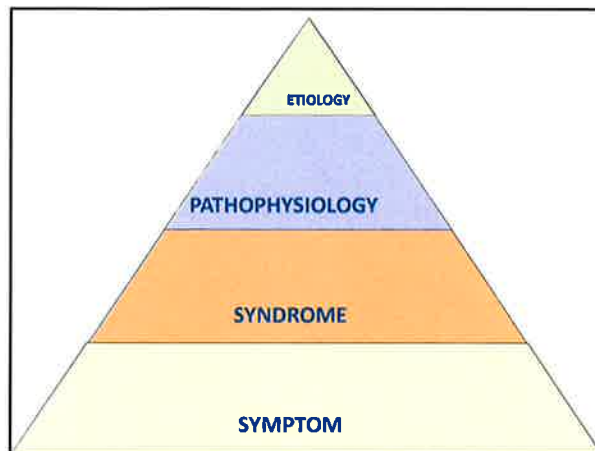


Overview of the Neurobiology of Major Depressive Disorder

Sheldon Preskorn, M.D.
Department of Psychiatry
Kansas University School of Medicine –
Wichita.



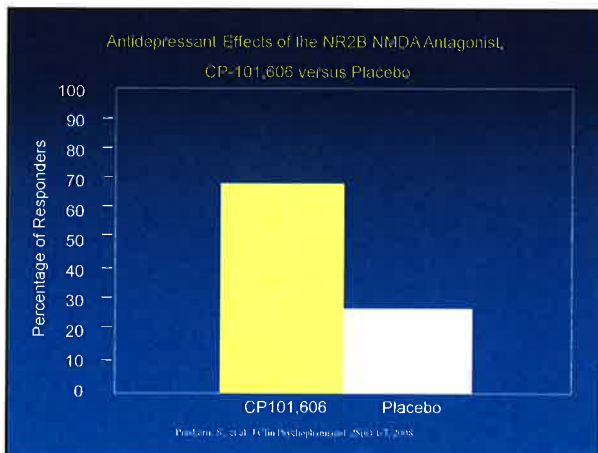
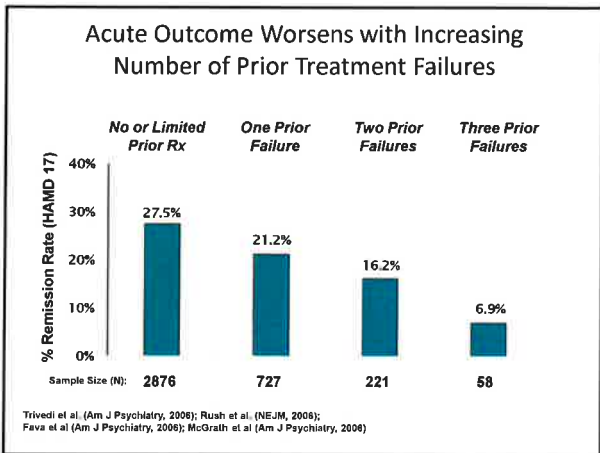
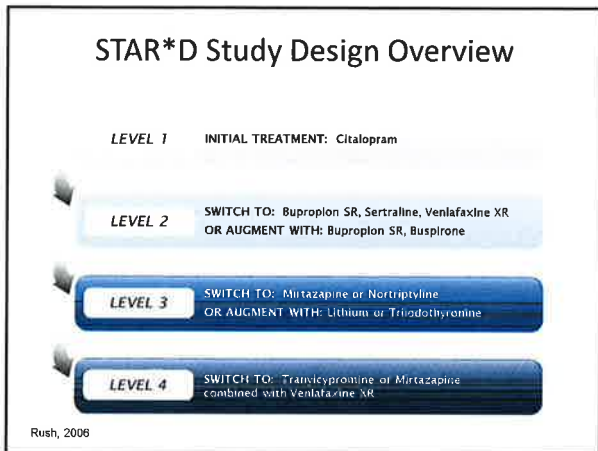
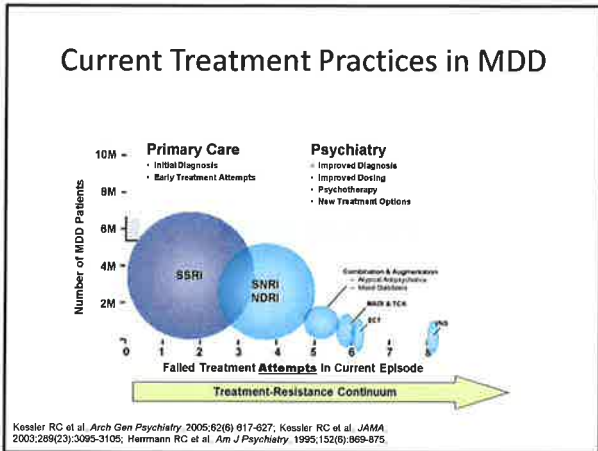
Psychiatric diagnoses

- “Symptoms and behaviors are the output of brain function, whereas syndromes are man-made constructions.”

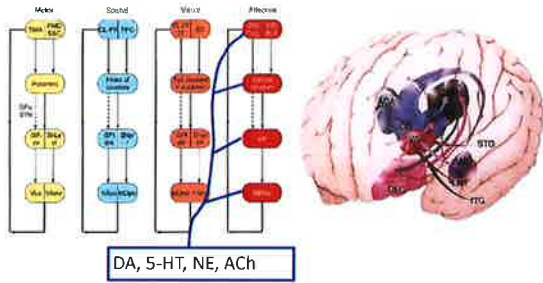
• *Preskorn S, 2014*

Research Domain Criteria (RDoC) initiative

- *Negative Valence Systems*
- *Positive Valence Systems*
- *Cognitive Systems*
- *Systems for Social Processes*
- *Arousal/Regulatory Systems*



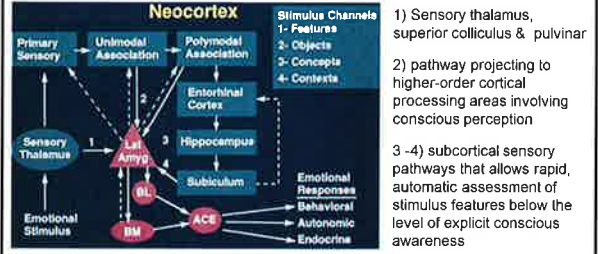
Affective Cortical-Striatal Circuits



Updated from Alexander GE, et al. *Ann Rev Neurosci* 1986;9:357-381. Salloway S, Cummings J. *J Neuropsychiatry Clin Neurosci* 1994;6:93-99.

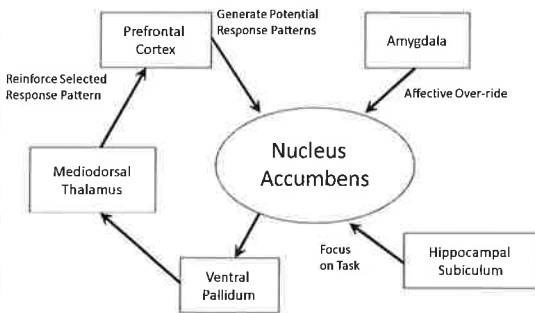
Evaluation of Emotionally Salient Information

The amygdala evaluates the emotional salience of sensory stimuli through a network of cortical and subcortical structures.



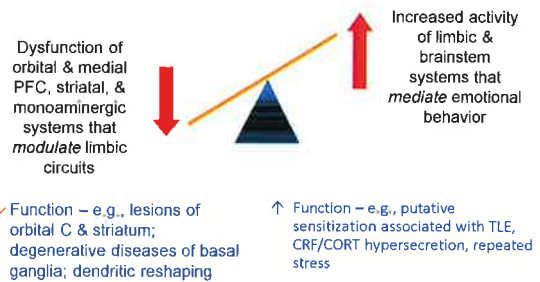
Le Doux JE, et al 1995

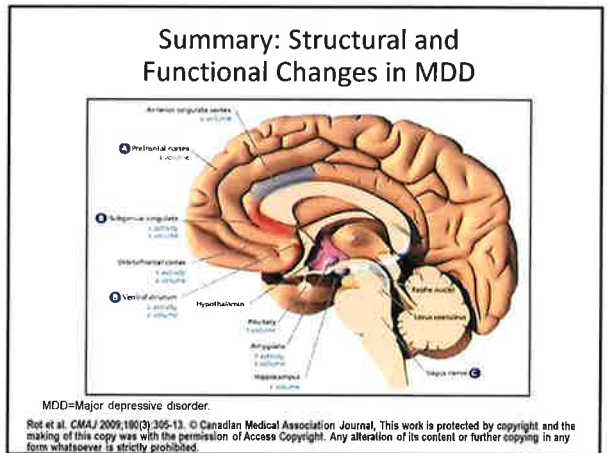
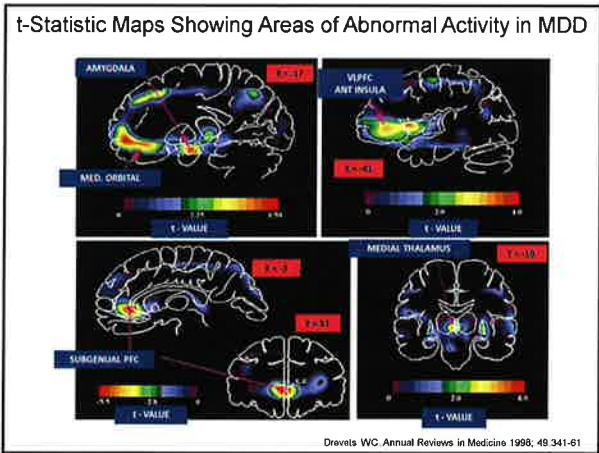
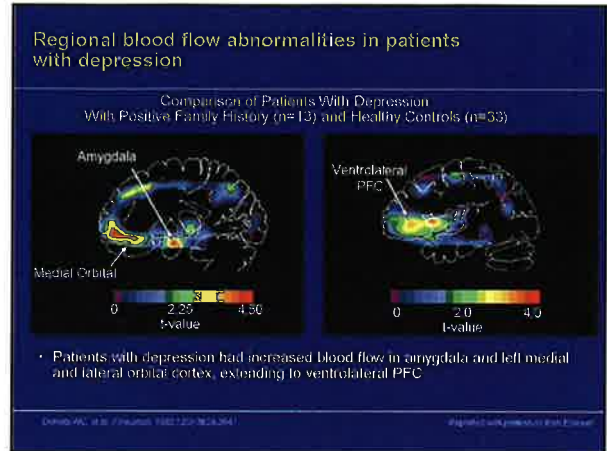
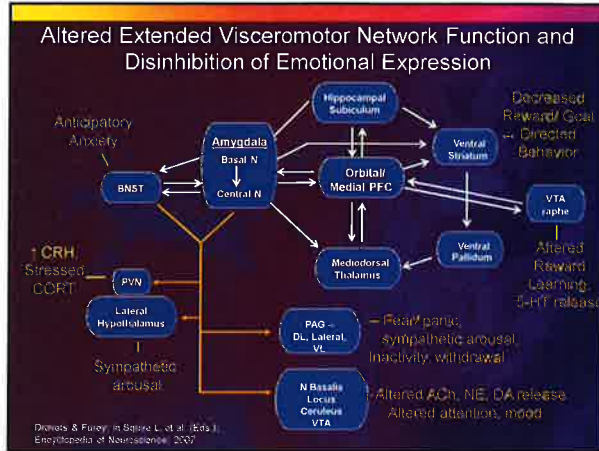
Gating Neural Processing through the Basal Ganglia: Grace, 2003



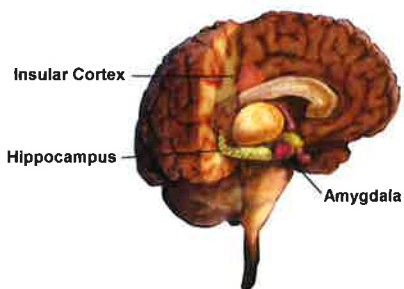
Neural Model of Mood Disorders

Dysfunction of PFC-striatal modulation of limbic circuitry alters emotional processing, behavior



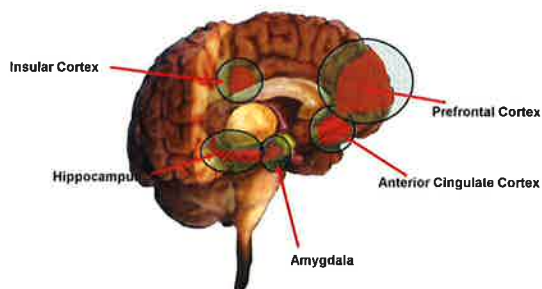


Areas of the brain implicated in MDD

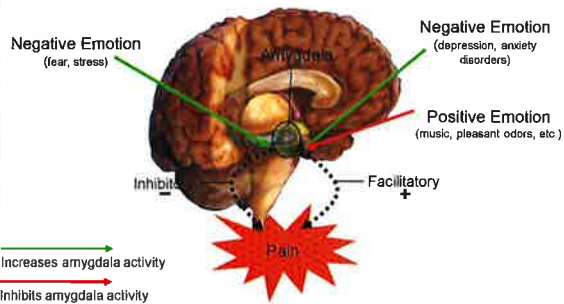


Charney DS, Nestler EJ. *Neurobiology of Mental Illness*; 2004.

Some key areas of the brain that may play a role in both MDD and pain



In MDD, the amygdala may facilitate painful symptoms (hypothetical model)



Modified from: Neugebauer V, et al. *Neuroscientist*. 2004;10:221-234.

Areas of prefrontal cortex (PFC) involved in MDD

- A. Ventromedial prefrontal cortex (VMPFC)¹
 - Modulates pain, aggression, and sexual and eating behaviors¹
- B. Lateral orbital prefrontal cortex (LOPFC)²
 - Corrects and inhibits maladaptive and perseverative emotional responses
- C. Dorsolateral prefrontal cortex (DLPFC)^{3, 4}
 - Maintains cognitive control, solving of complex tasks, and manipulation of information in working memory




Image from: Carter R. *Mapping the Mind*. University of California Press. 1999:162

1. Ongur D, Pfets J.L. *Cereb Cortex*. 2000;10(3):206-219.
2. Drevets WC. *Ann Rev Med*. 1998;49:341-361. 9(4):392-400.
3. MacDonald AW III, et al. *Science*. 2000;288(5472):1835-38.
4. Schweinhardt P, et al. *Curr Opin Neurol*. 2005;19(4):392-400.

Key brain areas involved in regulation of mood

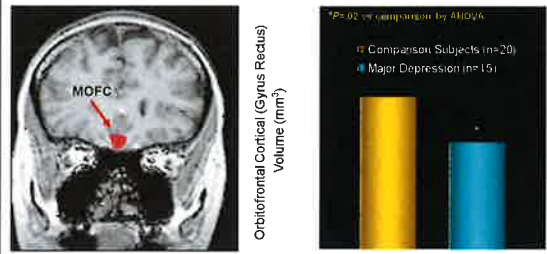
- (A) Ventromedial prefrontal cortex (VMPFC)¹
 - Modulates pain and aggression, and sexual and eating behaviors²
 - Regulates autonomic and neuroendocrine response
- (B) Lateral orbital prefrontal cortex (LOPFC)³
 - Activity is increased in depression, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and panic disorder
 - Corrects and inhibits maladaptive, perseverative, and emotional responses
- (C) Dorsolateral prefrontal cortex (DLPFC)⁴
 - Cognitive control, solving complex tasks, and manipulation of information in working memory
 - Hypoactivity of DLPFC in depression has been associated with neuropsychological manifestation of depression



1. Smith BA, et al. *Cereb Cortex* 2001;11:103-113
2. McClure LS, et al. *Science* 2004;306:921-924
3. Drevets WC, et al. *Arch Gen Psychiatry* 2002;59:615-624
4. Drevets WC, et al. *Arch Gen Psychiatry* 2002;59:615-624

Patients with MDD have 32% smaller medial orbitofrontal cortices (MOFC) (VMPFC) than controls

Image below reprinted with permission from Elsevier.



MOFC = ventromedial prefrontal cortex; ANOVA = analysis of variance

Bremner JD, et al. *Biol Psychiatry*. 2002;51:273-279

Anterior cingulate cortex (ACC) function: emotional and cognitive integration

A. Dorsal ACC (dACC)


- Part of cognitive/executive function network; involved in sustained attention, decision making, and effortful control of behavior; altered activity in MDD and pain^{1,3}

B. Rosirral ACC

- Interface between dorsal (cognitive) and ventral (visceral/affective) divisions of ACC²

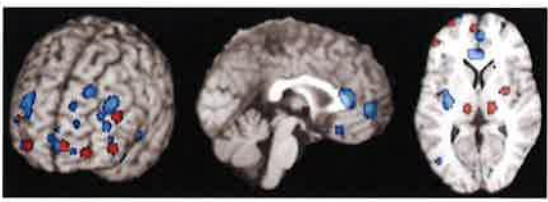
C. Ventral ACC (subcallosal and subgenual)

- Assesses the salience of emotional and motivational information and accordingly makes adjustments in the behavior; modulates sympathetic and neuroendocrine responses in depression, anxiety, and pain^{2,3}



1. McCormick LM, et al. *Neuroimage*. 2006;32(3):1167-1175
2. Whittle S, et al. *Neurosci Biobehav Rev*. 2008;32(6):S11-S25
3. Tracey I. *Curr Opin Neurobiol*. 2005;15(4):476-482

Decreased activity in DLPFC & dACC in MDD patients



Areas of increased activation in patients with MDD at rest (red) and decreased activation (blue) compared with controls.
Increased activity: LOPFC, VMPFC, amygdala, thalamus, caudate
Decreased activity: DLPFC, insula, pregenual and dACC, Sup. Temp. gyr.

LOPFC=lateral orbital prefrontal cortex. VMPFC=ventromedial prefrontal cortex. Sup. Temp. gyr.=superior temporal gyrus.
 Fitzgerald PB, et al. *Hum Brain Mapp*. [Epub ahead of print].

MDD may impact function and structure of the subgenual anterior cingulate

- Metabolism in the subgenual ACC increased compared to a control group¹
- Increases in subgenual ACC metabolism corresponded to increased depression severity¹



Patients with MDD had a 48% lesser volume in the subgenual PFC²

1. Drevets WC, et al. *Eur Neuropsychopharmacol.* 2002;12:527-544.
 2. Drevets WC, et al. *Nature.* 1997;386:824-827.

Brain atrophy in depression?

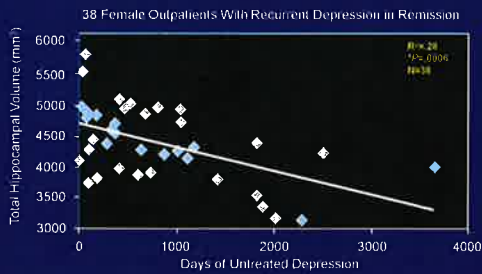
Atrophy of the Hippocampus in Depression



Blasen et al. *Arch Psychiatry* 2003;132:115-124

Reprinted with permission from JG Berke

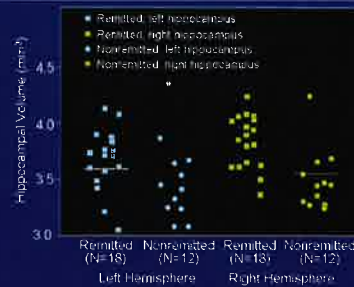
Correlation between hippocampal volume and duration of untreated depression



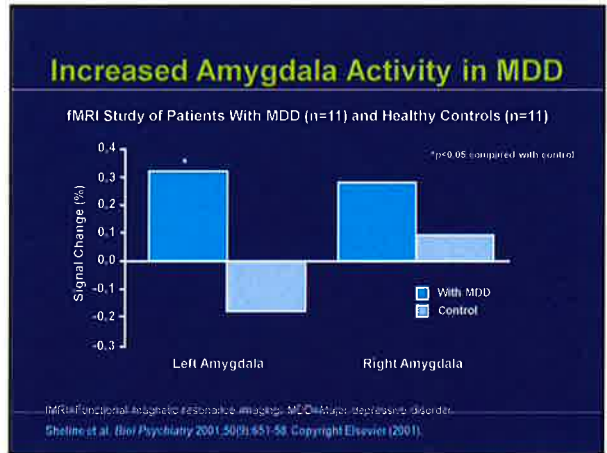
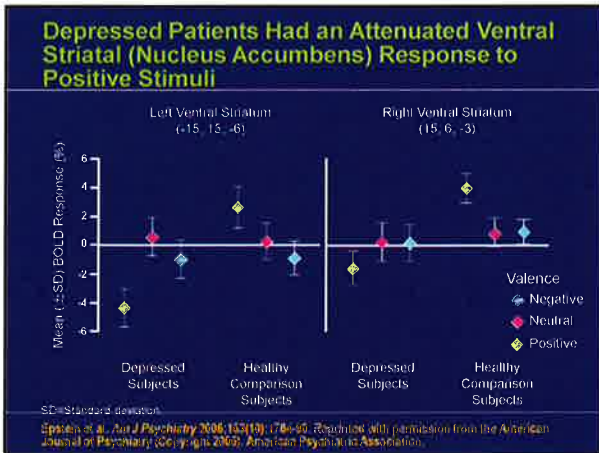
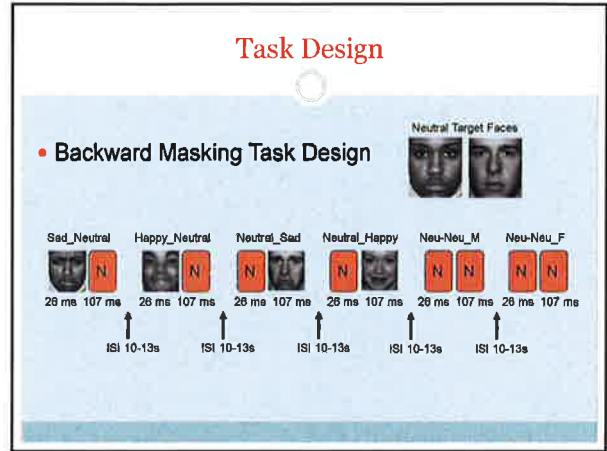
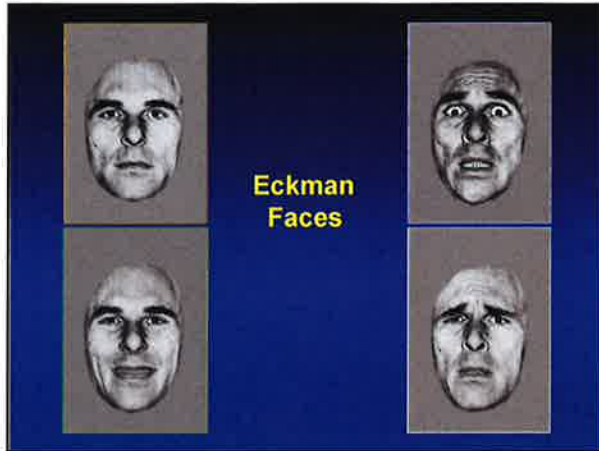
There was a significant inverse relationship between total hippocampal volume and the length of time depression went untreated

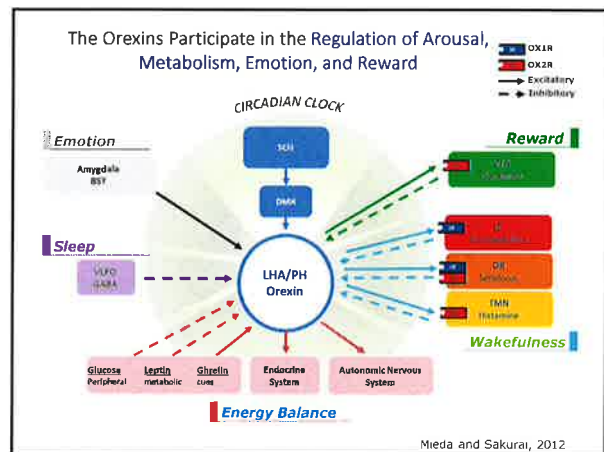
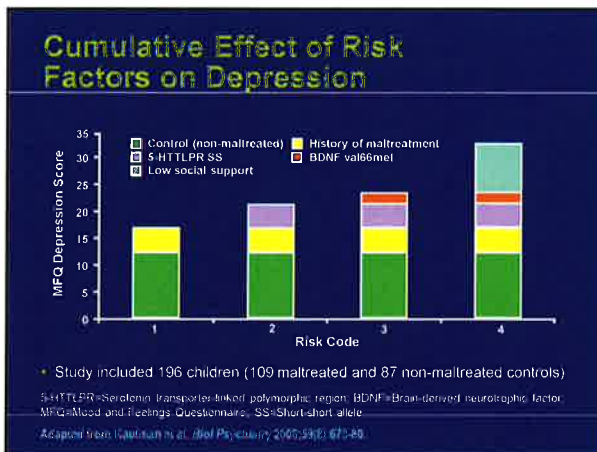
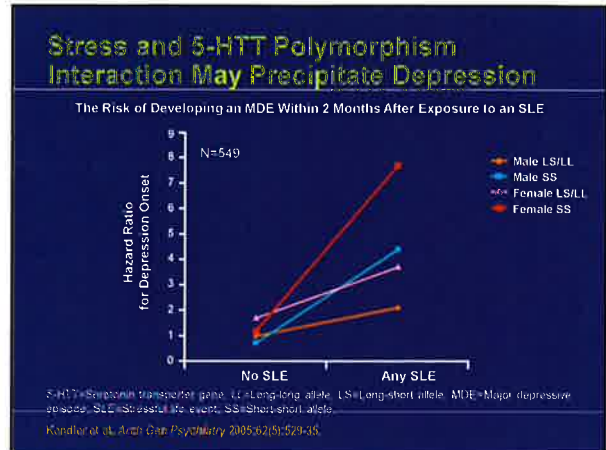
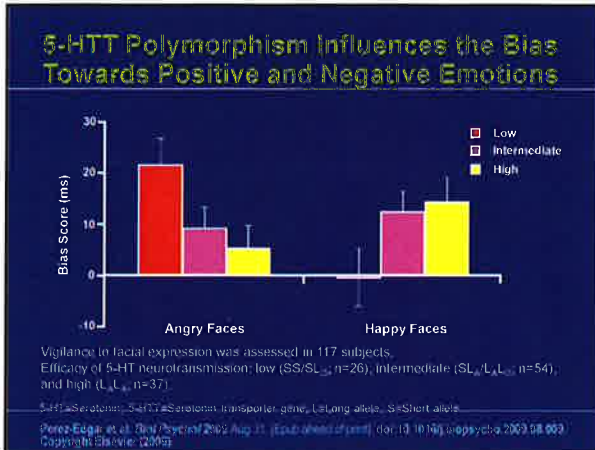
Sheline YI, et al. *Am J Psychiatry.* 2003;160(8): 1516-1518. Reprinted with permission from APA

Structural difference in the hippocampus of remitted vs nonremitted patients



Sheline et al. *J Clin Psychiatry* 2003;64:434-437





Domains influenced by orexin 2 receptor antagonism: Potential benefits in MDD

"Orexins primarily mediate behavior under situations of high motivational relevance, such as during physiological need states, exposure to threats or reward opportunities." *Mahler, Aston-Jones, et al. Nature Neuroscience, 2014*

Arousal/ Sleep-Wake/ Circadian Rhythms

- > Reduction in insomnia, *dysphoric* arousal
- > Promotion of physiological sleep (duration, deep sleep)
- > Health benefits of deep sleep include anti-inflammatory effects, preservation of insulin sensitivity, maintenance of adaptive BMI/appetite, reduced cardiovascular disease

Endocrine Function/ Energy Mobilization

- > Attenuation of limbic ("stressed") component of cortisol secretion
- > Normalization of GR sensitivity, depressive behaviors in mouse chronic stress model

Reward Processing/ Motivated Behavior/ Anhedonia

Persistent insomnia, GR insensitivity, anhedonia increase relapse risk

