PERSONALIZED INTERVENTION FOR PSYCHOLOGICAL PROBLEMS

Bonnie Klimes-Dougan, Ph.D., LP

Program of Research

- The overarching goal of my research is to understand and alleviate the suffering of those who struggle with distress, depression, and despair (self-injury and suicide).
  - Identify risk and protective factors
  - Identify optimal methods of intervening
    - Personalization

Premis

- Clinical practice in many areas of medicine is shifting toward personalized treatment. In other words, clinicians aim to treat patients based on their individual characteristics, including clinical presentation and/or biological markers.

- Biomarkers can help clinicians select the most effective treatments or reduce the risk of side effects by avoiding certain treatments in susceptible patients.

Outline

- I. Depression, adolescent development and disruption of the threat system.
- II. EBTs are Available to Treat Adolescent Depression
- III. The Solution of Personalization
- IV. Biological Markers Predicting Treatment Response for Adolescents with Depression

I. Depression, adolescent development, and functioning of the threat system

Depression

Affective

Cognitive

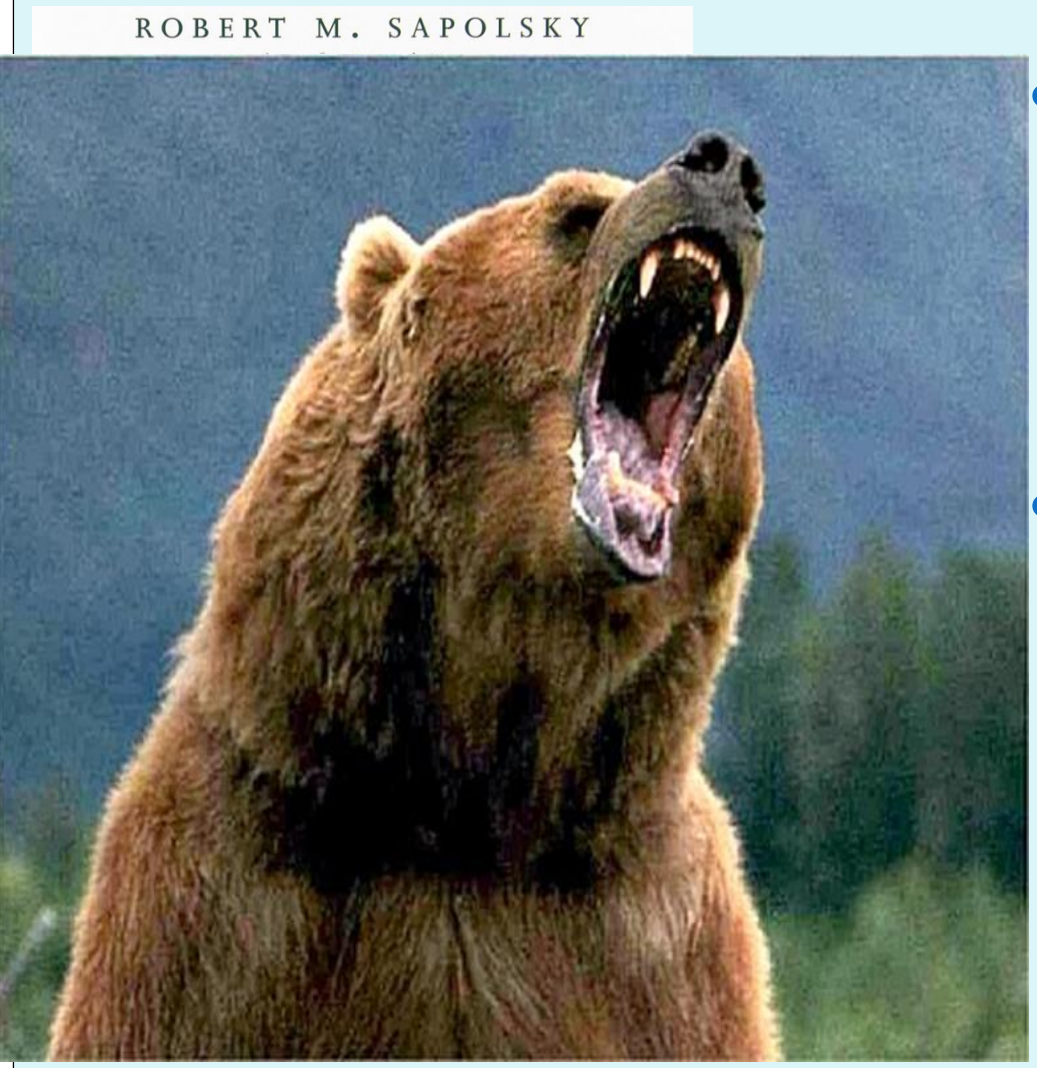
Vegetative

Depression

- Common Problem
  - 16% of the population
- Morbidity and Mortality
  - 60-70% of suicides are associated with a mood disorder
- Significant Impairment
  - Leading cause of economic global impairment worldwide
- Recurrent /Progressive
  - Early onset is associated with a poor prognosis
  - Brain plasticity may be critical

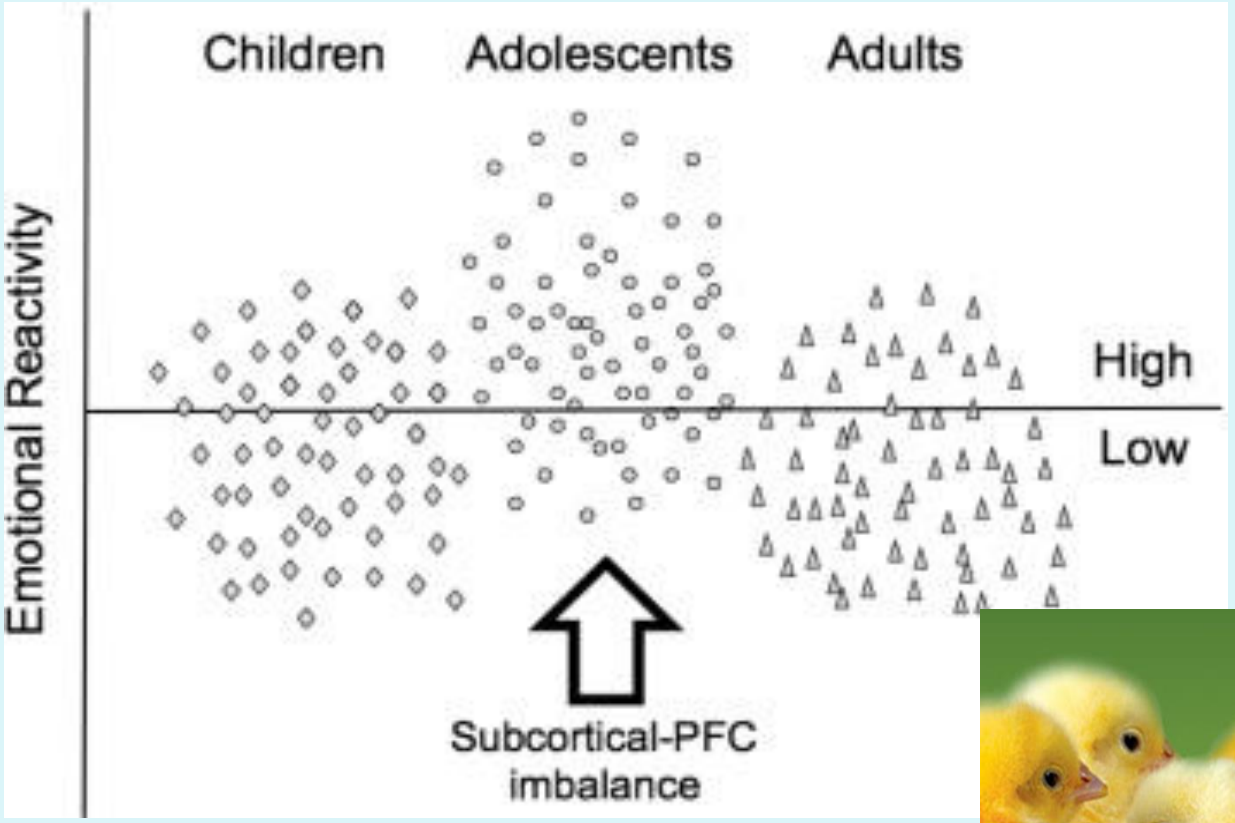
Brent & Kolko, 1990; www.sdchip.org/work_teams/wt_na/wt_na_pdfs/F-depression%

Functions of the Threat System



- SHORT TERM PROJECTS
  - Mobilizes energy – glucose
  - Raises HR/BP
  - Blunts pain
- LONG TERM PROJECTS
  - Slows digestion
  - Slows growth
  - Slows reproduction
  - Suppresses immune functioning
  - Speeds up aging

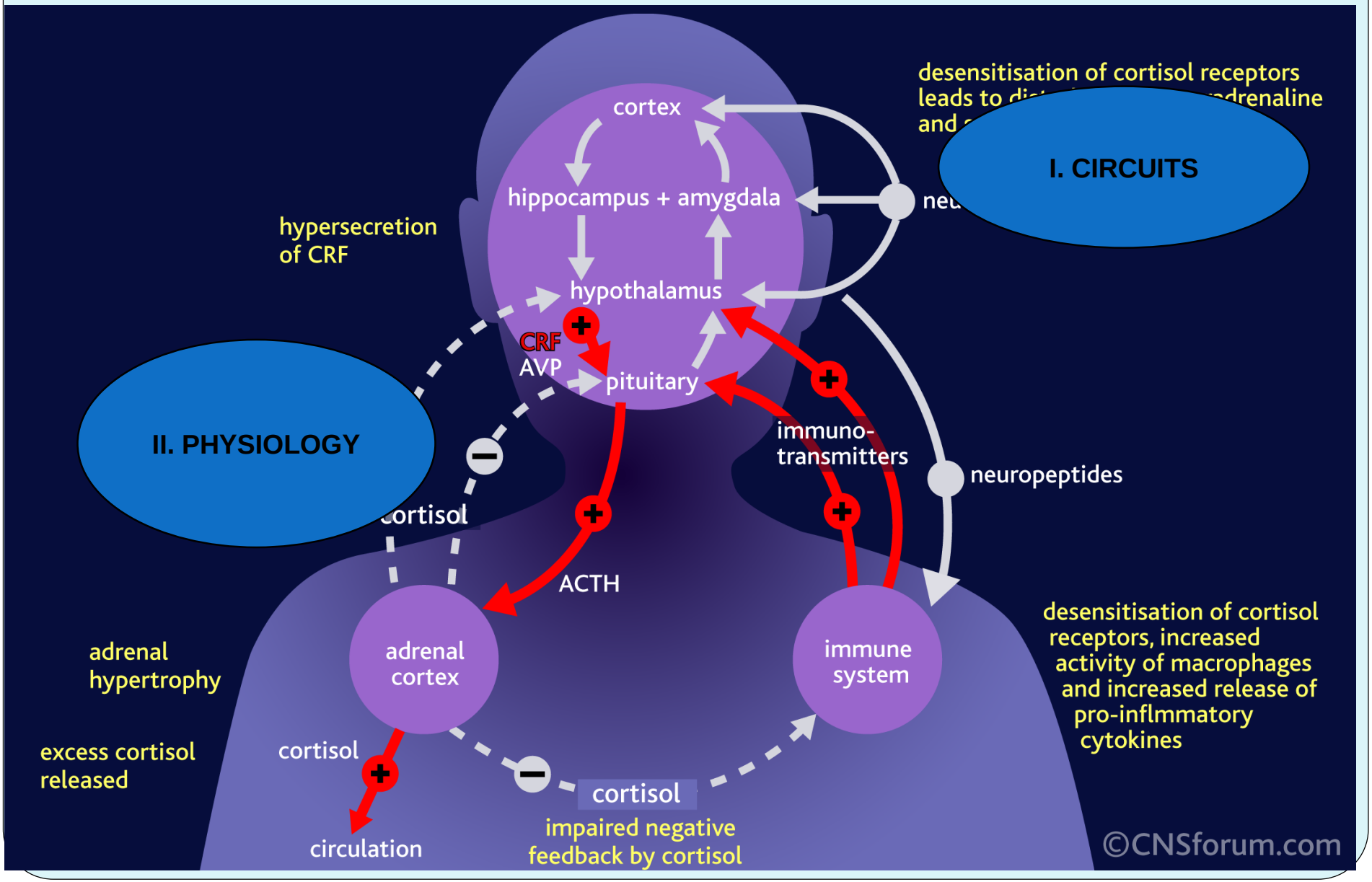
Adolescent Development



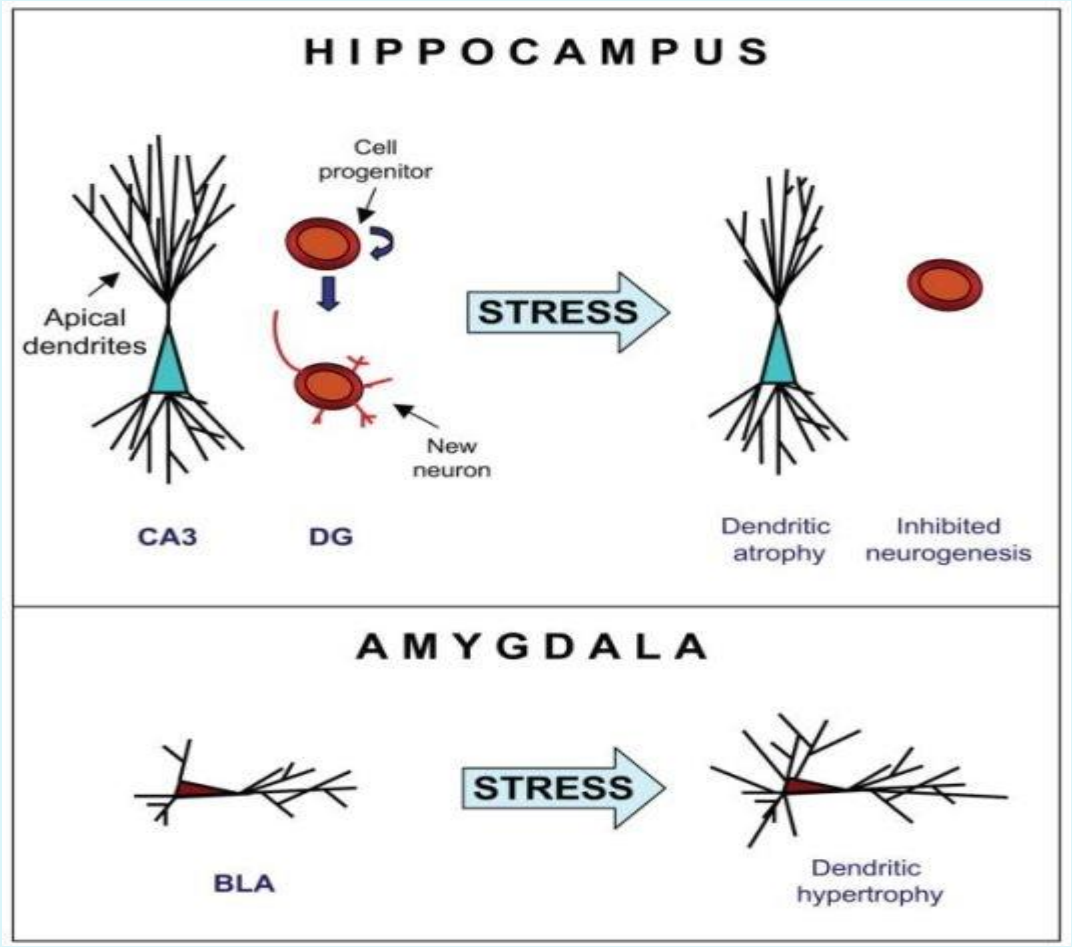
A. PFC
B. Subcortical/Limbic
   Amygdala - Threat
   Striatal - Reward

Somerville, Jones, & Casey, 2009

Threat System and Depression



Cortical and Limbic Structures



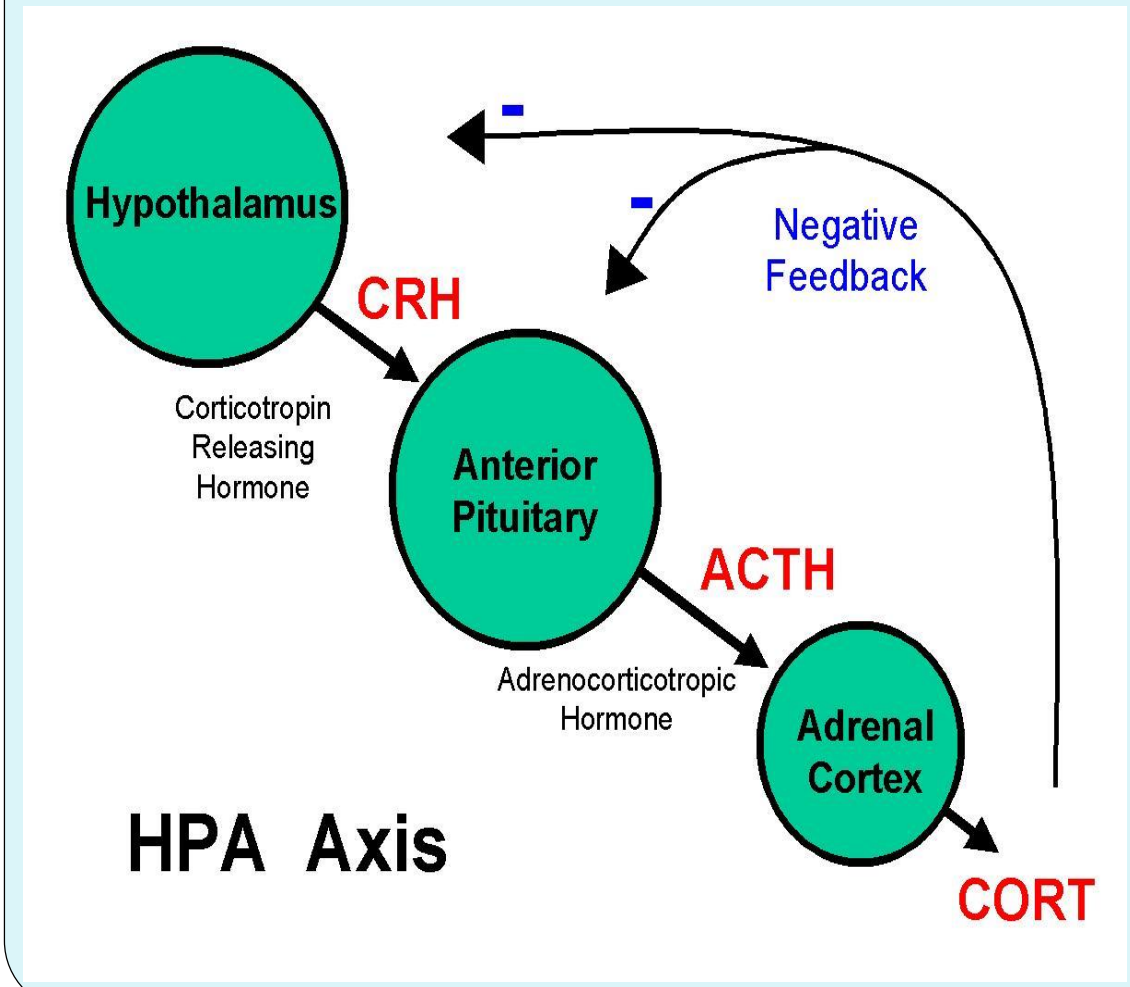
- Differentially influence these key brain regions

↓ Cortical (PFC)
↓ Limbic (Amygdala)

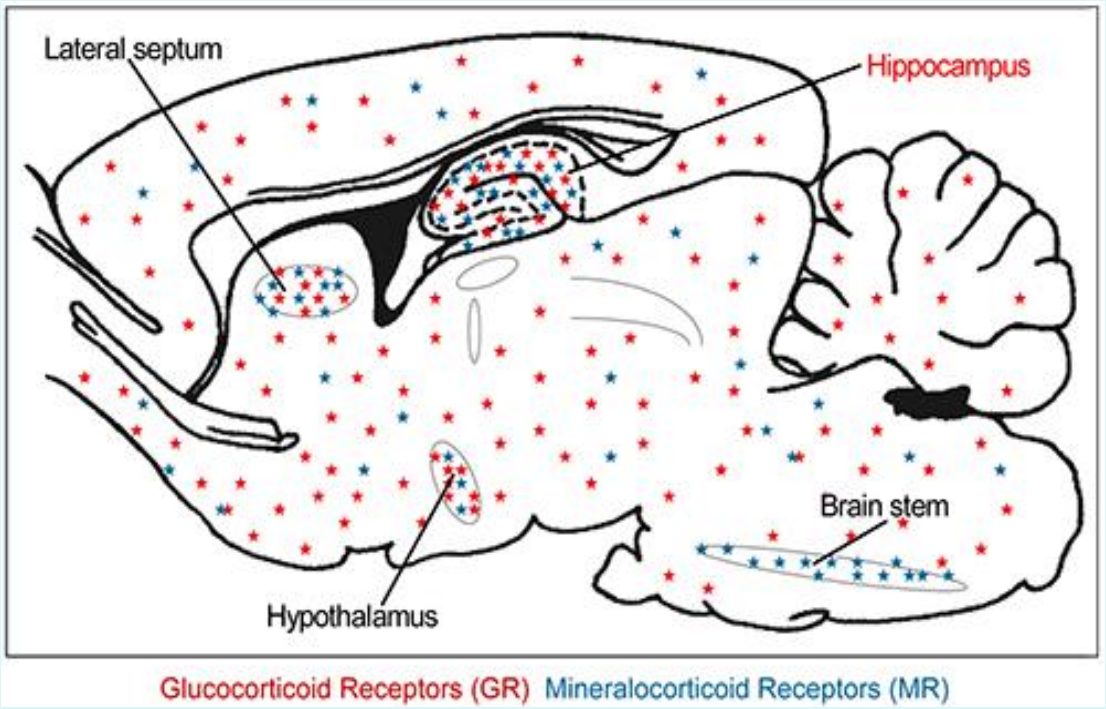
↑ Limbic (Hippocampus)

http://www.ncbi.nlm.nih.gov/books/NBK3914/figure/ch12.f6/?report=objectonly

HPA Axis Stress Model



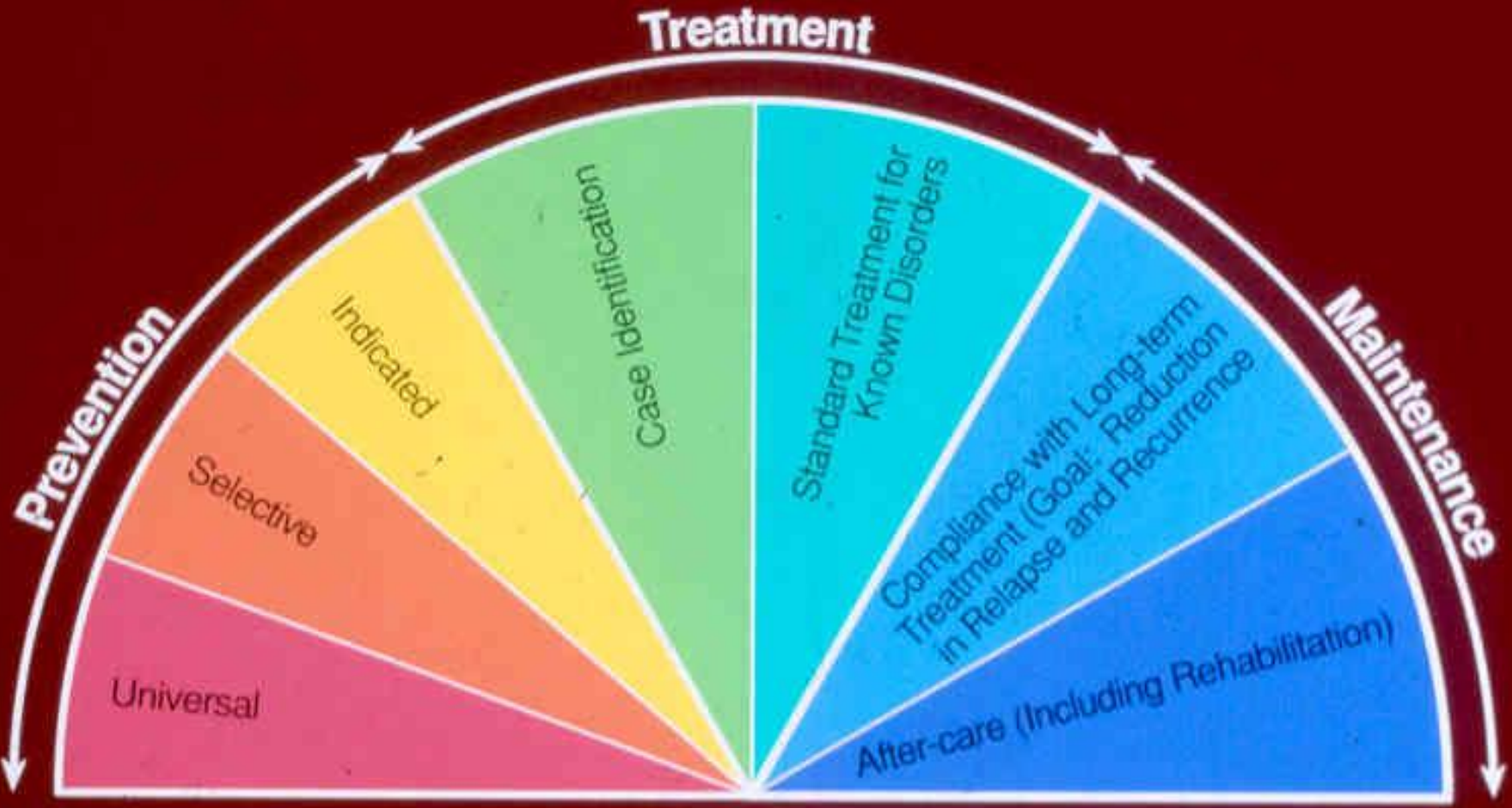
Impacts on the Brain



- Key Receptors
  - GR - glucocordicoid
  - MR - mineralcorticoid
- Receptor Regions of Concentration
  - Amygdala
  - Hippocampus
  - Hypothalamus
  - VMPFC

II. EBTs are Available to Treat Adolescent Depression

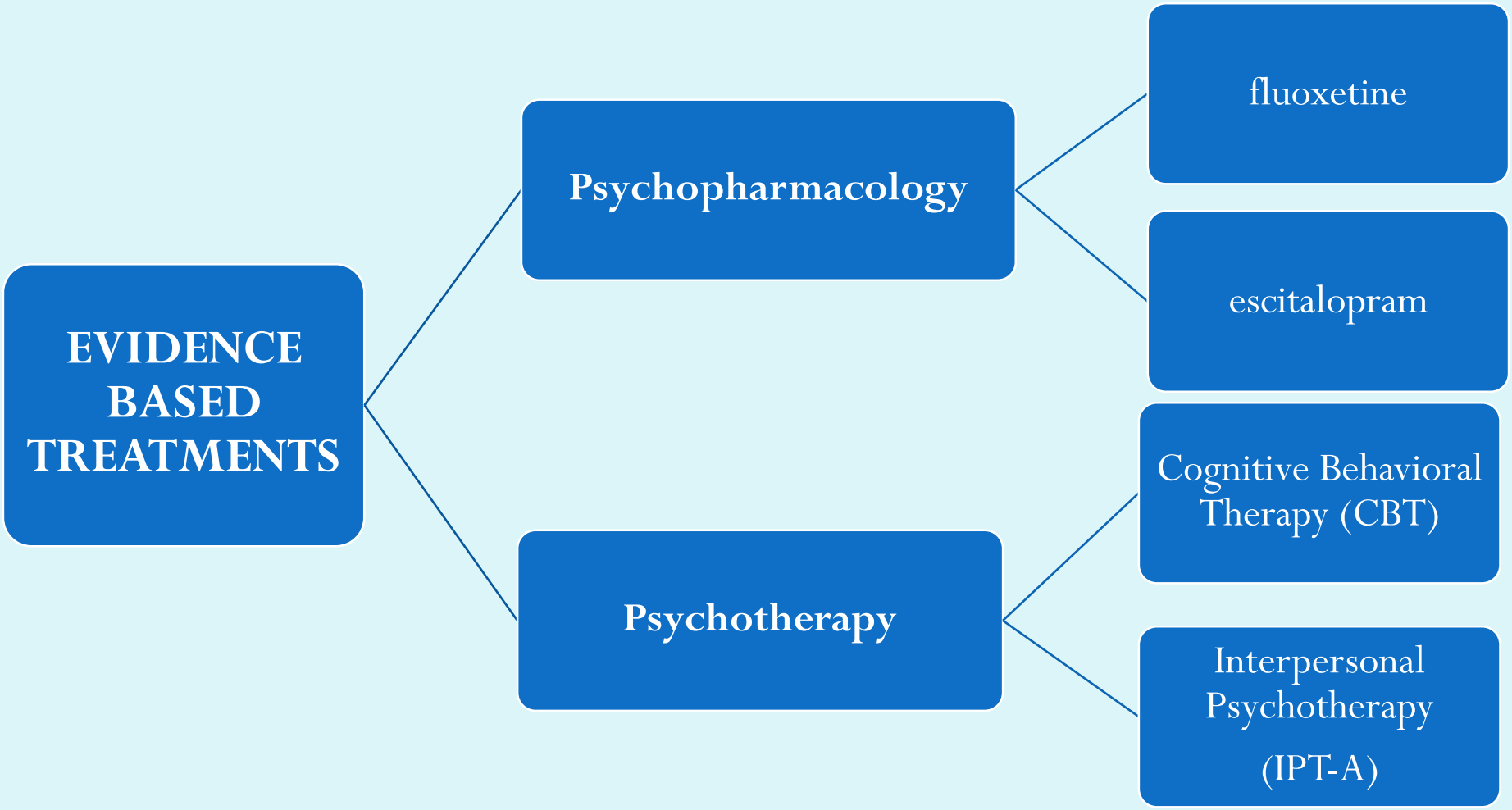
The Mental Health Intervention Spectrum for Mental Disorders



Note. From *Reducing Risks for Mental Disorders: Frontiers for Preventive Intervention Research* (p. 23), by P. J. Mrazek and R. J. Haggerty (Eds.), 1994, Washington, DC: National Academy Press. Copyright 1994 by National Academy Press. Reprinted with permission.

Evidence Based Treatments

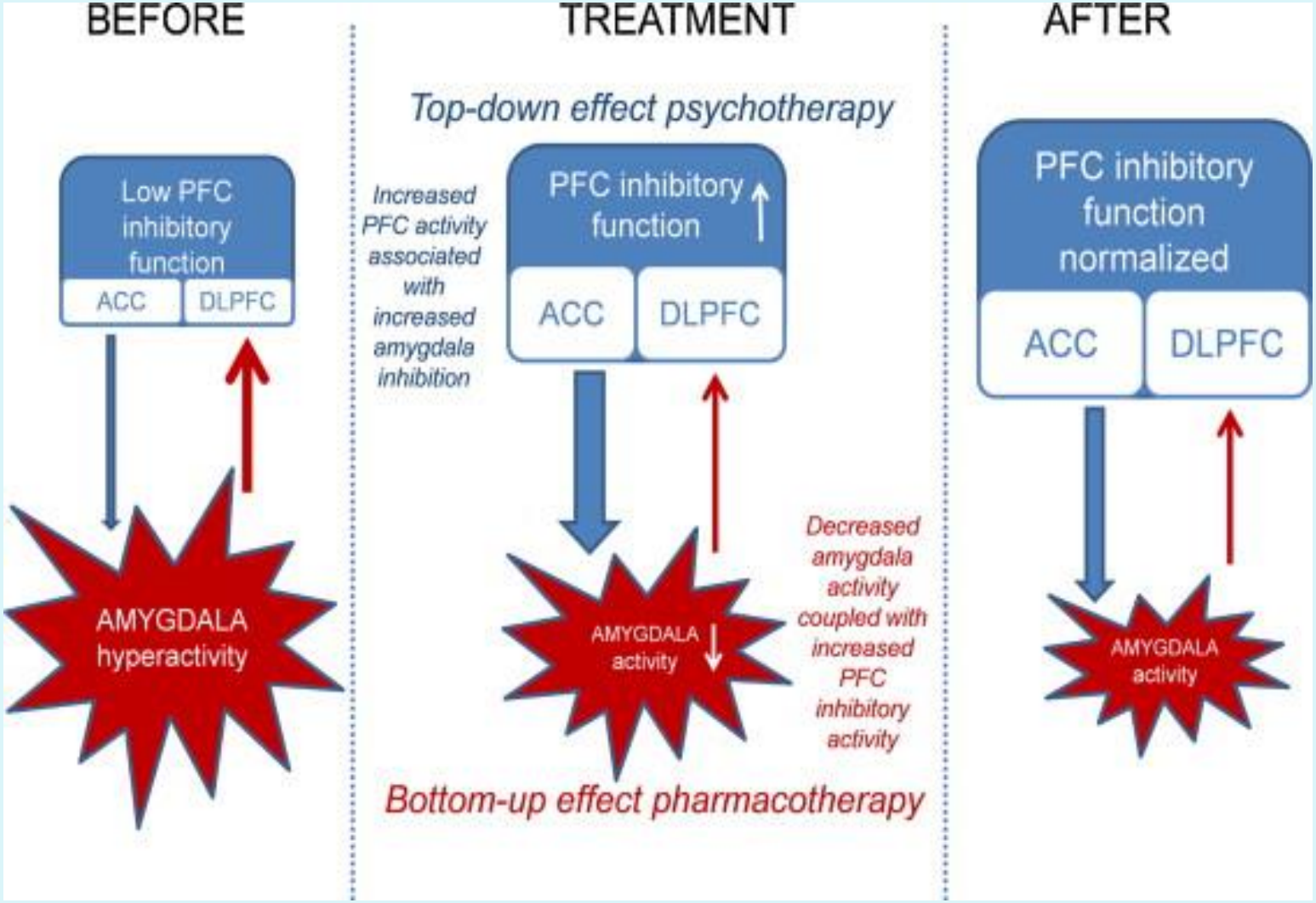
Adolescent Depression



Guidelines Based on Depression Severity

Mild	Mild to moderate	Moderate to Severe
•Psycho-education •Supportive Therapy	• Cognitive Behavioral Therapy (CBT) • Interpersonal Therapy (IPT)	•Medication •Medication + CBT or IPT

Birmaher B. et al. *J Am Acad Child Adolesc Psychiatry*. 2007;46:1503-1526.
Boylan K, et al. *Psychopharmacology*. 2007;191:27–38.



Hypothetical model of functional changes in amygdala and the main prefrontal areas involved in anxiety disorders and major depressive disorder.

Quide, Witteveen, El-Hage, et al., 2011

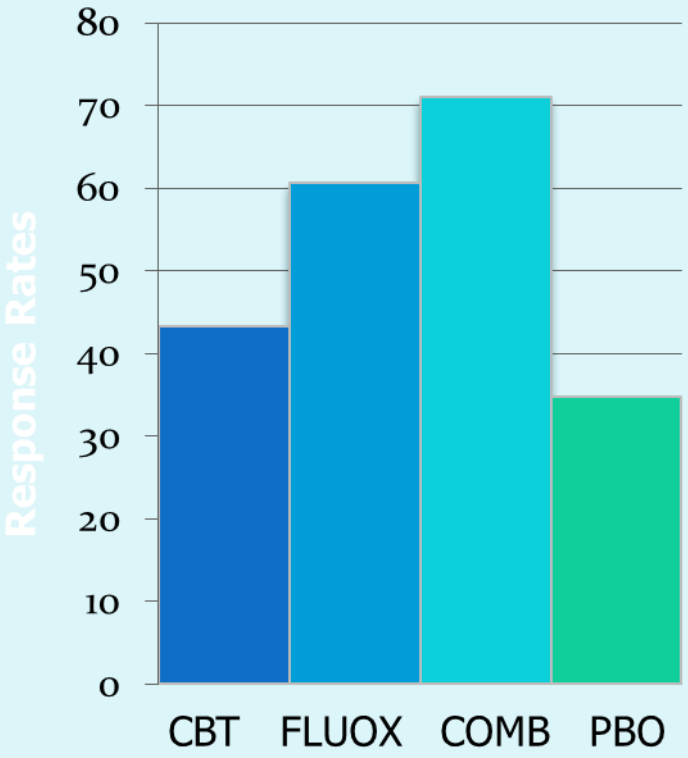
Limitations of EBTs

- The impact of EBTs will fall short if a one-size fits all assumptions continues to be made when utilizing EBTs

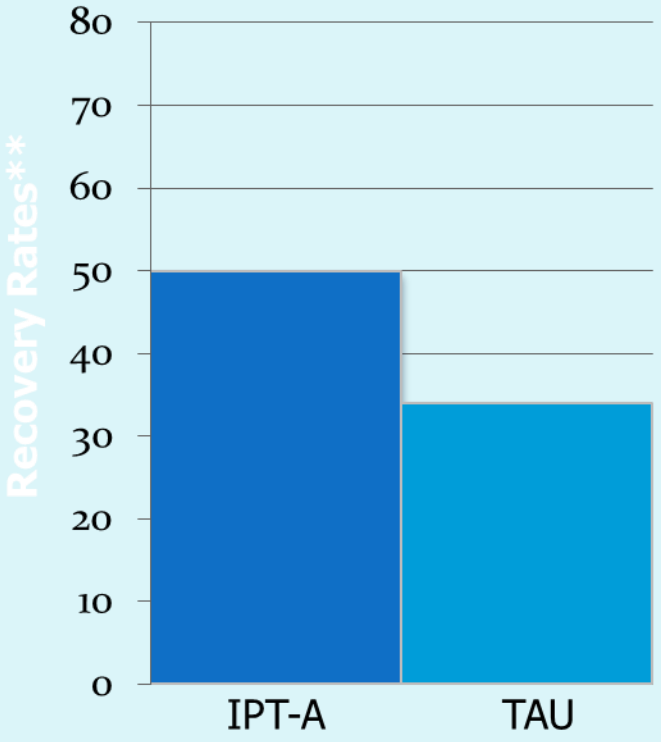
II. The Solution of Personalization

Current Treatments have Response/Recovery Rates of 43%-71%

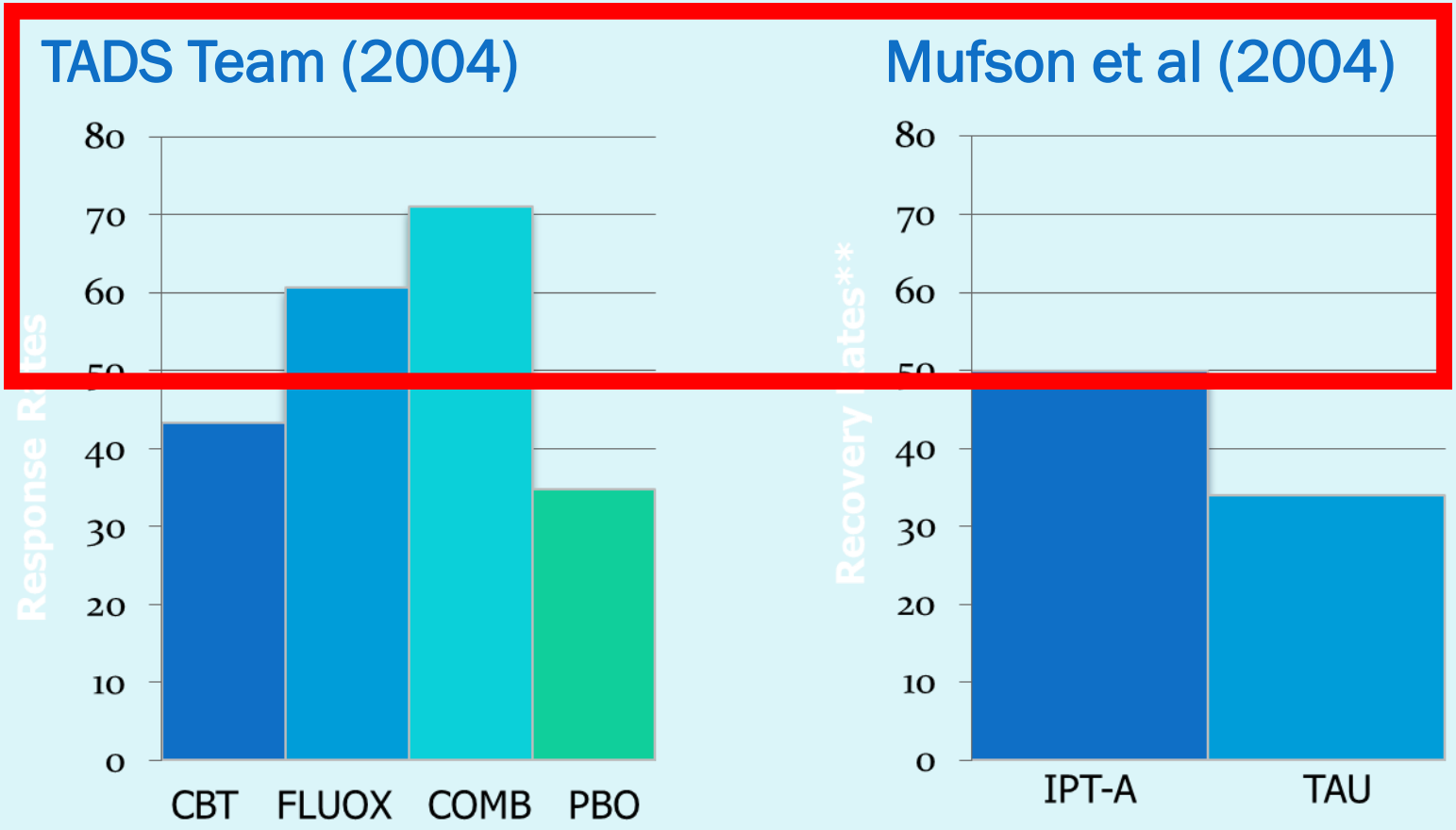
TADS Team (2004)



Mufson et al (2004)**



Current Treatments have Response/Recovery Rates of 43%-71%



The Cost of Choosing the "Wrong" Treatment

- Personal / Societal Problem
  - Loss of productivity (Global Burden of Dz)
  - Continued distress / Suicide risk
  - Discouragement from help-seeking
  - Wasted resources
    - Health-care costs
    - Practitioner time/money which could be treating those who will respond

McGrath et al, 2013

Solution Options

- Dosage change?
- Components adjust?
- Treatment add?
- Personalization?
  - Preference
    - (Mergl, et al, 2011)
  - Clinical Predictors

  - Biological Markers

Personalizing Treatment

- The next step: to move beyond determining what treatments *work* to identifying which treatments work *for whom*

- Identifying patient characteristics that predict or interact with (moderate) treatment can guide clinicians in selecting a treatment that more rapidly and efficiently manages depression for a specific group of individuals

Insel, 2009; National Institute of Mental Health Strategic Plan, 2008

Current Status of Search for Tailoring Variables

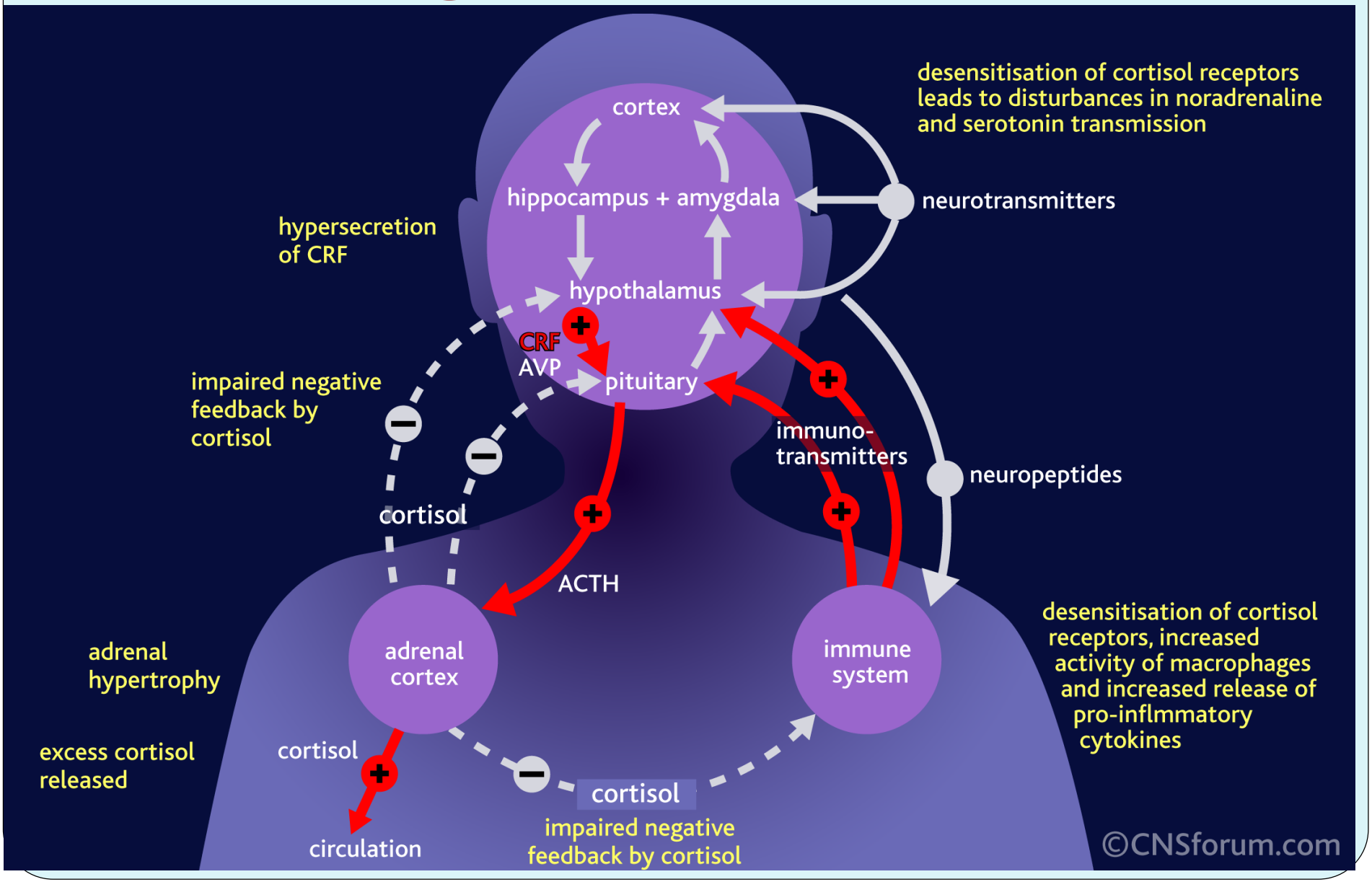
- Infinite Possibilities?
- Psychosocial
  - not yielded the wealth of findings
- Biological
  - There is excitement about the possibility of identifying indexes linked with underlying biological mechanisms (biomarkers) that can guide treatment decisions

Main Approaches for Biological Predictors

- Brain (circuits)
  - Neuroimaging
  - Neuropsychological testing
  - Neurotransmitters
- Body (physiology)
  - HPA Axis
- Genes
  - Molecular genetics
  - Epigenetics

IV. Biological Markers Predicting Treatment Response

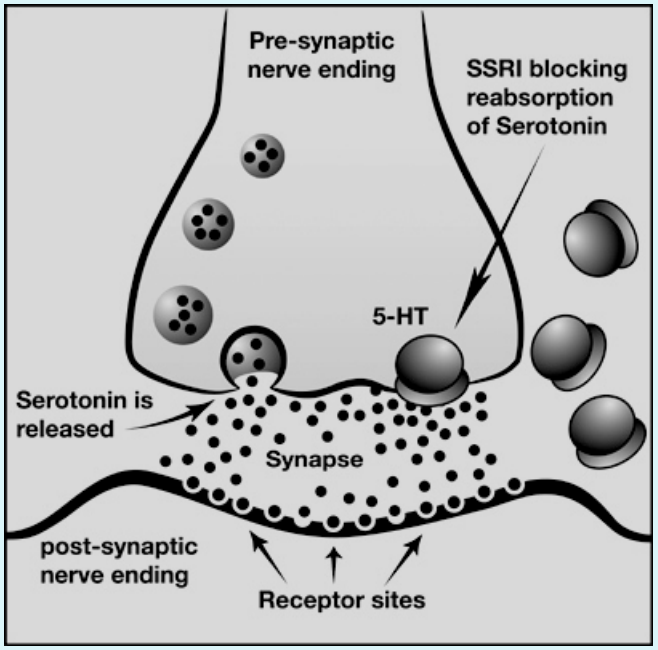
Neurobiology of Depression



SSRIs:

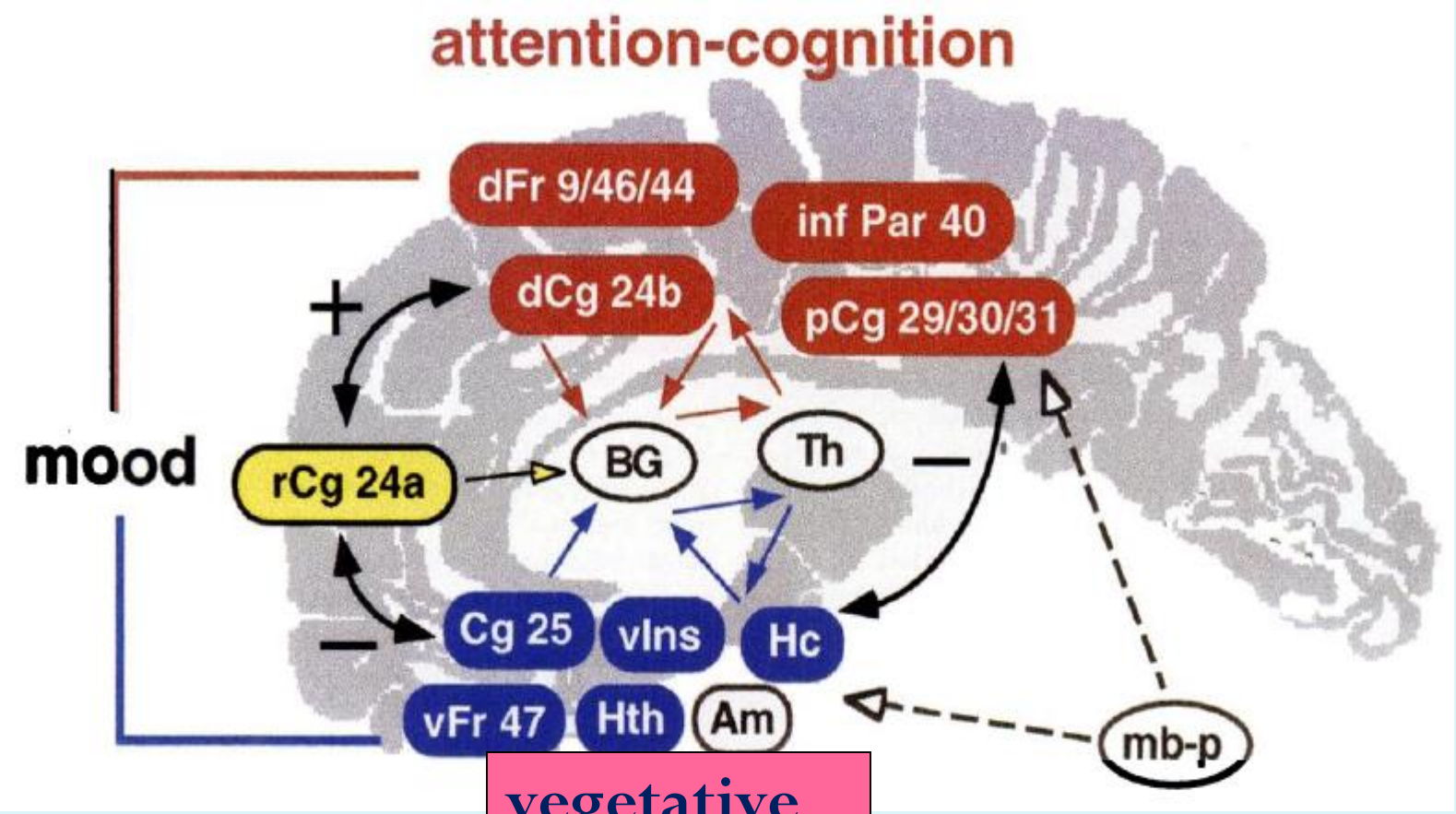
Common Choice of Medication for Depression

- Exact mechanisms of SSRIs are still fully not understood
  - extracellular increases in serotonin levels (partially do to SSRI blocking reabsorption due to abnormalities in 5-HT1A receptor)
- SSRIs may alter brain functioning
  - decreased limbic activation
  - increased cortical activation (ACC, PFC)
- SSRIs may alter HPA axis functioning
  - antidepressants increase GR function, thus leading to resolution of glucocorticoid resistance



http://www.myhealthyfeeling.com/wp-content/uploads/2011/07/ssris2.jpg

Fronto-limbic Neural Circuitry



Red: dFr = dorsolateral prefrontal; inf Par = inferior parietal; dCg = dorsal anterior cingulate; pCg = posterior cingulate. Blue: Cg 25 = subgenual (infralimbic) cingulate; vlns = ventral anterior insula, Hc = hippocampus; vFr = ventral frontal; Hth = hypothalamus. Yellow: rCg = rostral anterior cingulate. White: mb-p = midbrain-pons; BG = basal ganglia; Th = thalamus; Am = amygdala.

Mayberg H. *J Neuropsychiatry Clin Neurosci*. 1997;9(3):471-481.

From: **Toward a Neuroimaging Treatment Selection Biomarker for Major Depressive Disorder**

JAMA Psychiatry. 2013;():1-9. doi:10.1001/jamapsychiatry.2013.143

Table 2. Treatment by Outcome Interaction Results and Post hoc Analyses of Extracted Regions of Interest

Region	MNI Coordinates, Peak X	Y	Z	Side	Cluster Size,[a] Voxels	Effect Sizes[b] REM–NR to CBT	REM–NR to sCIT	CBT–sCIT in NR	CBT–sCIT in REM	Average Marginal ES
Anterior insula	+30.0	+24.0	−13.5	R	529	1.69	1.17	1.52	1.33	1.43
Inferior temporal (BA 20)	+42.0	−33.0	−25.5	R	469	1.23	1.45	2.09	0.59	1.34
Amygdala	−27.0	−7.5	−27.0	L	233	0.98	1.61	1.89		
Premotor (BA 6)	−27.0	+1.5	+58.5	L	233	1.40	1.03	1.75		
Motor (BA 4)	+25.5	−27.0	+60.0	R	147	0.61	1.78	1.80		
Precuneus (BA 7)	−18.0	−67.5	+43.5	L	101	1.18	1.27	1.37		

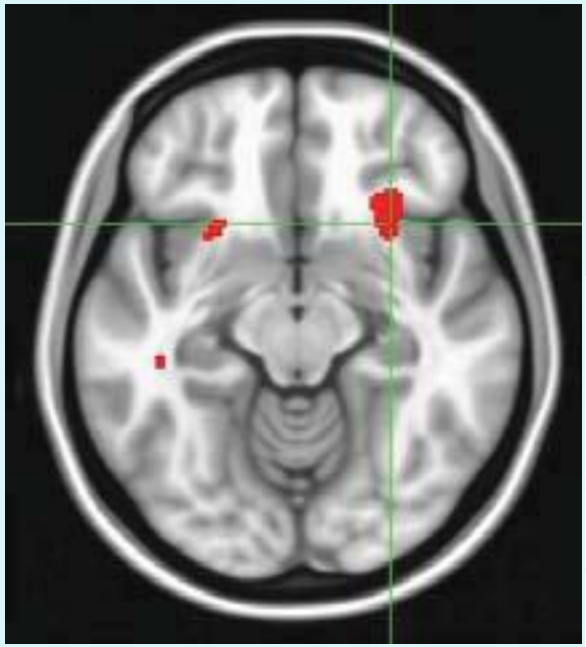
Abbreviations: BA, Brodmann area; CBT, cognitive behavior therapy; CBT−sCIT, mean difference between CBT and escitalopran Montreal Neurological Institute; NR, nonresponders; REM, remitters; REM−NR, mean difference between remitters and nonrespo escitalopram oxalate.

[a] Whole-brain 2-way analysis of variance with $P < .001$ uncorrected; voxel size, 1.5 mm × 1.5 mm × 1.5 mm.

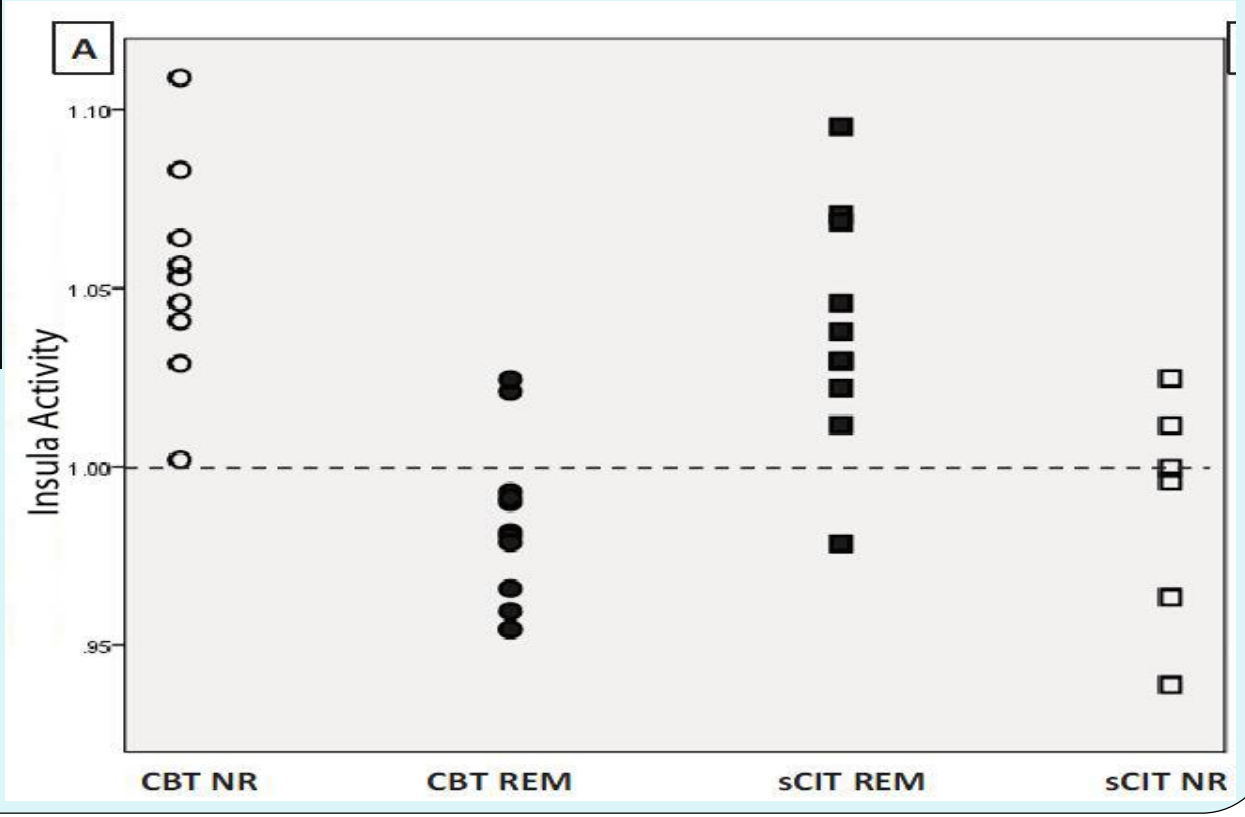
[b] Effect size = mean difference divided by pooled standard deviation.

Figure Legend:

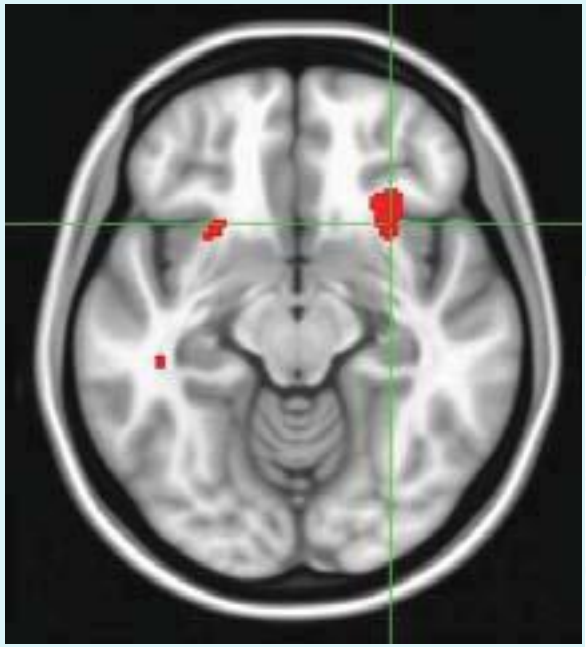
Mayberg:



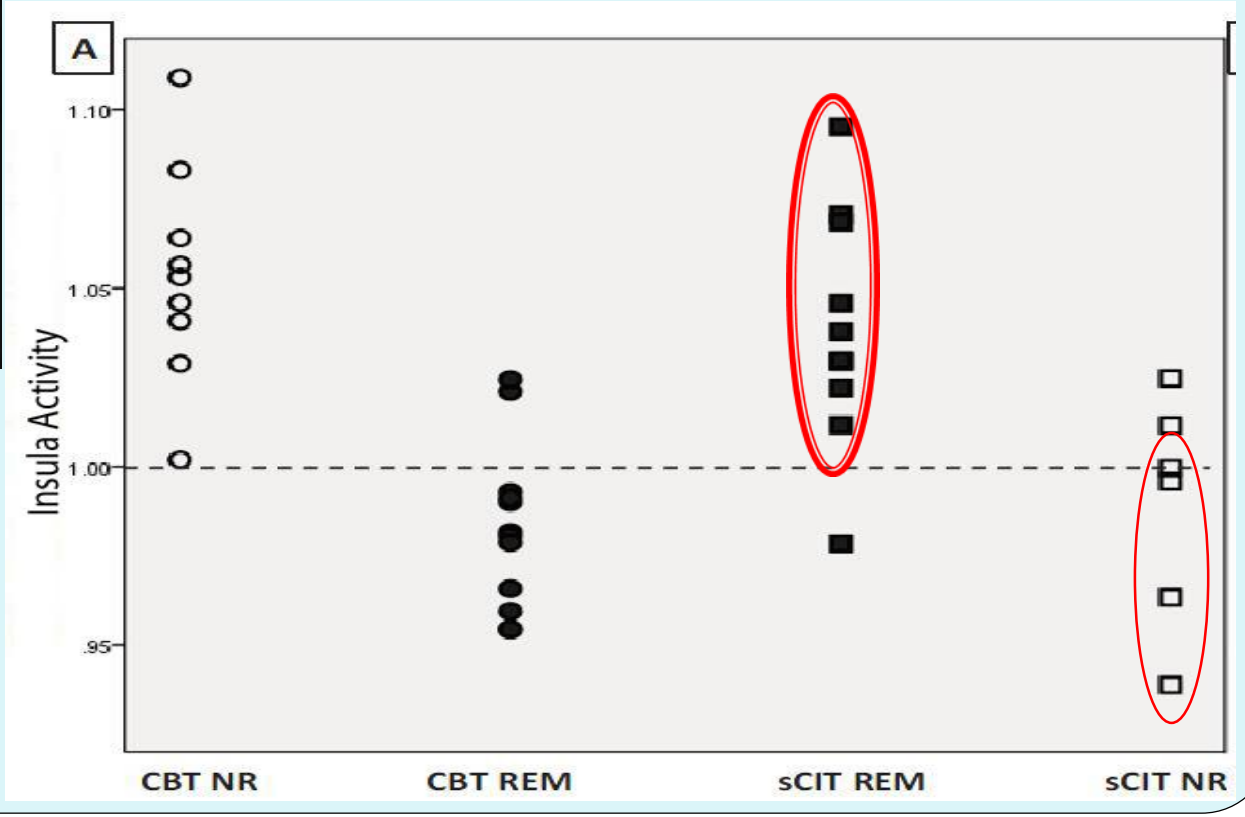
http://www.nimh.nih.gov/news/science-news/2013/scan-predicts-whether-therapy-or-meds-will-best-lift-depression.shtml



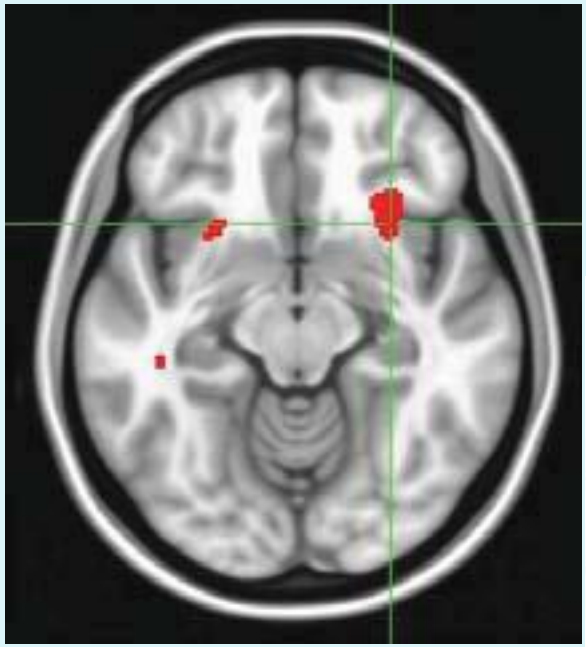
Mayberg:



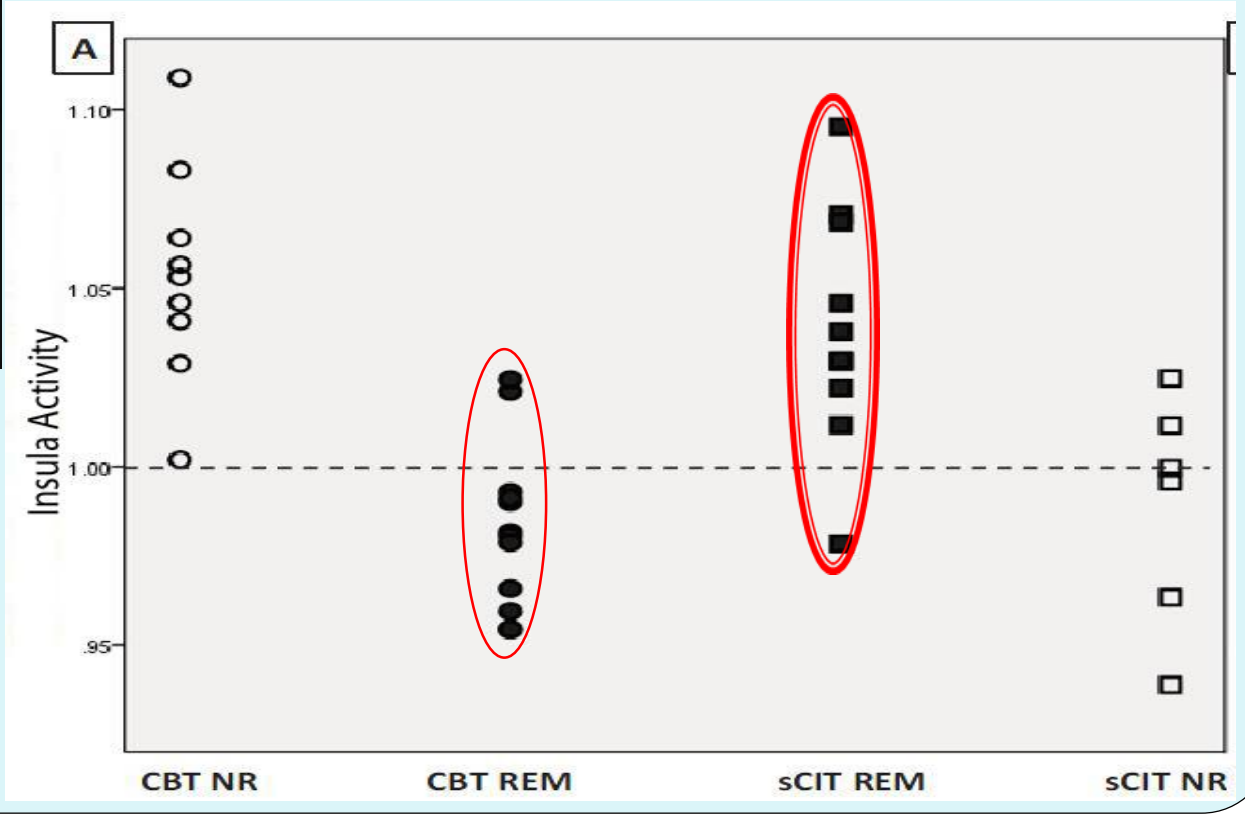
http://www.nimh.nih.gov/news/science-news/2013/scan-predicts-whether-therapy-or-meds-will-best-lift-depression.shtml



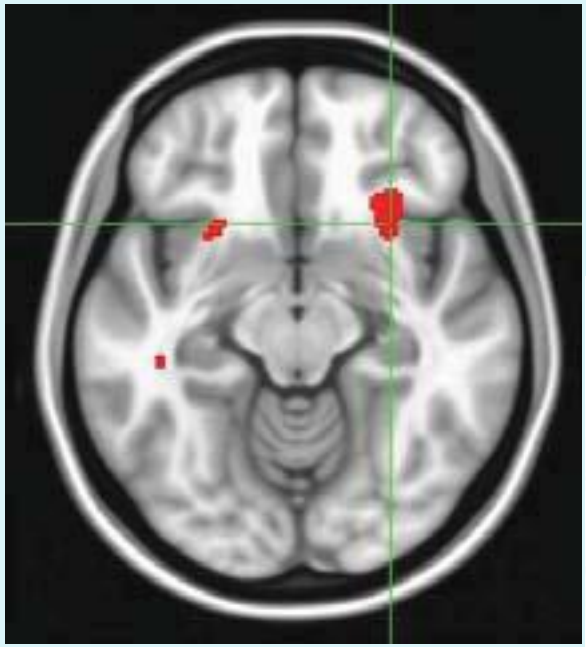
Mayberg:



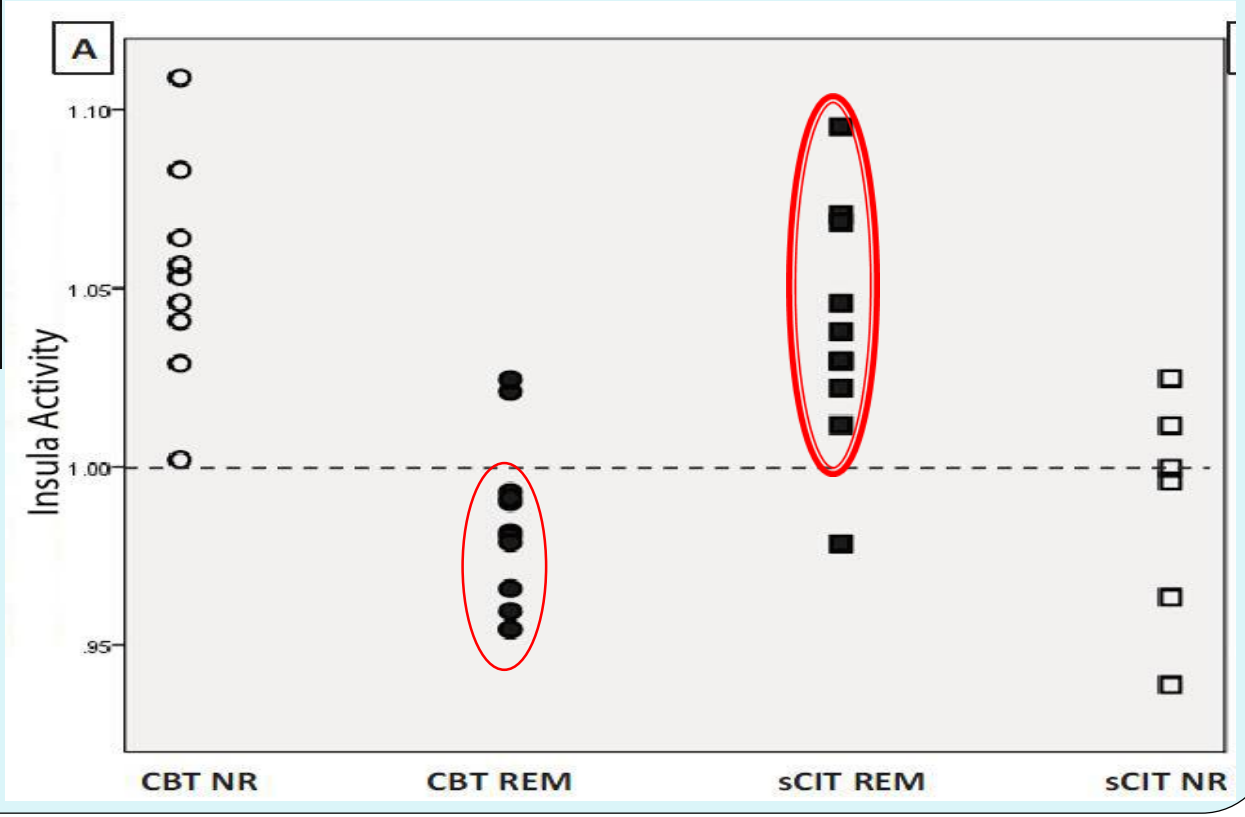
http://www.nimh.nih.gov/news/science-news/2013/scan-predicts-whether-therapy-or-meds-will-best-lift-depression.shtml



Mayberg:



http://www.nimh.nih.gov/news/science-news/2013/scan-predicts-whether-therapy-or-meds-will-best-lift-depression.shtml



Research on Adolescent Depression

- Aim: To identify whether neurobiological functioning is associated with favorable antidepressant response in adolescents with depression

  - Frontolimibic (rest and task) functioning at baseline will predict a decline in depressive symptoms

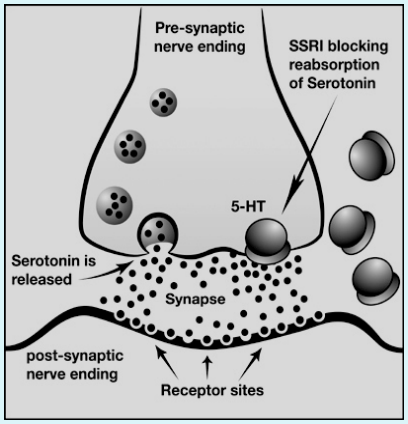
  - Neuroendocrine functioning at baseline will predict a decline in depressive symptoms

Klimes-Dougan, Cullen et al., in preparation

Antidepressant Intervention Pilot Study

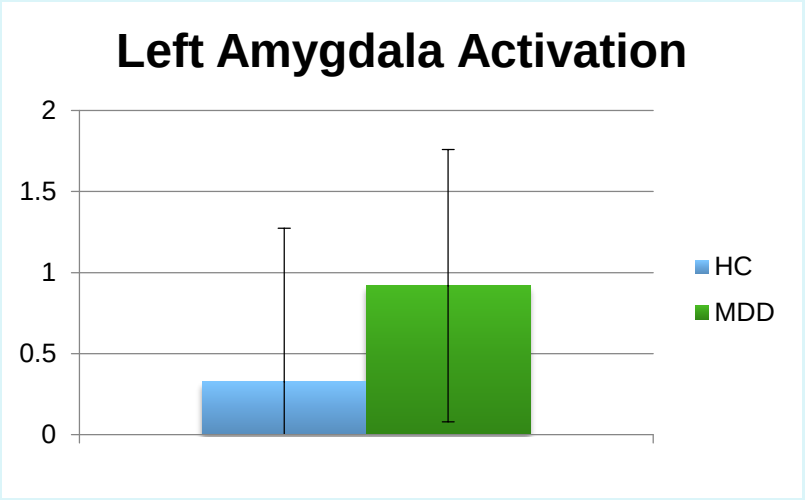
Baseline Demographic Characteristics	
N	13
Age (mean years, SD)	15.5, 2.3
Sex (male/female)	4/9 (69% female)
Right Handed-n(%)	12 (92%)
Ethnicity -n(%)	
Caucasian	13 (100%)
Hispanic	4 (31%)
Current Comorbidities -n(%)	9 (69%)
Attention Deficit and Hyperactive Disorder	3 (23%)
Generalized Anxiety Disorder	4 (31%)
Post-traumatic Stress Disorder	1 (8%)
Social Anxiety	1 (8%)
Dysthymia	1 (8%)
Specific Phobia	1 (8%)
Anxiety NOS	1 (8%)
Med-Naive-n(%)	11 (85%)
Duration of illness (mean months, SD)	15.5, 16.1
Global Assessment of Functioning (mean, SD)	55, 77
Positive Family History	11 (85%, n = 13)
CDRS-R (mean T-score, SD)	73.2, 7.3
BDI-II (mean, SD)	28.79.3 (n=13)

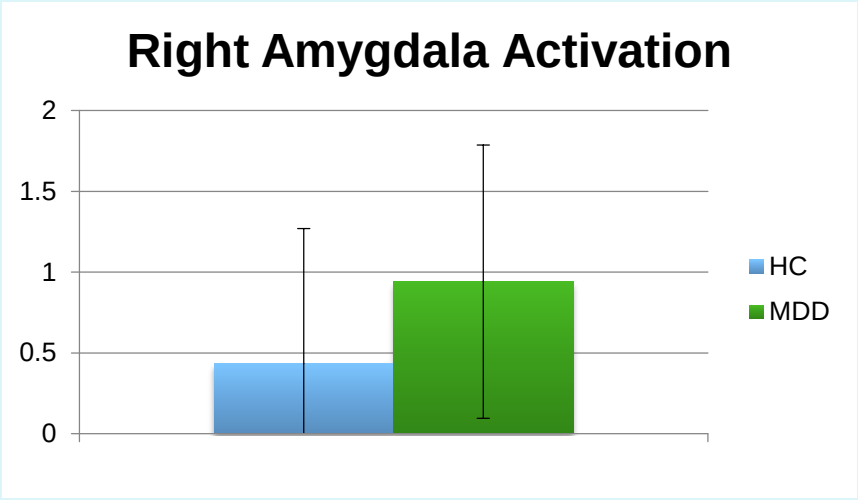
- 8 Week Trial of Antidepressant Medication (SSRIs)
- Baseline
  - Circuits
  - Neuropsych
  - Physiology

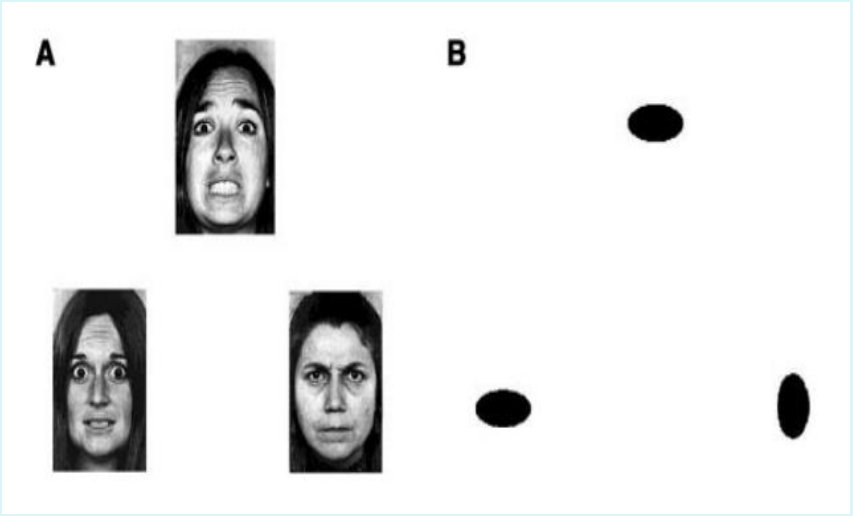


http://www.myhealthyfeeling.com/wp-content/uploads/2011/07/ssris2.jpg

Task Based fMRI Differences



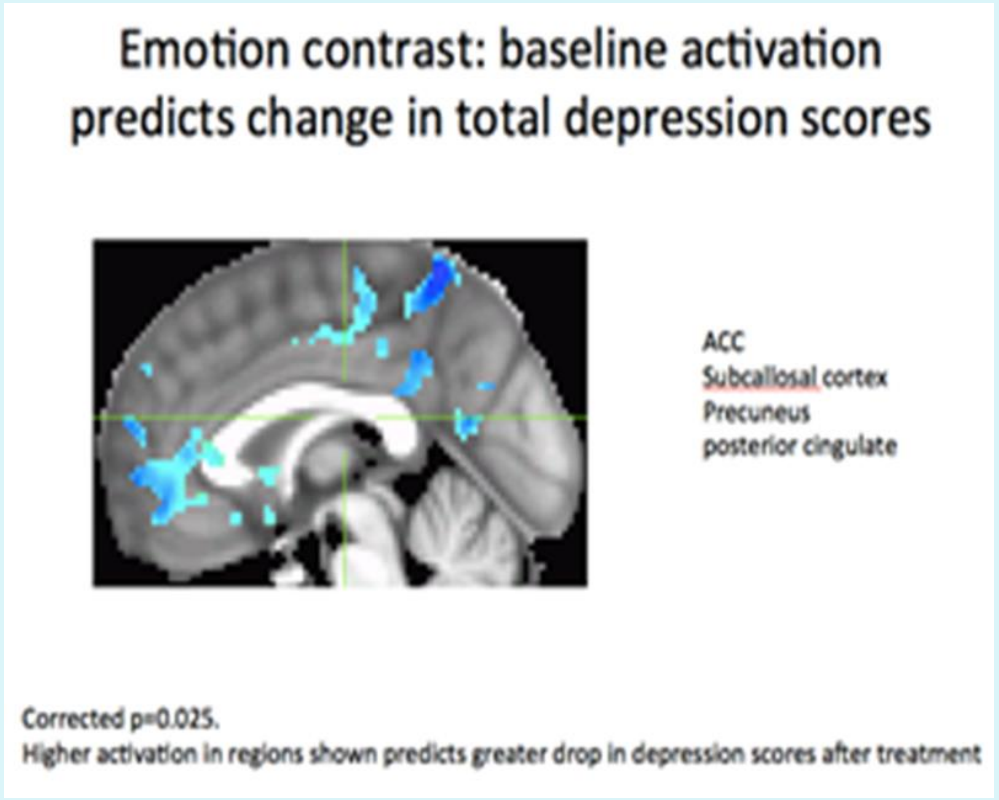


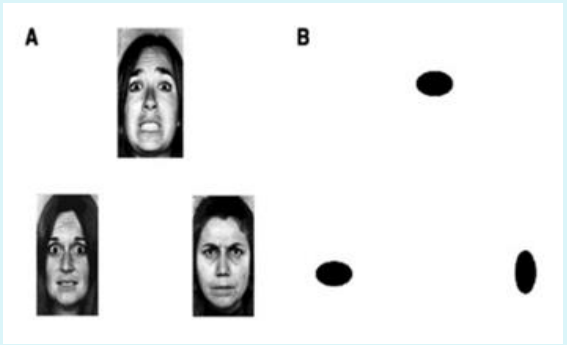


Klimes-Dougan, et al, 2014

Neurocircuits – SSRI Results

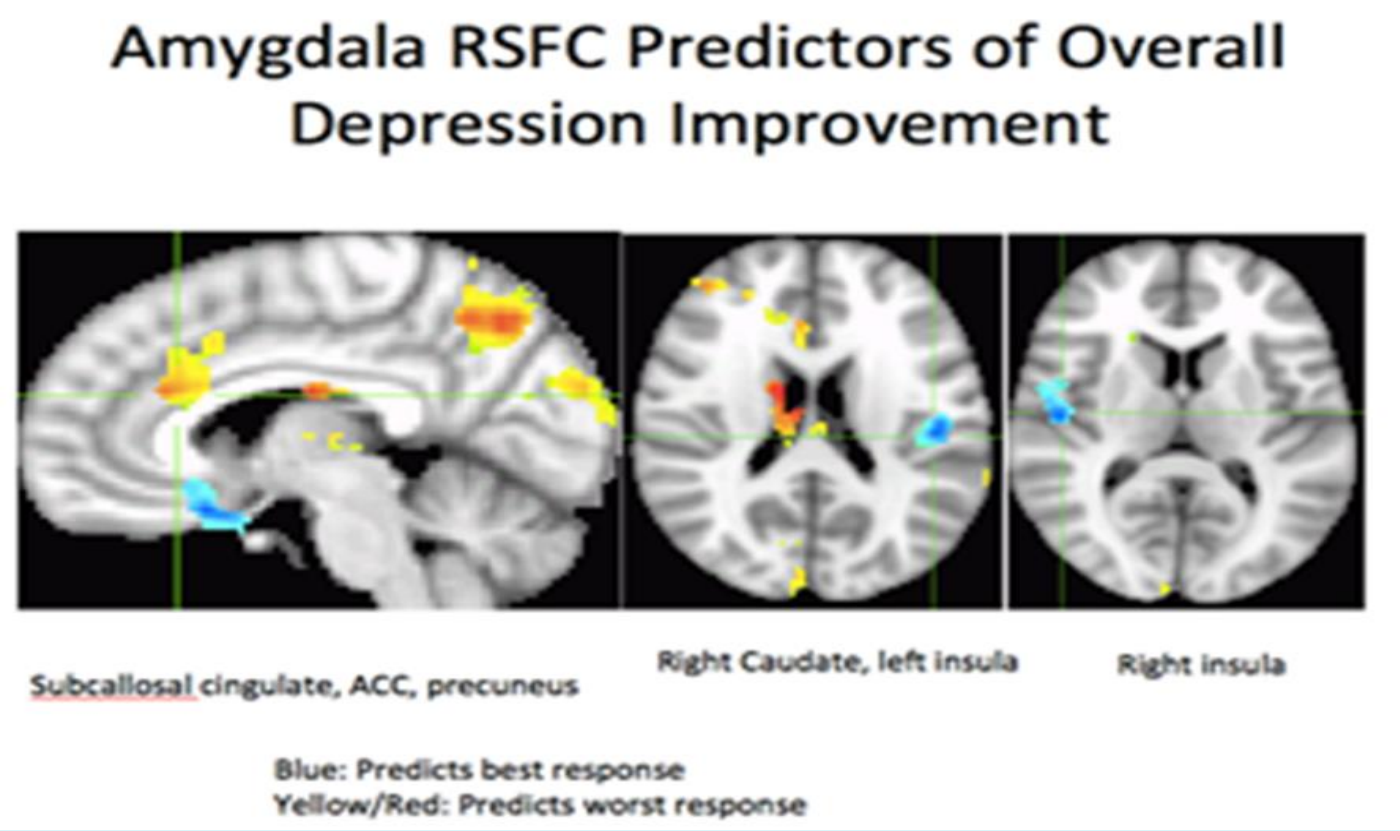
- Emotion task: Responders showed greater limbic activation (more different from HC) than non-responders.





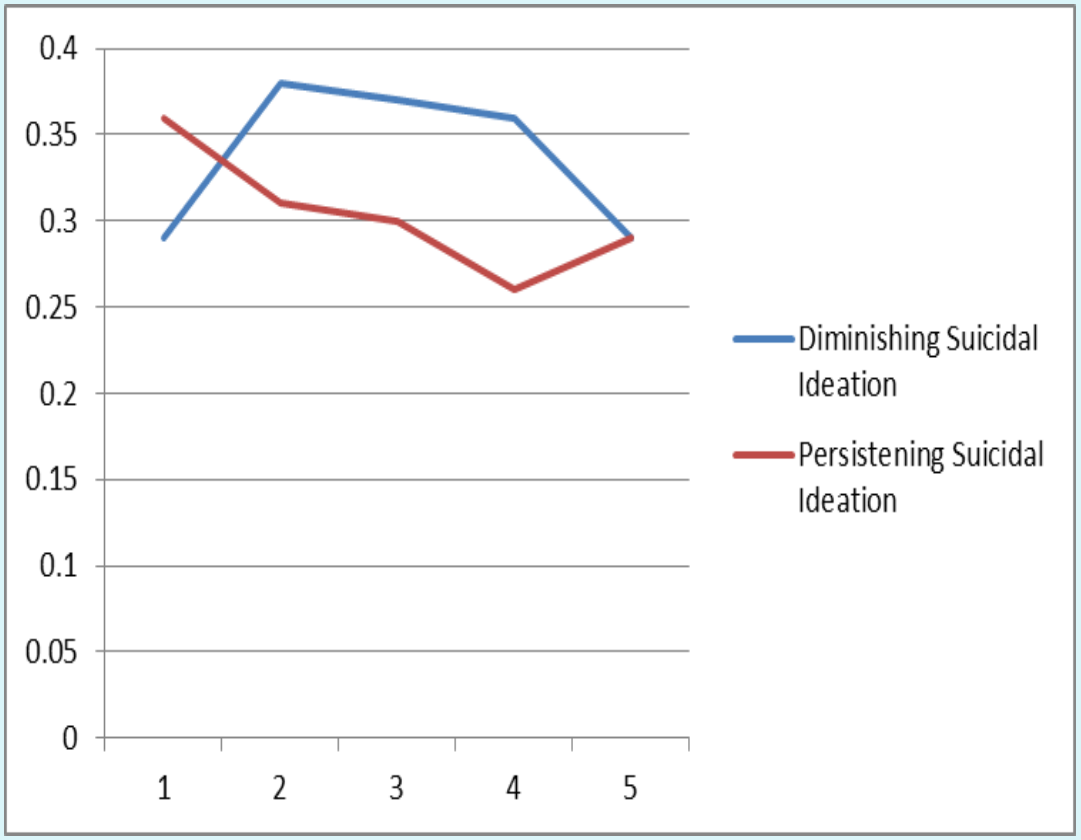
Klimes-Dougan, Cullen et al, in preparation

Neurocircuits – SSRI Results



Klimes-Dougan, Cullen et al., in preparation

Adolescents' Pre-Treatment Cortisol Trajectories Predict Suicide Ideation Patterns Across an 8-week trial of SSRIs



Klimes-Dougan, Cullen et al, in preparation

Summary and Conclusions

- The goal of this line of work it to provide some practical solutions for determining who will respond best from which treatment.
  - Identify Biological Predictors
    - Brain functioning
    - Physiological functioning
    - Genetic functioning
- Cautions
  - How predictive of treatment response?
  - How feasible would these procedures be?

- EXCITING POSSIBILITIES!!!

Acknowledgements

Adolescent MDD Studies

Kathryn Cullen, M.D.
Kelvin Lim, M.D.
Bryon Mueller, Ph.D.
Meredith Gunlicks-Stoessel, Ph.D.

Research on Adolescent Depression (RAD) Lab

Leah Jappe Hall, Ph.D.
Melinda Westlund Schreiner, ABD
Michelle Thai, B.A.
Many other graduate and undergraduate students

FUNDING: NIMH, NARSAD, Engdahl Family Research Fund, UMN-GIA, DPOWH, MMF, CNBD (No conflicts of interest)

Thank You!

Ongoing Recruitment of Studies: University of Minnesota

•Ketamine: • **Study Coordinator: Palistha Amatya** • **Email: amaty008@umn.edu** • **Phone: 612-626-8534** • Ketamine infusion efficacy for 12-18 year olds with treatment resistant depression	**•Mood:** • **Study Coordinator: Nathan Horek** • **Email: nahorek@umn.edu** • **Phone: 612-626-7635** • Neurological functioning of 13-18 year olds with a diagnosis of a bipolar disorder, depressive disorder, or mood disorder not otherwise specified
•TMS: • **Study Coordinator: Palistha Amatya** • **Email: amaty008@umn.edu** • **Phone: 612-626-8534** • Transcranial Magnetic Stimulation for 12-18 year olds with treatment resistant depression	**•BRIDGES:** • **Study Coordinator: Palistha Amatya** • **Email: kamp0182@umn.edu** • **Phone: 612-626-8534** • Brain development in young adolescent girls (12-14 years old) with and without a history of self-injury
•High Field: • **Study Coordinator: Nathan Horek** • **Email: nahorek@umn.edu** • **Phone: 612-626-7635** • High-field brain imaging in 13-17 year old adolescents with Major Depressive Disorder	HEALTHY CONTROLS: AGES 12 to 19