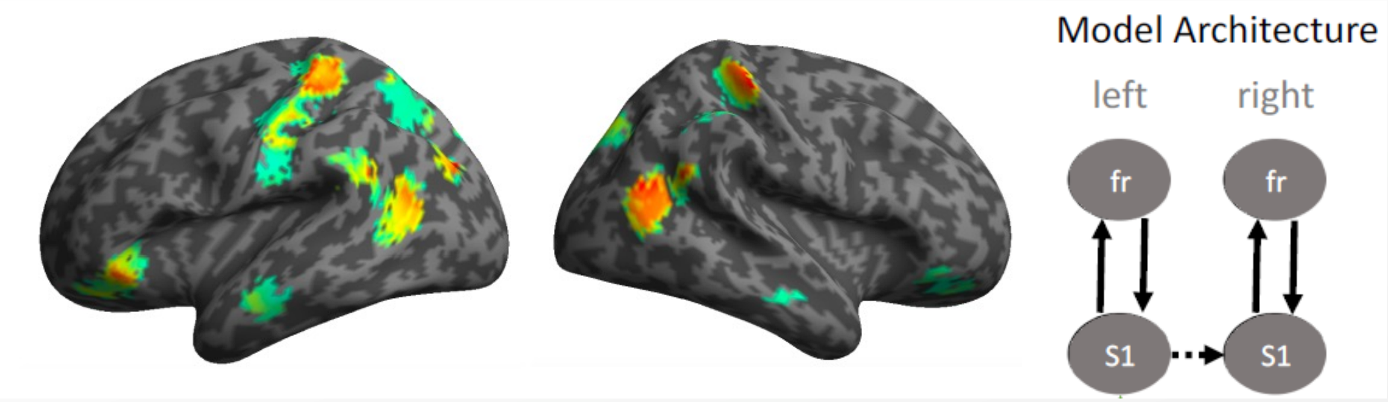
MEG in MDD: Somatosensory Task

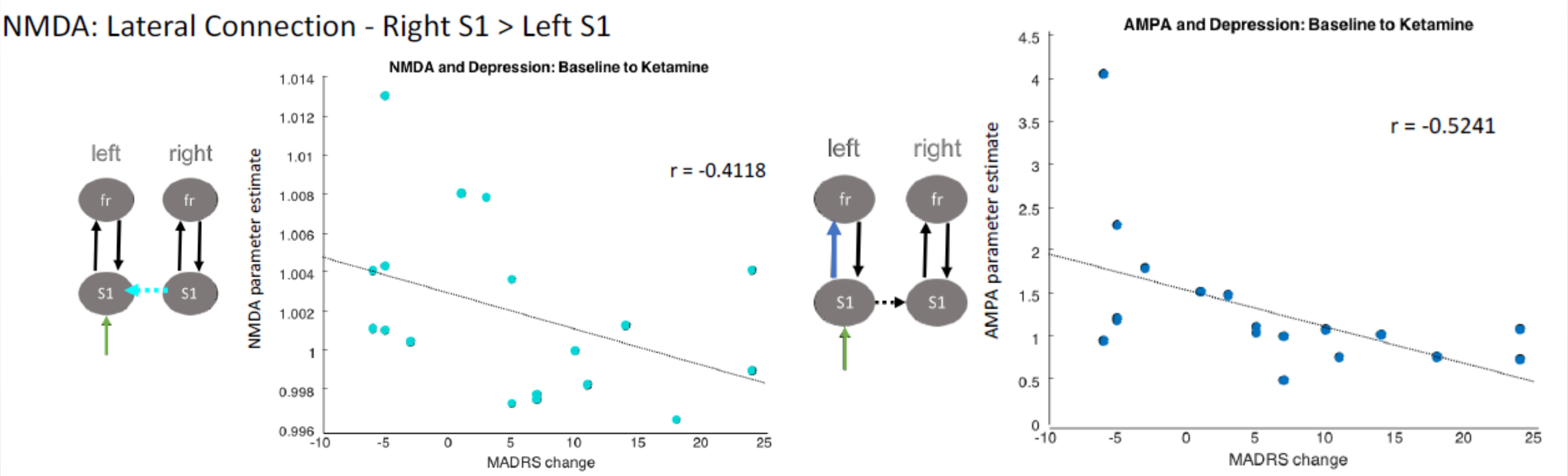




Nugent, et al.

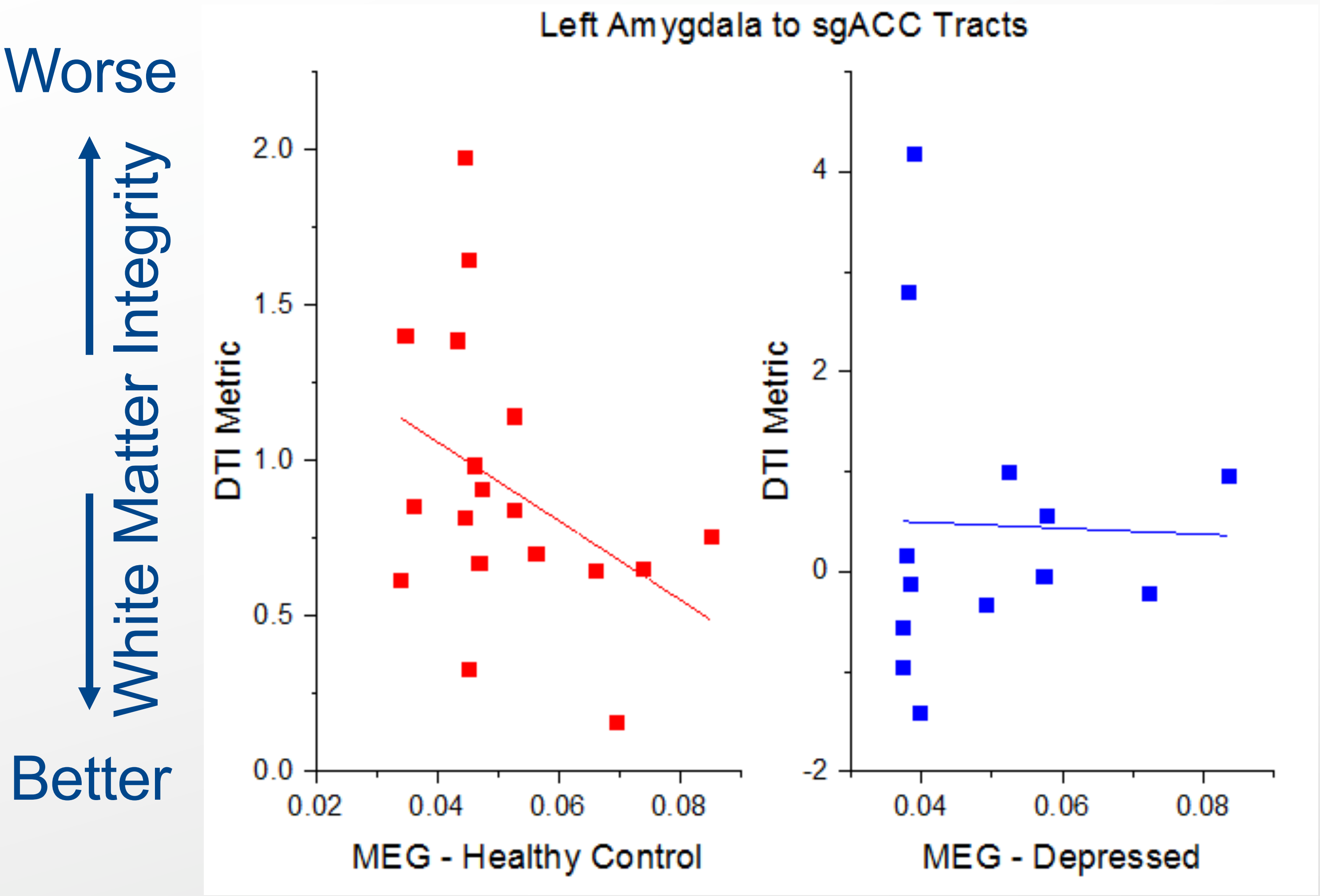
MEG in MDD: Somatosensory Task





 Gilbert, et al.

Multimodal Analyses: DTI and MEG



Recap!

- Structural Imaging
  - Volumetric alterations in limbic and ACC areas
  - Alterations in corticolimbic tracts
- Cognitive Function and Functional Imaging
  - Differential responses to negative and positive emotional stimuli differ in limbic regions and cortical regions in the three core networks
  - Ketamine treatment appears to reverse some neural biases
  - Novel tasks may uniquely assess new symptom domains
- Intrinsic Connectivity
  - Complex alterations in triple network system connectivity, at baseline and in response to ketamine
- Neurophysiology
  - Enables refinement of previously observed limbic abnormalities into the temporal/frequency domain
  - Ketamine has robust effects on gamma power in limbic and cortical areas of the triple network model.
- Multimodal Imaging
  - Cortico-limbic tracts show complex alterations when integrating multiple modalities, such as gamma power.

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