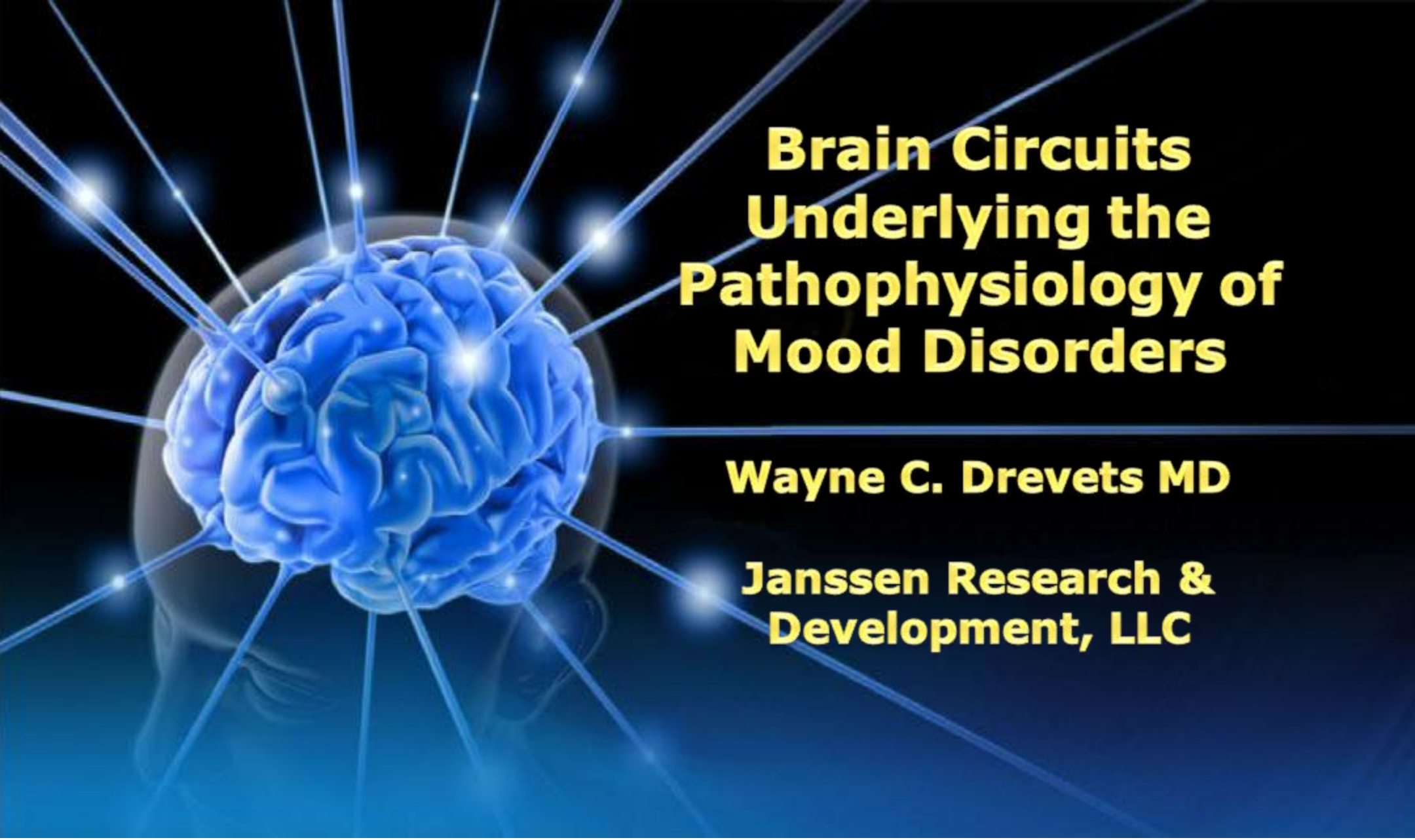


Brain Circuits Underlying the Pathophysiology of Mood Disorders

Wayne C. Drevets MD

Janssen Research & Development, LLC

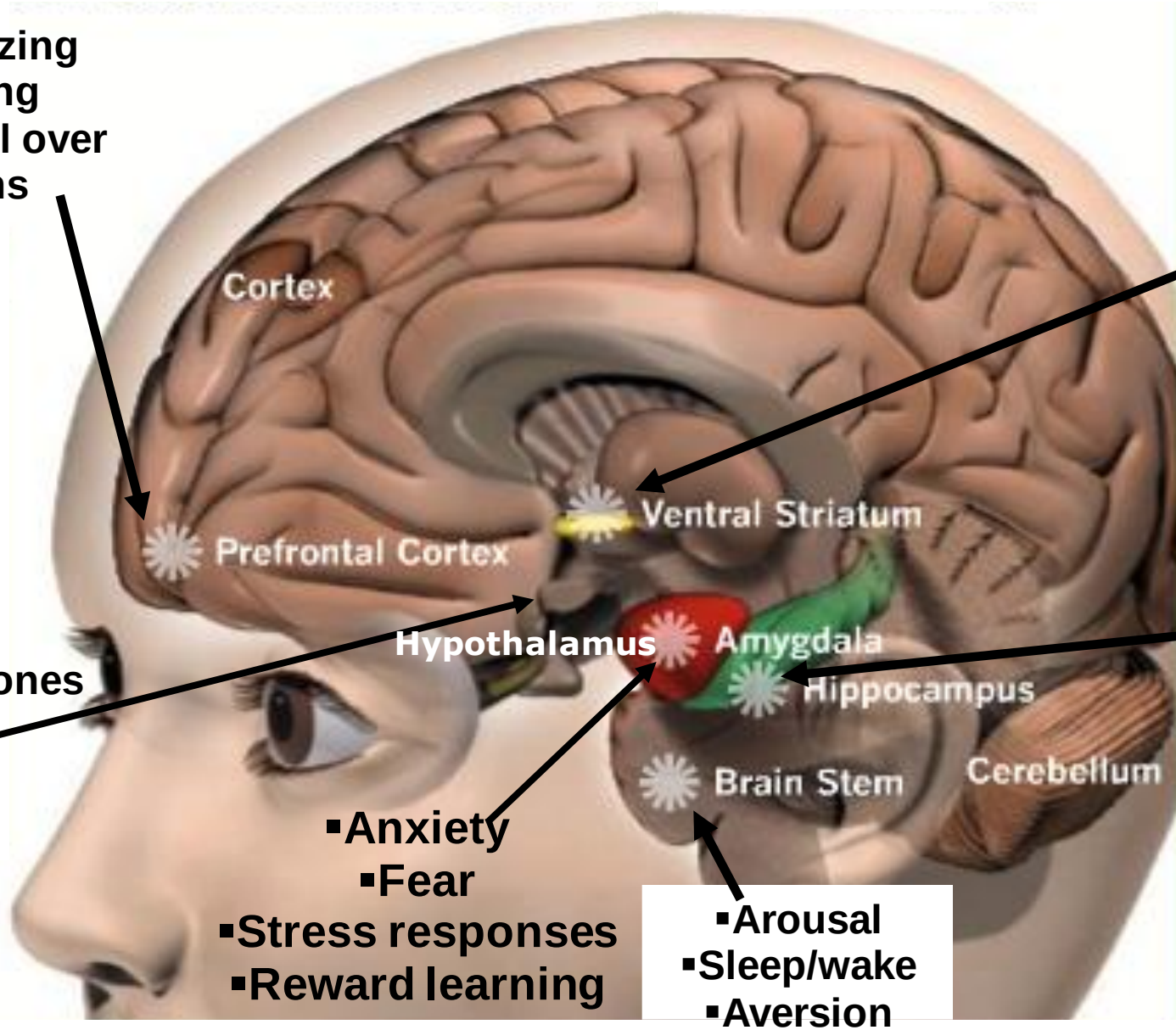
Presenter's Disclosure of Interest

Presenter: Wayne C. Drevets, M.D.

- Sources of Current or Past Research Support
  - NIMH, MRC
  - Janssen Research & Development, LLC
  - NARSAD (BBRF)
  - Stanley Medical Research Institute
  - William K. Warren Foundation
  - Wellcome Trust
- Current Employment and Equity Interest
  - Janssen Research & Development, LLC , one of the Pharmaceutical Companies of Johnson & Johnson

Note: This presentation contains personal views and opinions which may not represent those of my employer or its affiliates.

Brain Regions Involved in Mood Disorders



- Organizing
- Planning
- Control over emotions

- Pleasure
- Motivation
- Anxiety

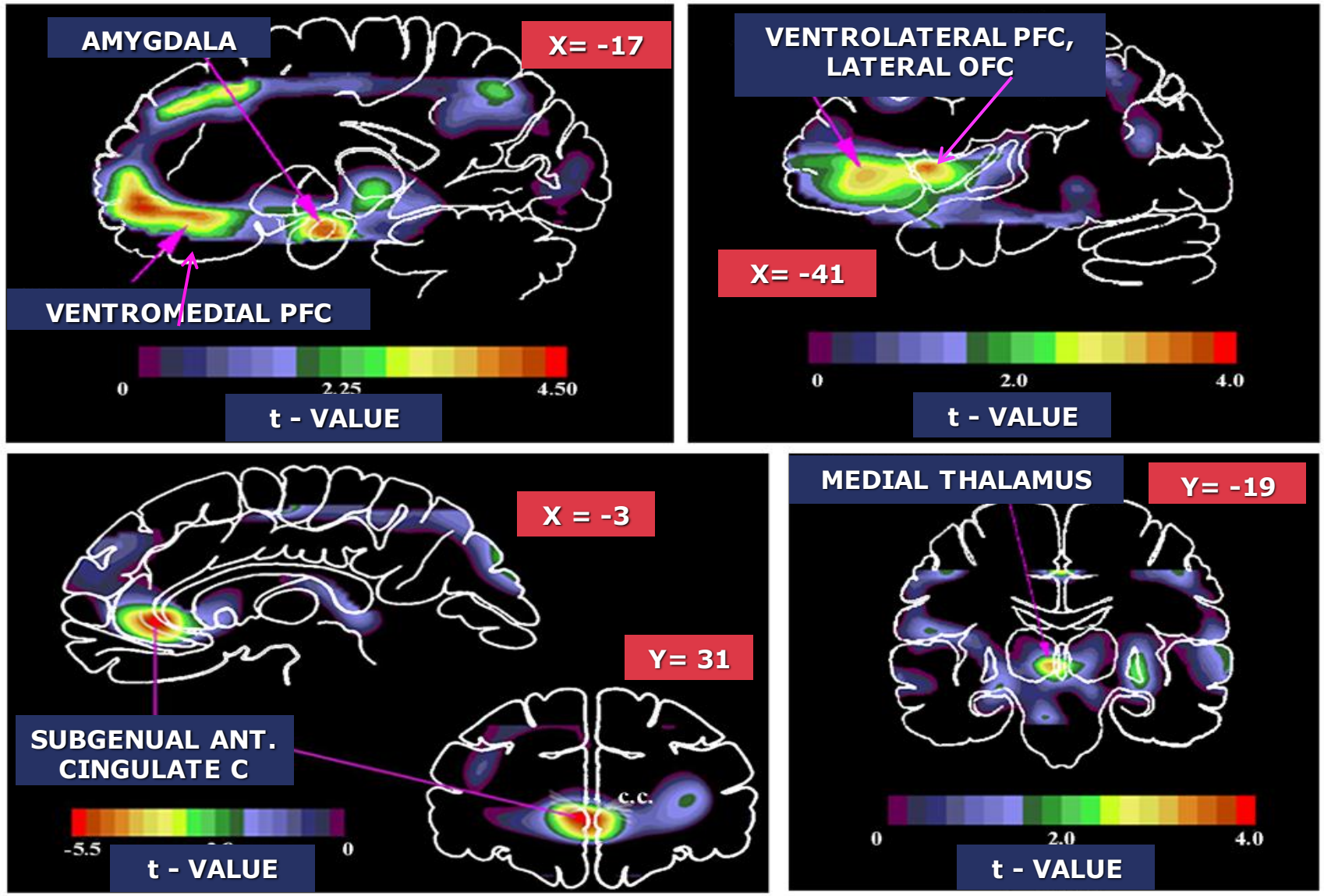
- Stress hormones
- Sleep
- Appetite
- Energy

- Memory
- Stress response
- Context

- Anxiety
- Fear
- Stress responses
- Reward learning

- Arousal
- Sleep/wake
- Aversion
- Reward

Areas of Abnormal Flow and Metabolism in MDD

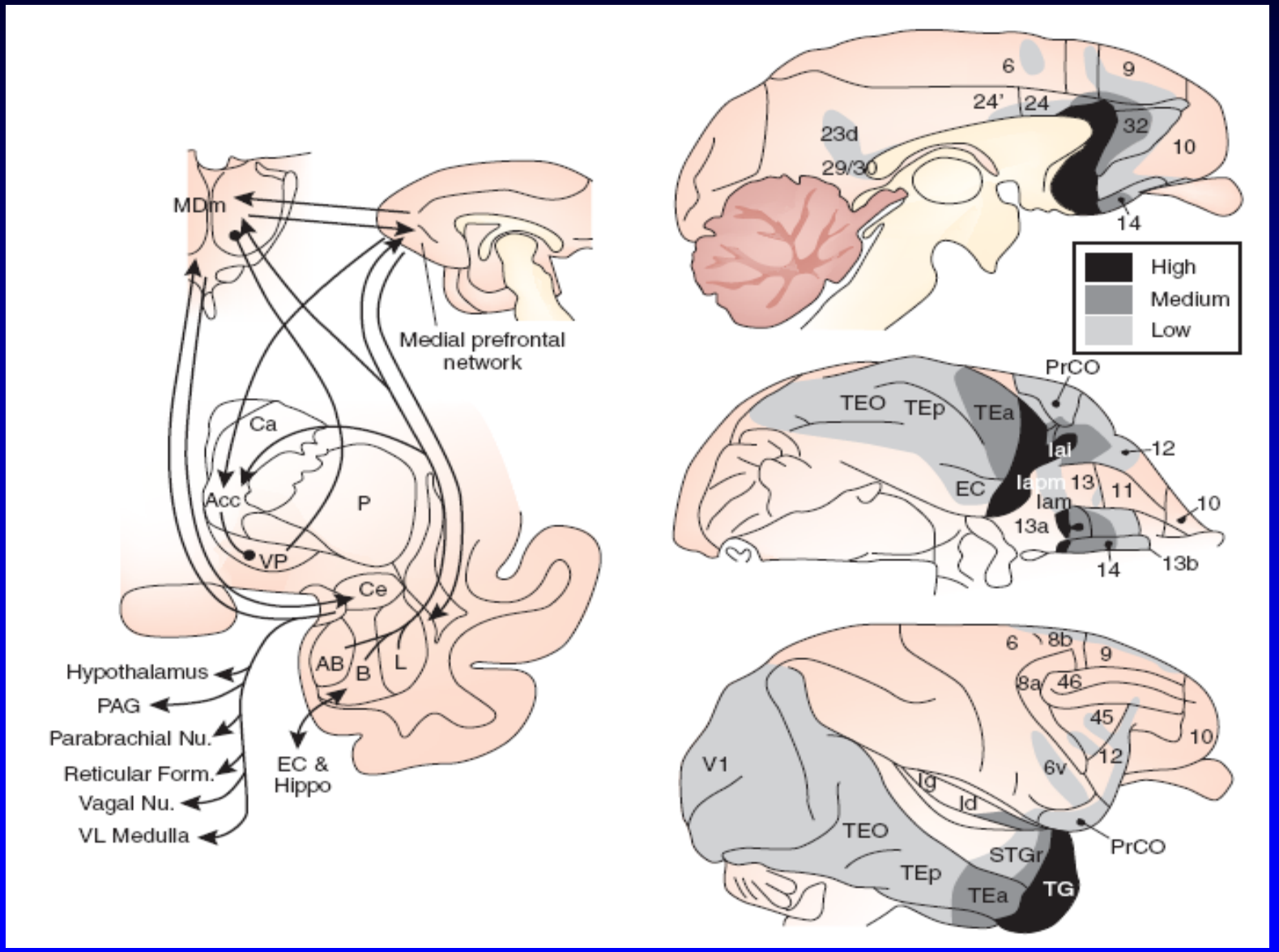


Drevets WC. Annual Reviews in Medicine 1998; 49:341-61

Summary of Amygdala efferent projections

Left: amygdaloid circuits involving the striatum, pallidum, thalamus and PFC, and output to the hypothalamus and brainstem.

Right: Areas of cerebral cortex that receive axonal projections from the amygdala.

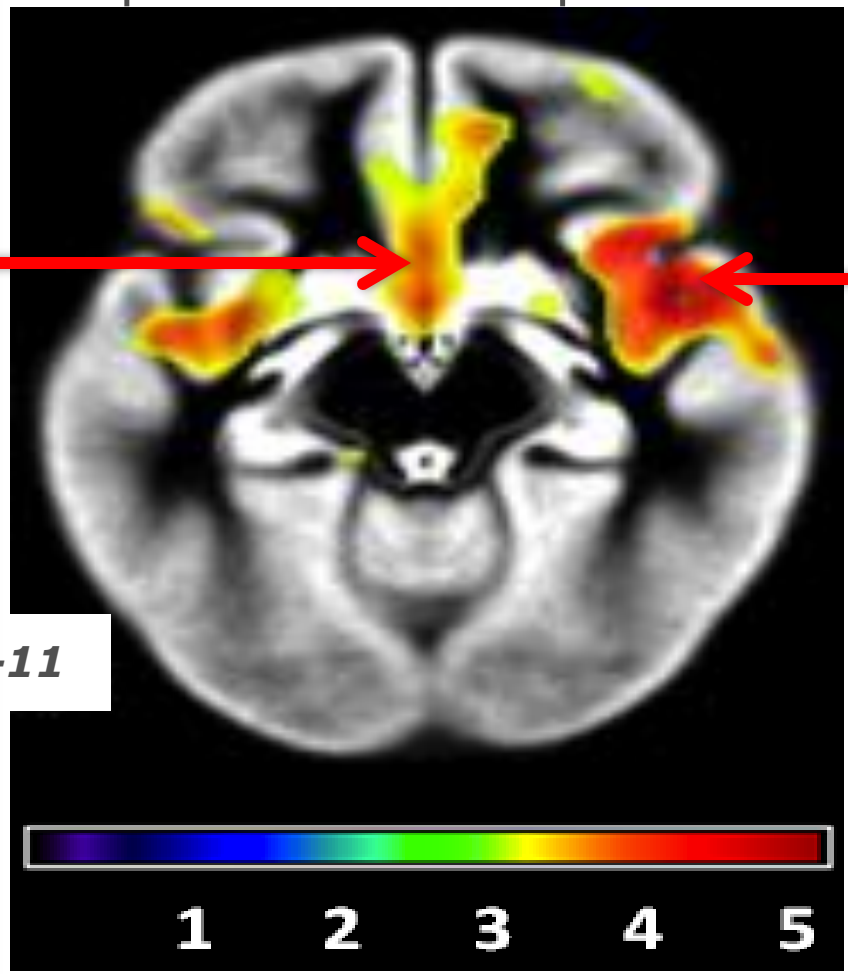


Amaral D, et al. 1992; Price JL, Drevets WC, NPP Reviews, 2009

Target for Course Modification in MDD? – More persistent disabling illness associated with grey matter loss in corticolimbic networks

Voxel-Based Morphometry: Reduced gray matter in chronic/ highly recurrent depression versus persistent remission

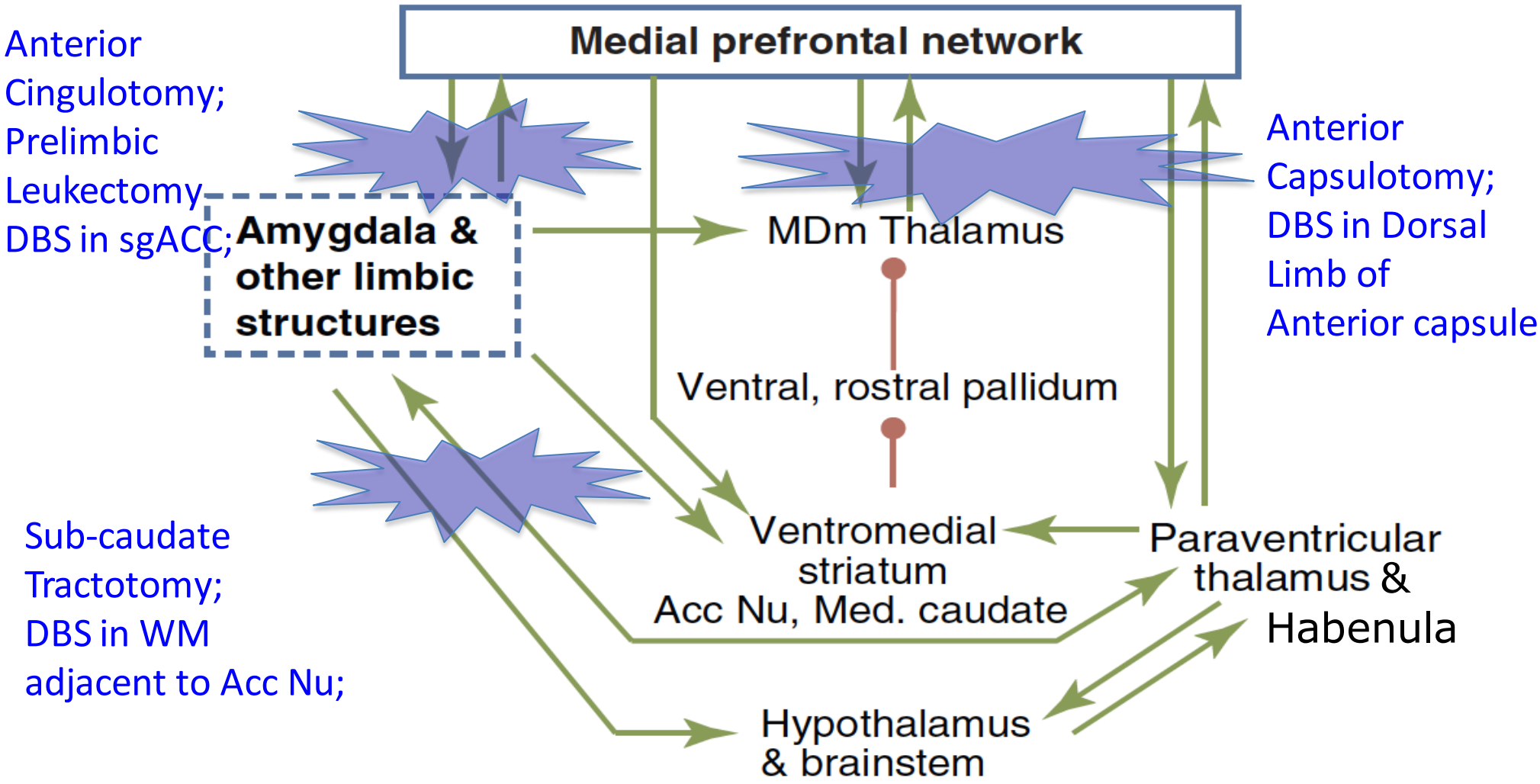
Subgenual Anterior Cingulate Cortex



Anterior Temporal cortex

Salvadore G, et al. NeuroImage, 2011; 54(4):2643-51

Neurocircuitry of Mood Disorders, Neurosurgical Sites for Tx refractory MDD

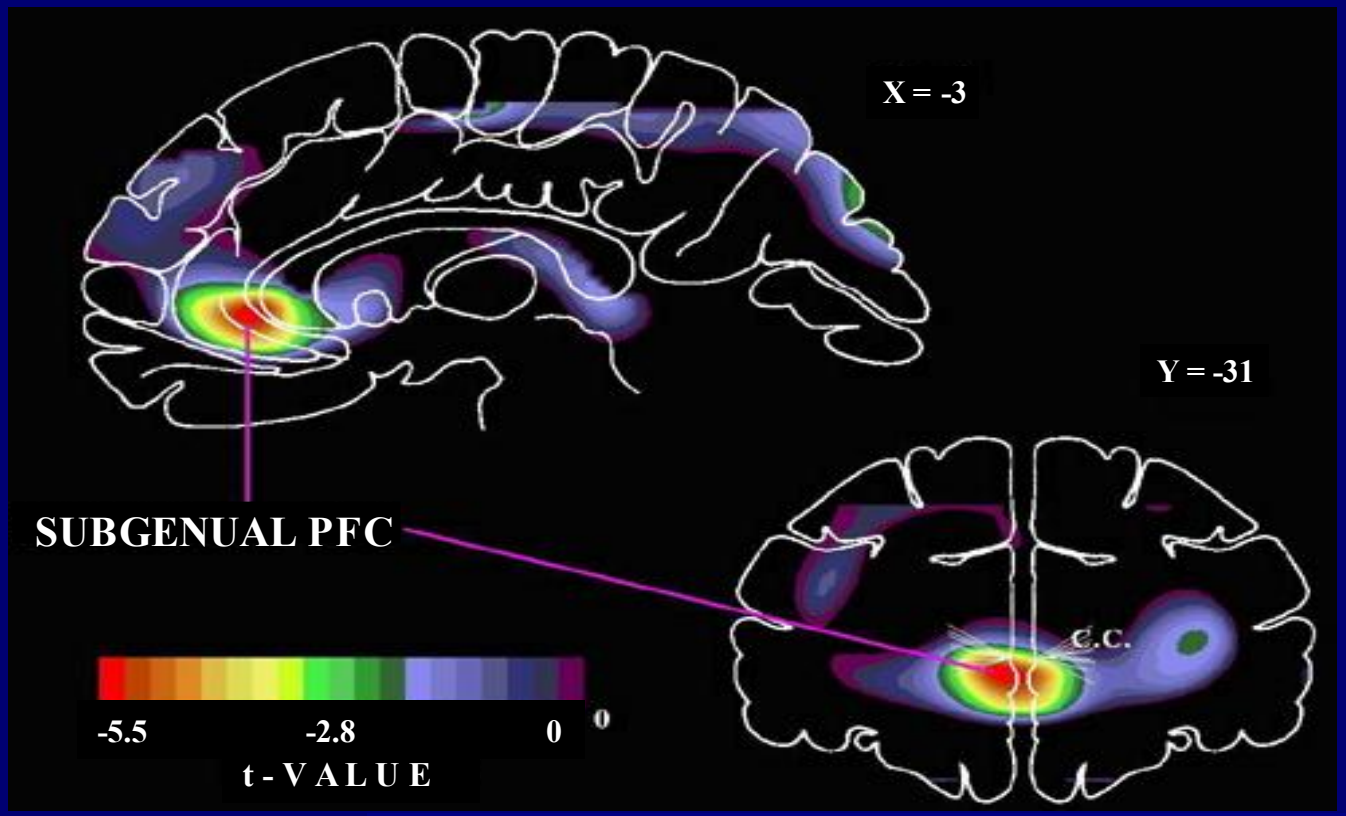


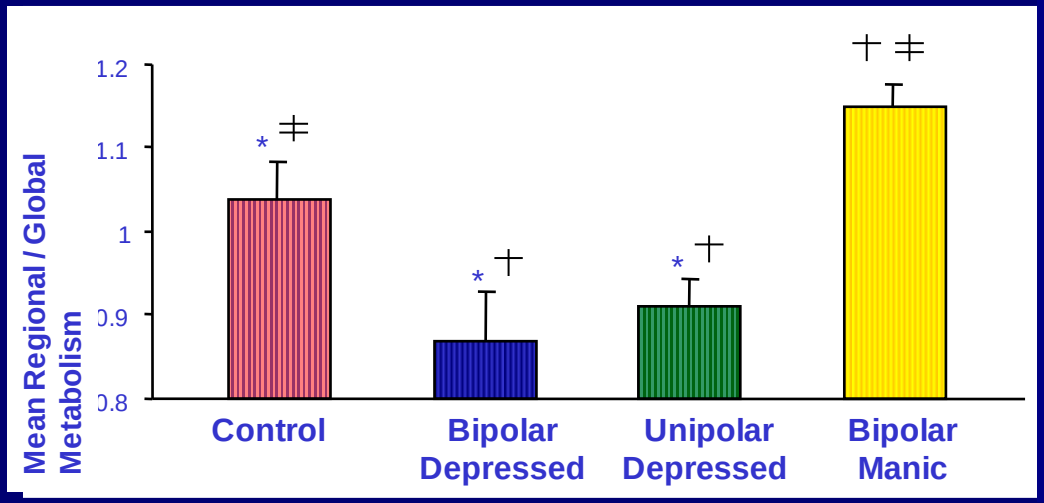
Modified from Price JL, Drevets W; TICS, 2012

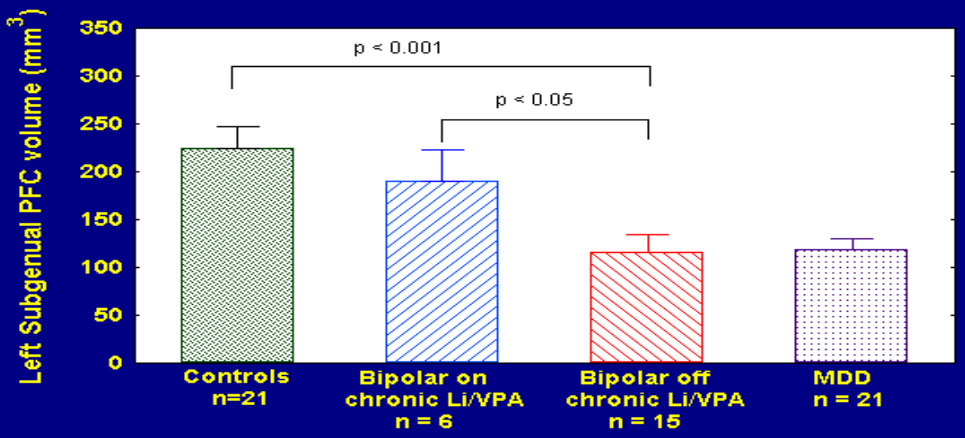
TRENDS in Cognitive Sciences

Persistent Reduction in Metabolism Pinpoints Corresponding Reduction in Cortex Volume

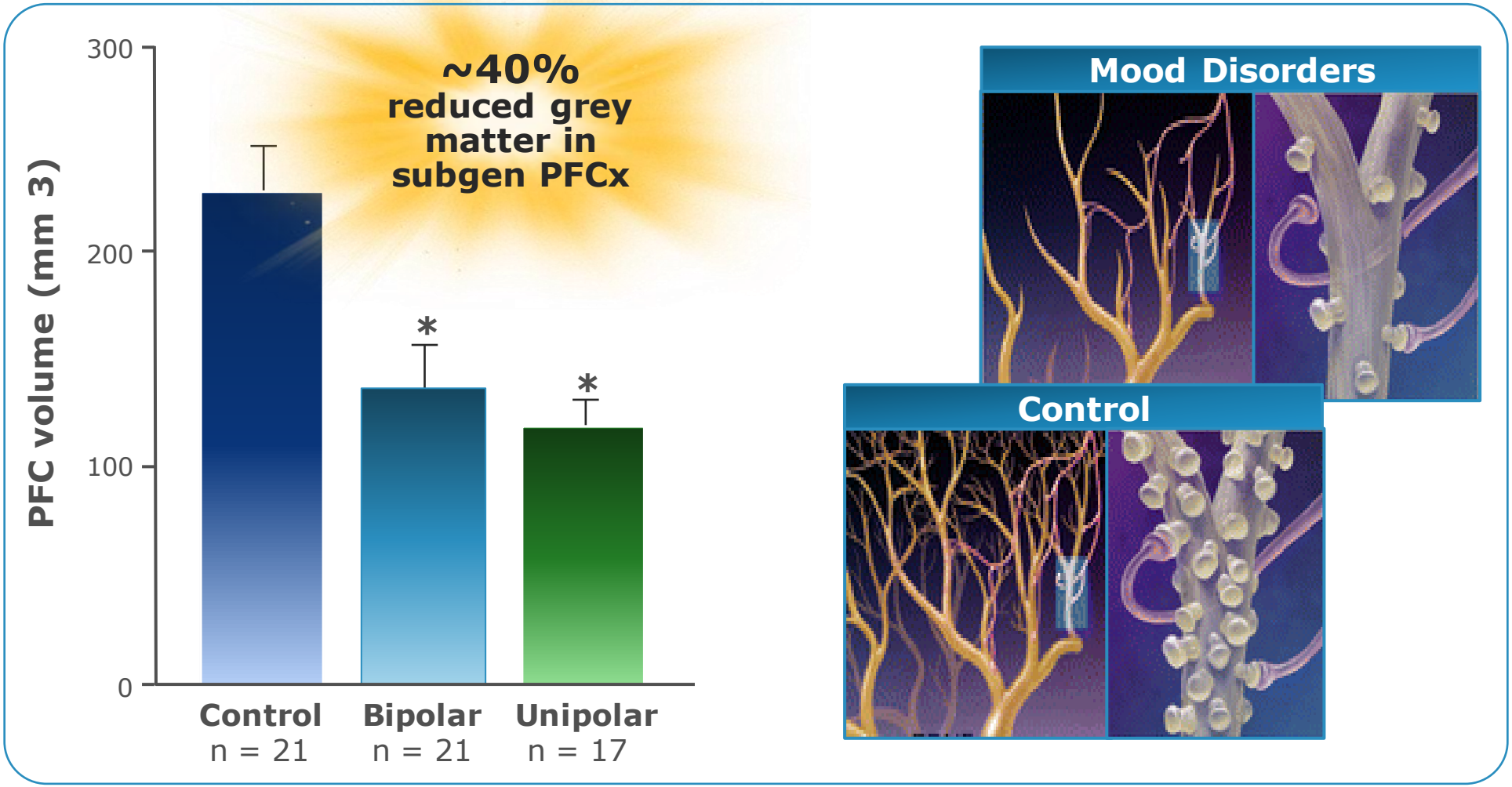
Drevets et al;
Nature 1997







Recurrent Mood Disorders Show Dendritic Atrophy in Stress Related Brain Regions (e.g., medial PFC, hippocampus)

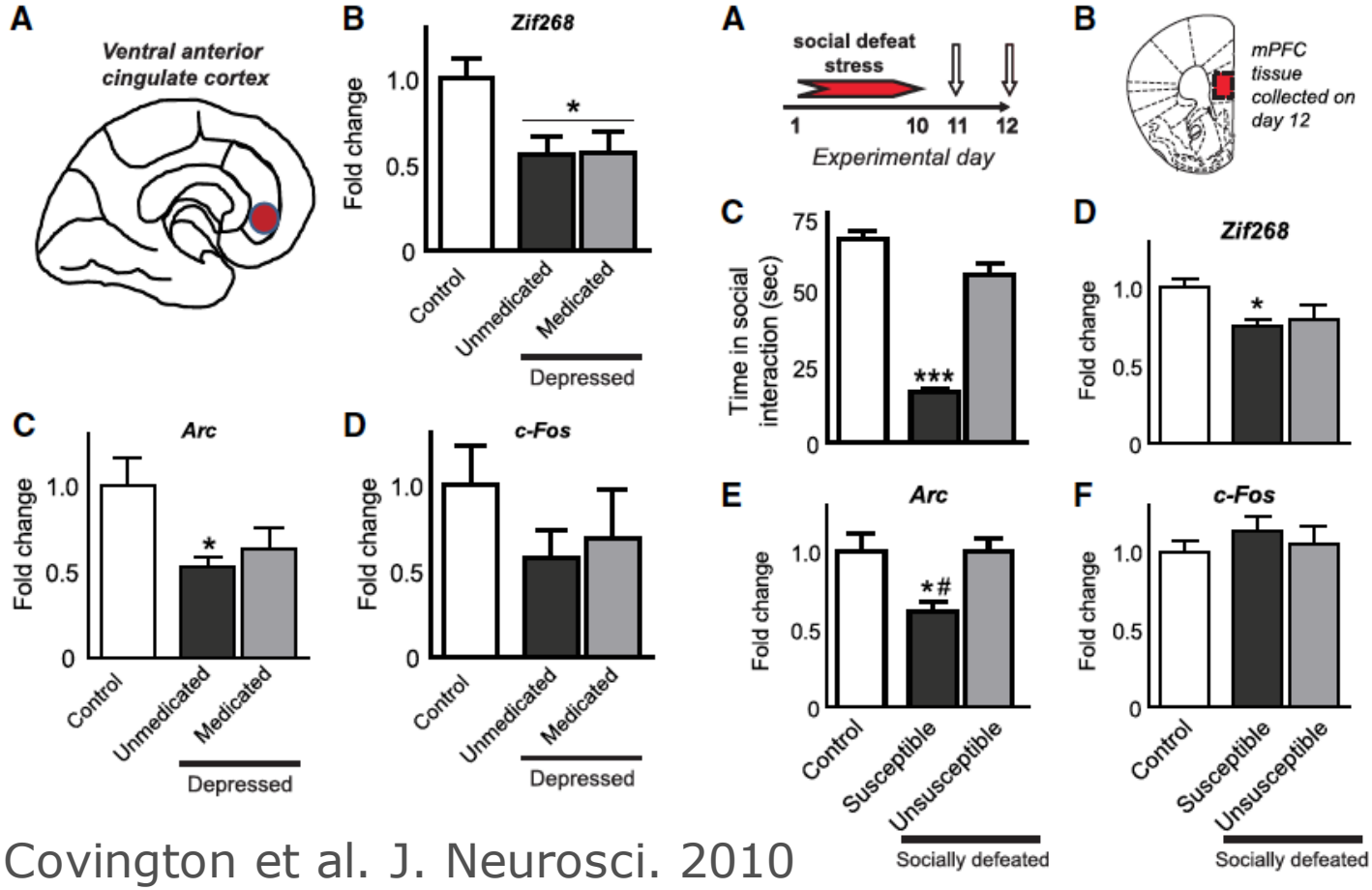


Drevets et al *Nature*, 1997

Nestler et al, *Nature Neuroscience*

mPFC Activity a Key Determinant of Depression-like Behavior

(*LEFT*) Reduced expression of immediate early genes (IEG), zif268 (egr1), c-fos and arc, in ventral ACC (BA 24sg) of clinically depressed humans (postmortem), consistent with deficit in regional neuronal activity. (*RIGHT*) Mice subjected to chronic social defeat stress exhibit similar reductions in IEG expression in mPFC (though some changes not seen in defeated mice that escape the deleterious consequences of stress, i.e., resilient animals).



Covington et al. J. Neurosci. 2010

mPFC Activity a Key Determinant of antidepressant responses

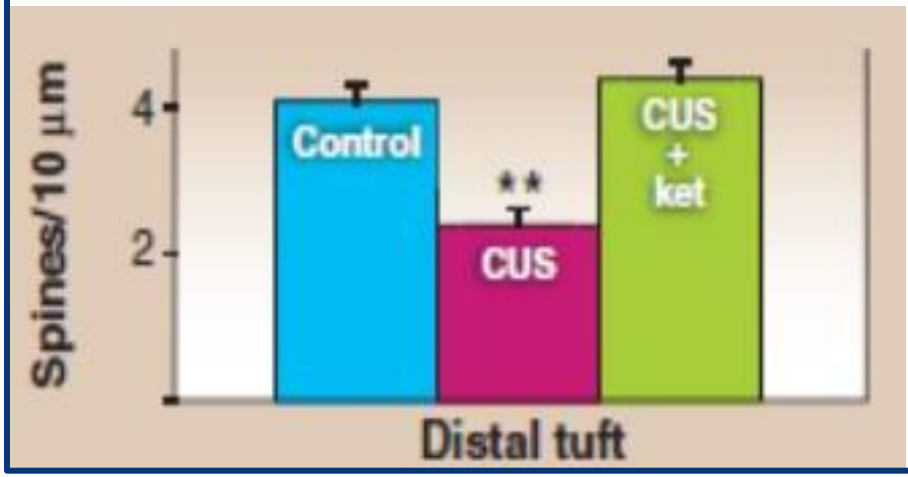
Method: Optogenetically drive "burst" patterns of cortical firing *in-vivo* using viral vectors to overexpress channel rhodopsin 2 (a light-activated cation channel) in mouse ventral mPFC

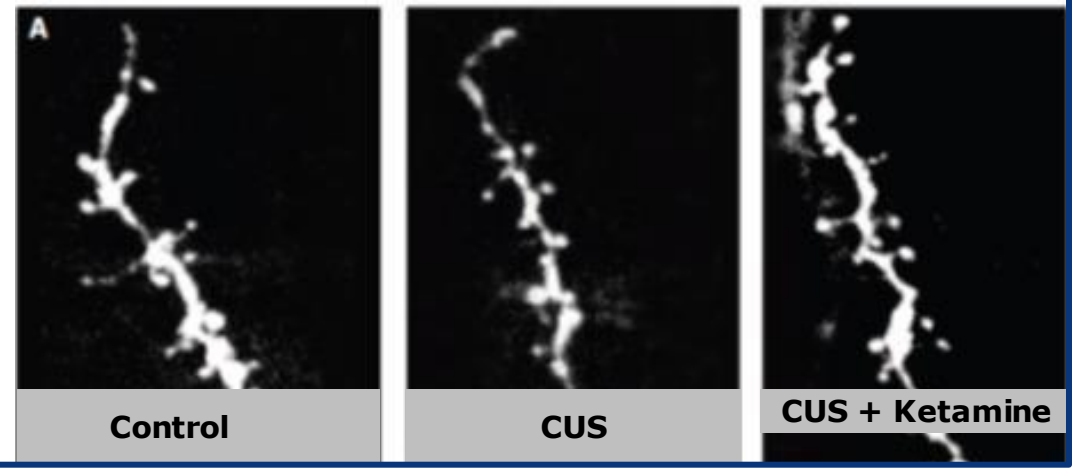
Result: In mice expressing a depressive-like phenotype, optogenetic stimulation of mPFC exerted antidepressant-like effects, without affecting general locomotor activity, anxiety-like behaviors, or social memory.

Covington et al J Neurosci 2010

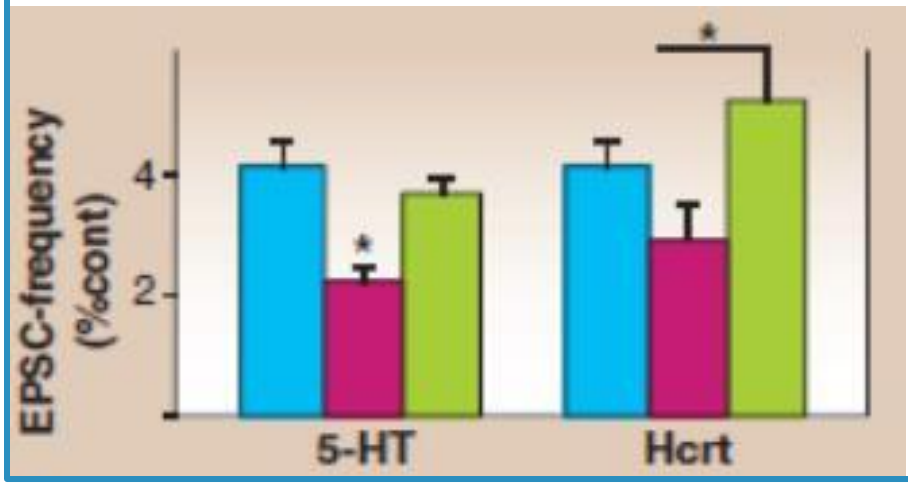
Chronic unpredictable stress (CUS) exposure decreases spine density in medial PFC, changes rapidly reversed by ketamine within 24 hrs

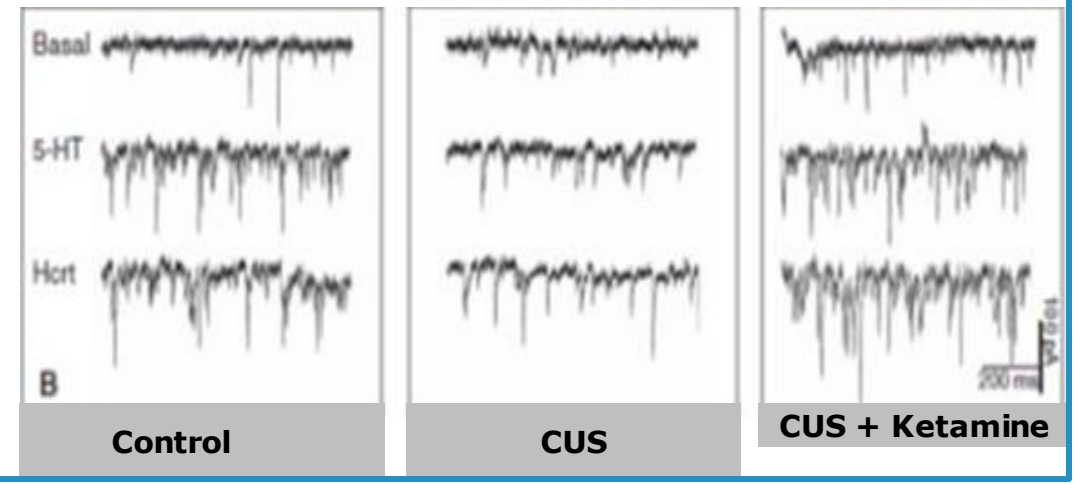
High magnification projections of distal segments of the layer V pyramidal cell apical tuft dendrites





Decreased EPSC responses in PFC layer V pyramidal cells show rapid reversal by ketamine





Meta-Analysis of ketamine (single dose, 0.5 mg/kg IV) shows rapid antidepressant effect 24h post dose, with attenuation by one week

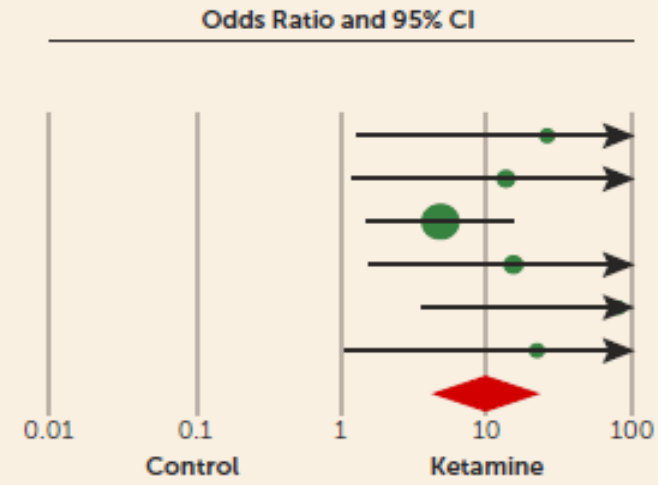
FIGURE 2. Forest Plots of Therapeutic Response Rates One Day and One Week After Initiation of Ketamine[a]

Results one *day* post ketamine

A

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	26.053	1.359	499.339	2.164	0.030
Lapidus et al. (84)	13.600	1.238	149.455	2.134	0.033
Murrough et al. (87)	4.833	1.578	14.803	2.759	0.006
Sos et al. (91)	15.294	1.610	145.305	2.374	0.018
Zarate et al. (88)	79.545	3.762	1681.833	2.811	0.005
Zarate et al. (86)	22.176	1.133	434.158	2.042	0.041
	9.865	4.366	22.293	5.503	0.000

Statistics for Each Study

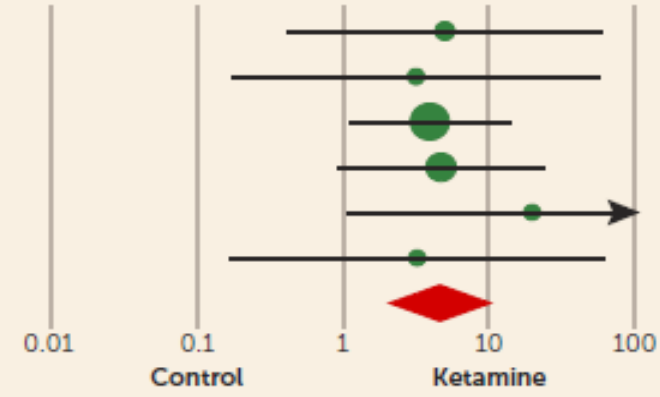


Results one *week* post ketamine

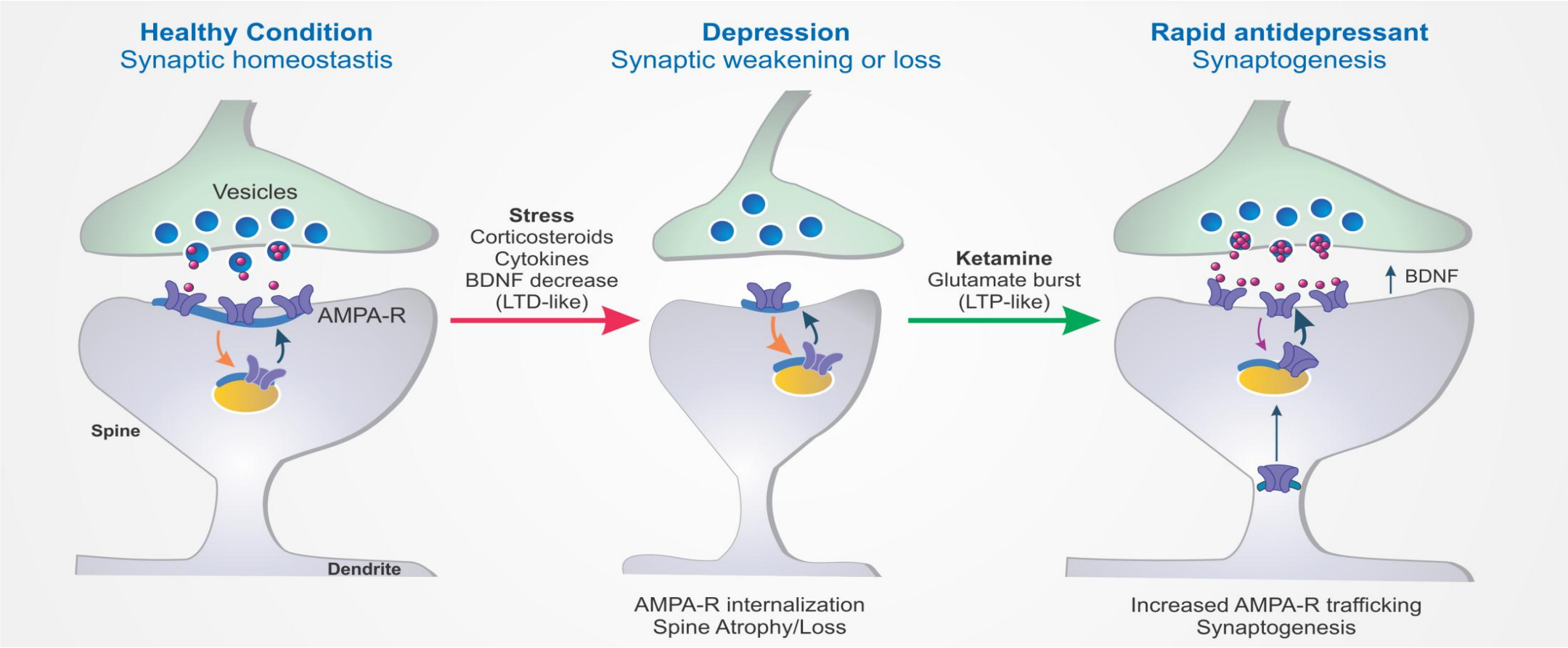
B

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	5.000	0.426	58.636	1.281	0.200
Lapidus et al. (84)	3.171	0.179	56.222	0.787	0.431
Murrough et al. (87)	3.937	1.149	13.492	2.181	0.029
Sos et al. (91)	4.706	0.950	23.302	1.898	0.058
Zarate et al. (88)	19.783	1.060	369.109	1.999	0.046
Zarate et al. (86)	3.222	0.176	58.849	0.789	0.430
	4.610	2.076	10.236	3.754	0.000

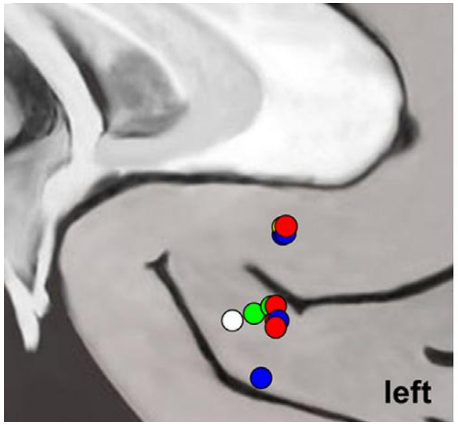
Statistics for Each Study

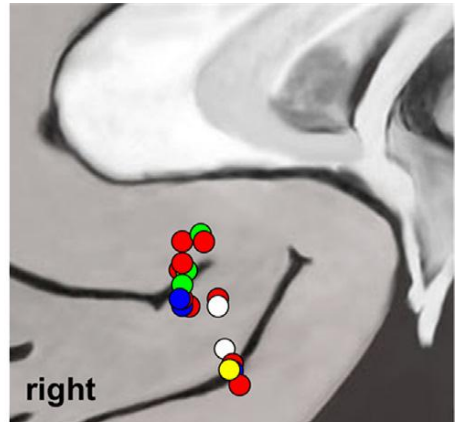


Synaptic Loss in Depression Countered by Synaptogenesis During Treatment with Ketamine



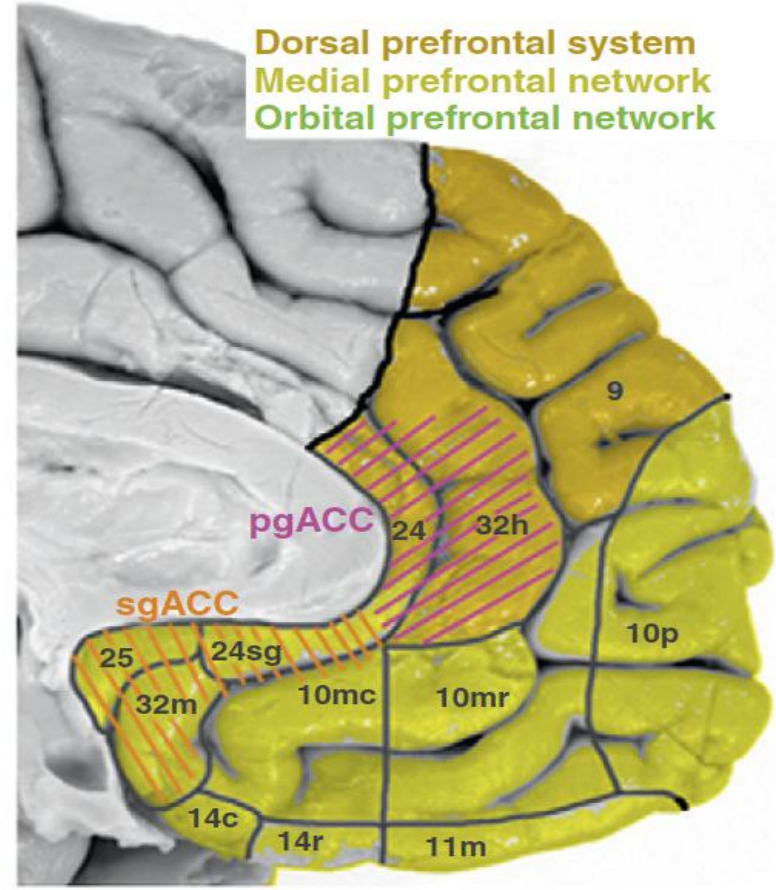
Subgenual (subcallosal) PFC loci for emotion processing and DBS





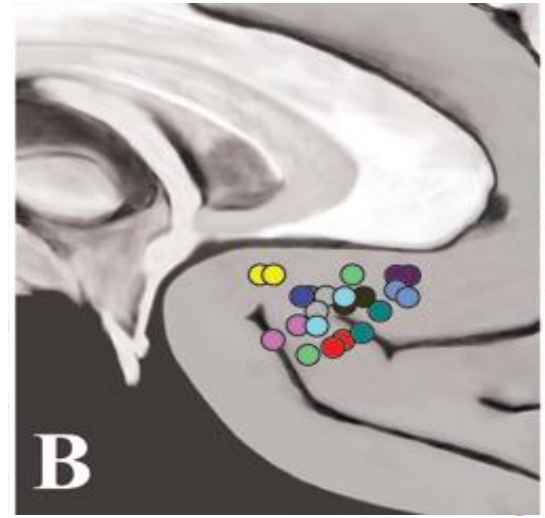
Microelectrode recording site for each emotion category responsive neuron. Red-disturbing, blue-sad, white-neutral, yellow-happy), green-exhilarating.
Laxton et al. Biol Psych 2013

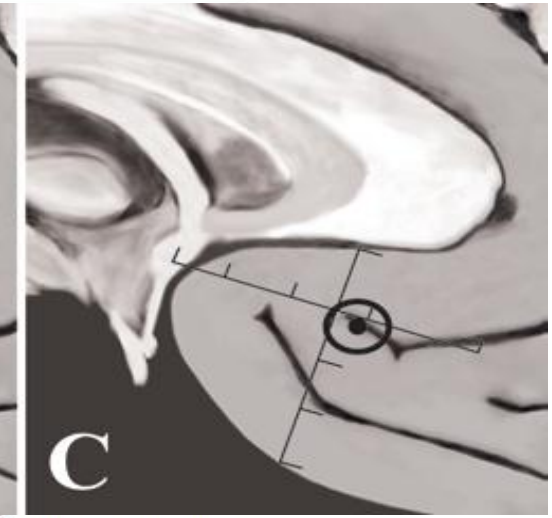
Loci of electrode contacts loci in patients who responded to DBS *(*procedure was bilateral, so 2 circles of same color for each patient). C: Average location of active contact in responders (+SD).
Hamani et al. J Neurosurgery 2009



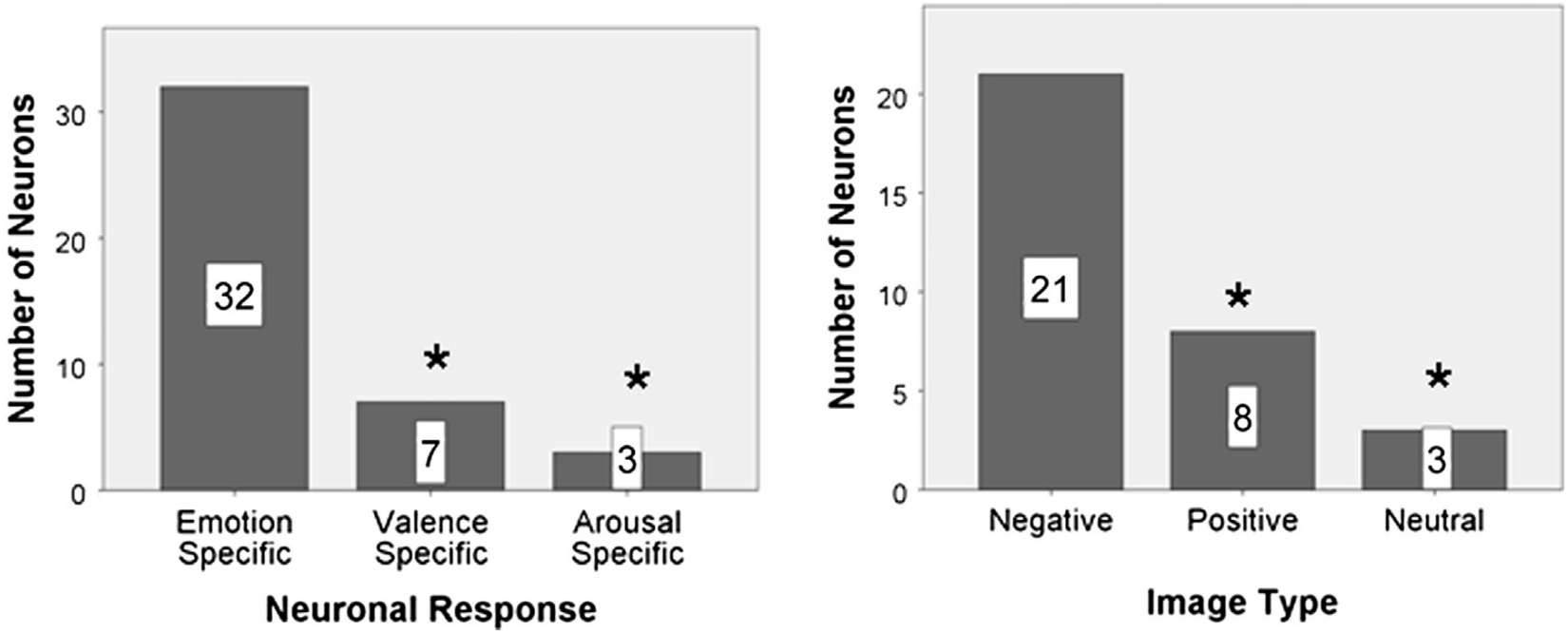
Medial surface of human brain subgenual (sgACC & pregenual (pgACC) anterior cingulate C

Price & Drevets, TICS, 2012





Neuronal Coding of Implicit Emotion Categories in Subgenual (Subcallosal) PFC in Depressed Patients

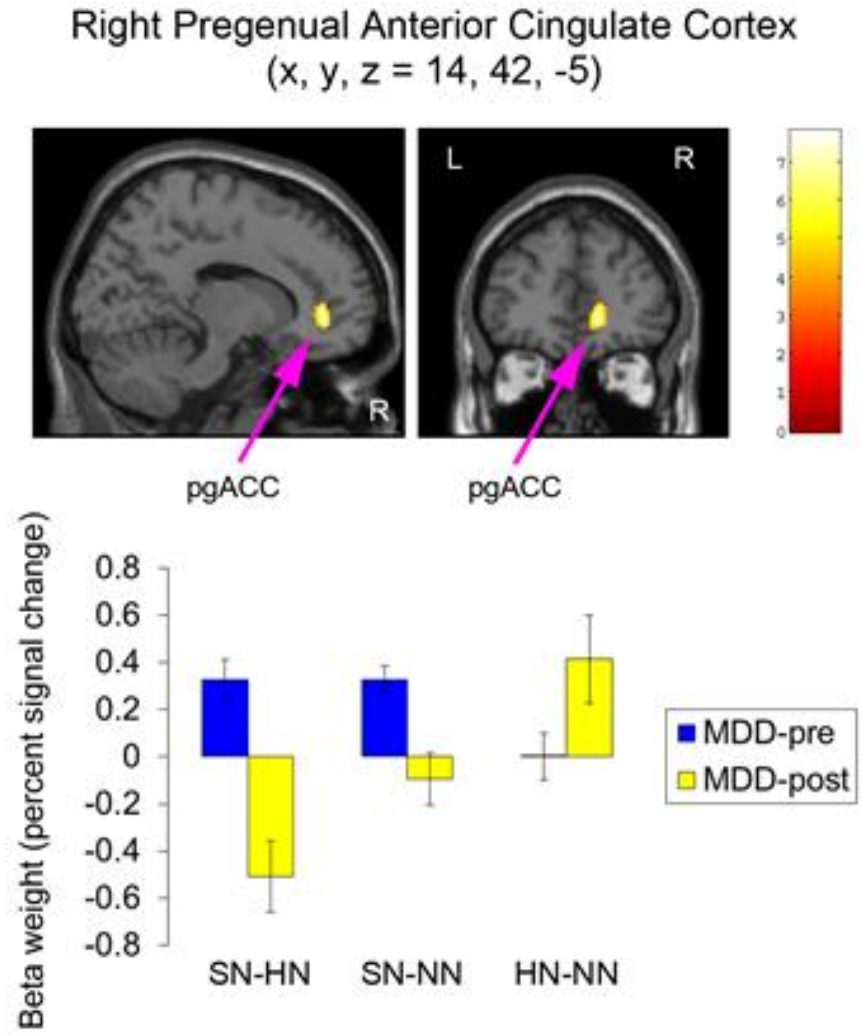


(A) Responsive neurons of sgACC and adjacent vmPFC show specificity for complex emotion categories rather than valence or arousal alone (*p<.001). (B) Preferential responsiveness for negative emotion categories over positive or neutral categories (*p <.001).

56/136 neurons responded to IAPS stimuli, of which 32 responded to a single emotion category, of which 44% responded to disturbing, 22% to sad, 9.4% to neutral, 9.4% to happy images, 16% to exhilarating images. *Laxton et al. Biol Psychiatry, 2013*

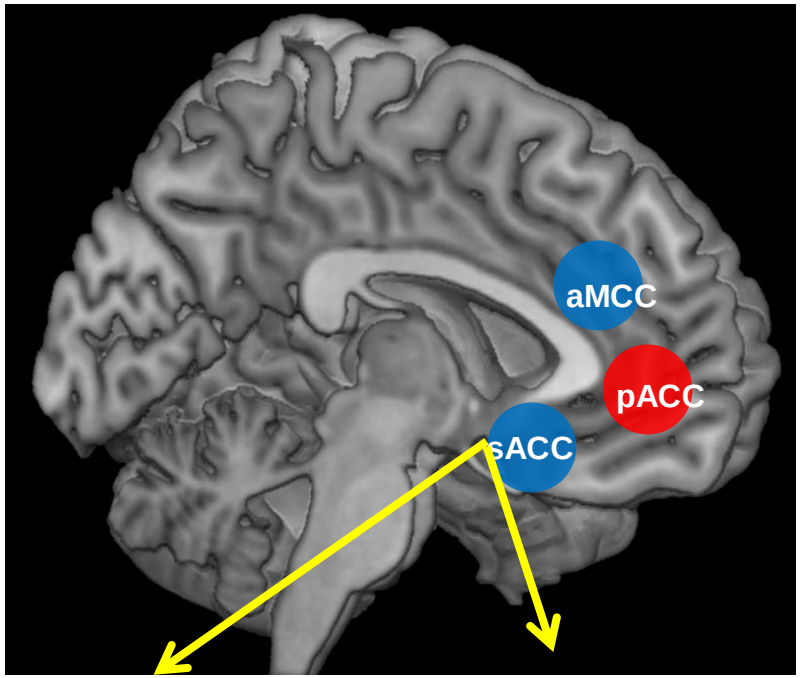
Rostral anterior cingulate response to Sad vs Happy stimuli changes during sertraline treatment & predicts response

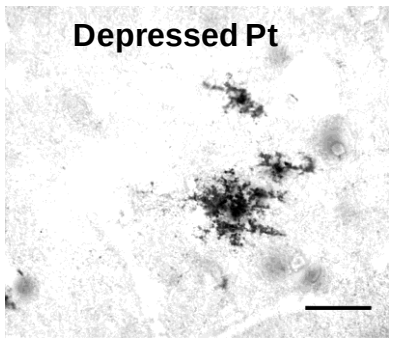
- In MDD, antidepressant-induced reversal of the negative processing bias is associated with shifts in the pattern of hemodynamic activity of pregenual and subgenual ACC.
- Under SSRI Tx the pre-treatment BOLD response of pregenual ACC to masked sad vs masked happy faces correlated with subsequent improvement in depression severity (r=0.67, p<0.05)
- Pretreatment baseline activity of pregenual ACC predicts response to various antidepressant treatment modalities (including ketamine).
- Rostral ACC shares substantial anatomical connections with amygdala and hippocampus, through which they modulate neural and behavioral responses to emotional stimuli.

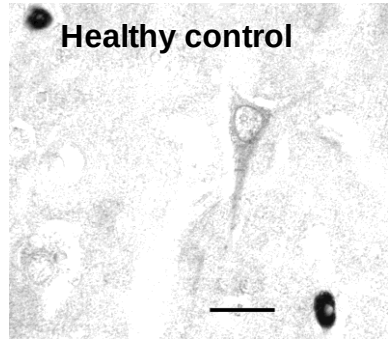


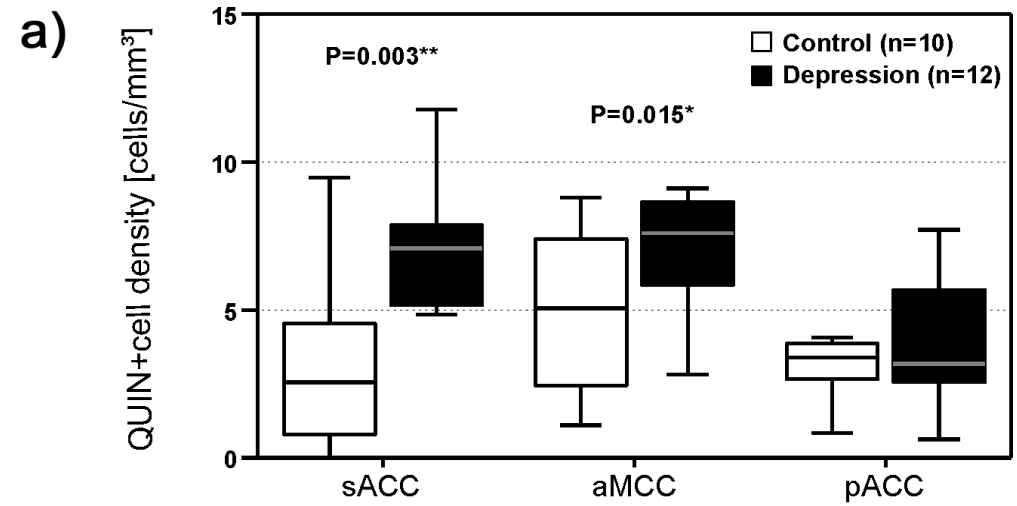
Pizzagalli, 2011. Neuropsychopharmacology
Victor T, et al. Int. J. Psychopharmacology, 2013
Salvadore et al. Neuropsychopharmacology, 2010

Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus

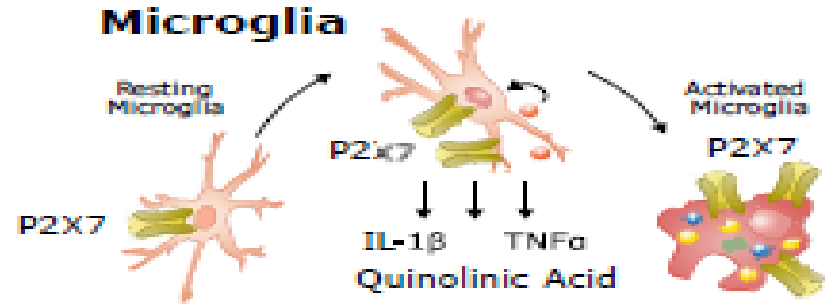




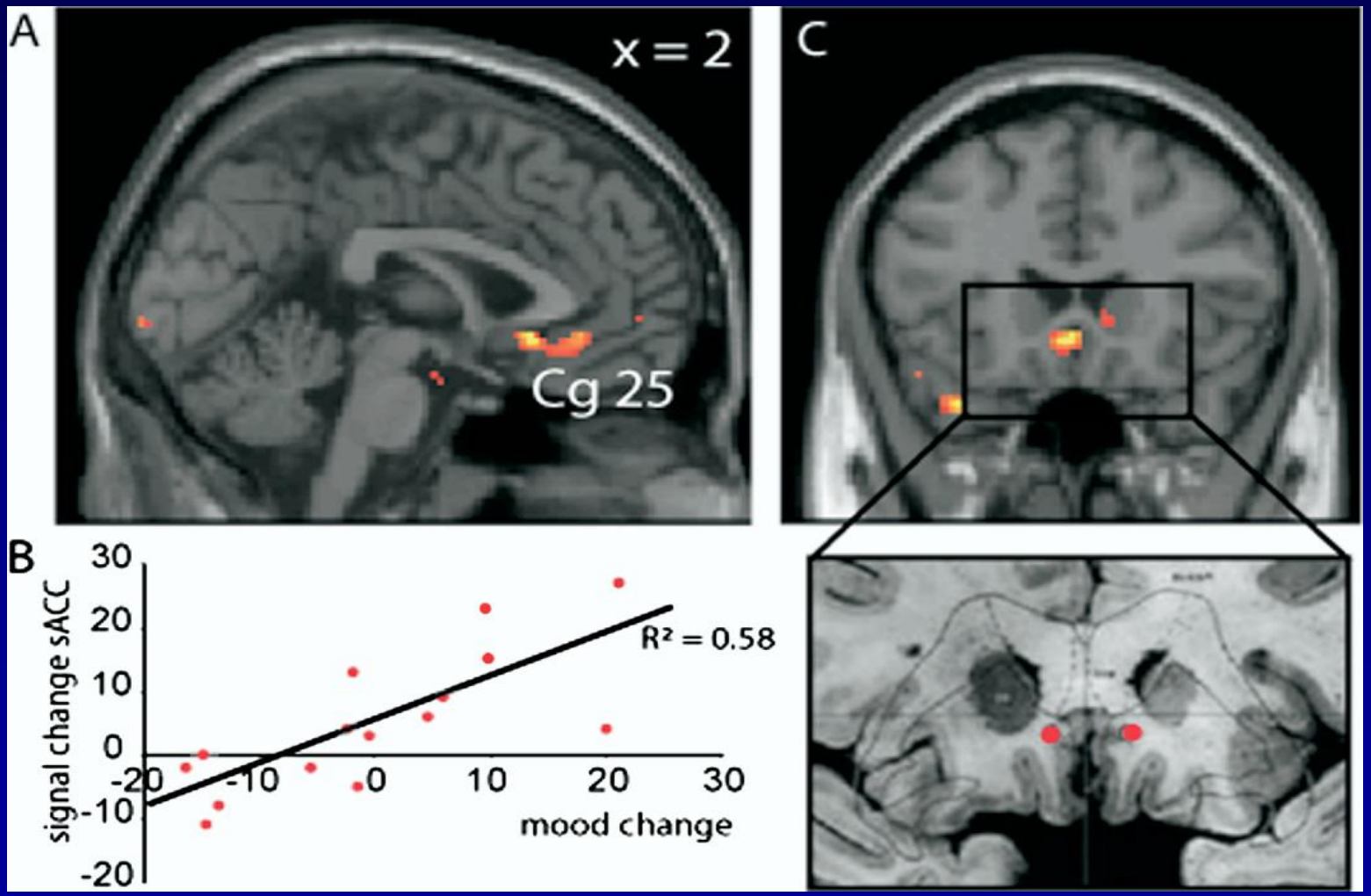




Strong QUIN immunoreactivity found only in vascular monocytes and microglia. Immunoreactive microglia showed smooth, ovoid or elongated cell form in controls, but numerous granular structure processes in depressives in aMCC and sACC.



Subgenual anterior cingulate cortex activity predicts inflammation-associated mood change

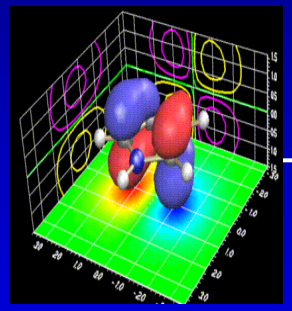


Hemodynamic response to emotional faces during mood change and cytokine release under typhoid Vaccine

Harrison et al. Biol Psychiatry 2009

Complex Neuropsychiatric Disorders: Targeting Treatment at Multiple Levels

Environment: e.g., "stressors" (psychological, physiological)



Mood Disorders

Genes
Common susceptibility alleles of small effect (BDNF, P2X7, ANK3); Infrequent mutations of intermediate effect (K+ and Ca++ channels)

Proteins,
Neurotransmitters & receptors (e.g., 5-HT, orexin), Hormones (e.g., cortisol, CRH, ghrelin/ leptin), Proinflammatory cytokines, chemokines, Autoantibodies, Kynurenine metabolites

Cells
Glial and neuronal dysfunction, mitochondrial dysfunction; Microglial activation, Glia-based glutamate transport

Systems
Abnormal function & information processing in interacting circuits & homeostatic systems regulating emotion, stress biology (e.g., glucocorticoid, immune, endocannabanoid)

Behavior
Complex interactions affecting emotional, motivational, cognitive, visceromotor domains; Illness course, treatment outcome, Comorbid psychiatric, medical syndromes