



Depression is a Brain Disease

Charles B. Nemeroff, MD, PhD

Leonard M. Miller Professor and Chairman
Department of Psychiatry and Behavioral Sciences
Director, Center on Aging
University of Miami, Miller School of Medicine
Miami, Florida 33136



UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

CHARLES B. NEMEROFF, M.D., PH.D.

DISCLOSURES

- **Research/Grants:** National Institutes of Health (NIH), Agency for Healthcare Research and Quality (AHRQ)
- **Speakers Bureau:** None
- **Consultant:** Xhale, Takeda, SK Pharma, Shire, Roche, Lilly
- **Stockholder:** CeNeRx BioPharma, Inc., PharmaNeuroBoost, Revaax Pharma, Xhale
- **Other Financial Interest:** CeNeRx BioPharma, PharmaNeuroBoost
- **Patents:** Method and devices for transdermal delivery of lithium (US 6,375,990B1), Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)
- **Scientific Advisory Board:** American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), PharmaNeuroBoost, Anxiety Disorders Association of America (ADAA), Skyland Trail
- **Board of Directors:** AFSP, Gratitude America

Canst thou not minister to a mind diseased?
Pluck from the memory a rooted sorrow,
Raze out the written troubles of the brain,
And with some sweet oblivious antidote
Cleanse the stuffed bosom of that perilous
Stuff which weighs upon the heart?

MACBETH

All his life he suffered spells of depression, sinking into the brooding depths of melancholia, an emotional state which, though little understood, resembles the passing sadness of the normal man as a malignancy resembles a canker sore.

*William Manchester,
The Last Lion, Winston Spencer Churchill, Vol. I: Visions of Glory
(New York: Little, Brown & Company, 1989, p. 23)*

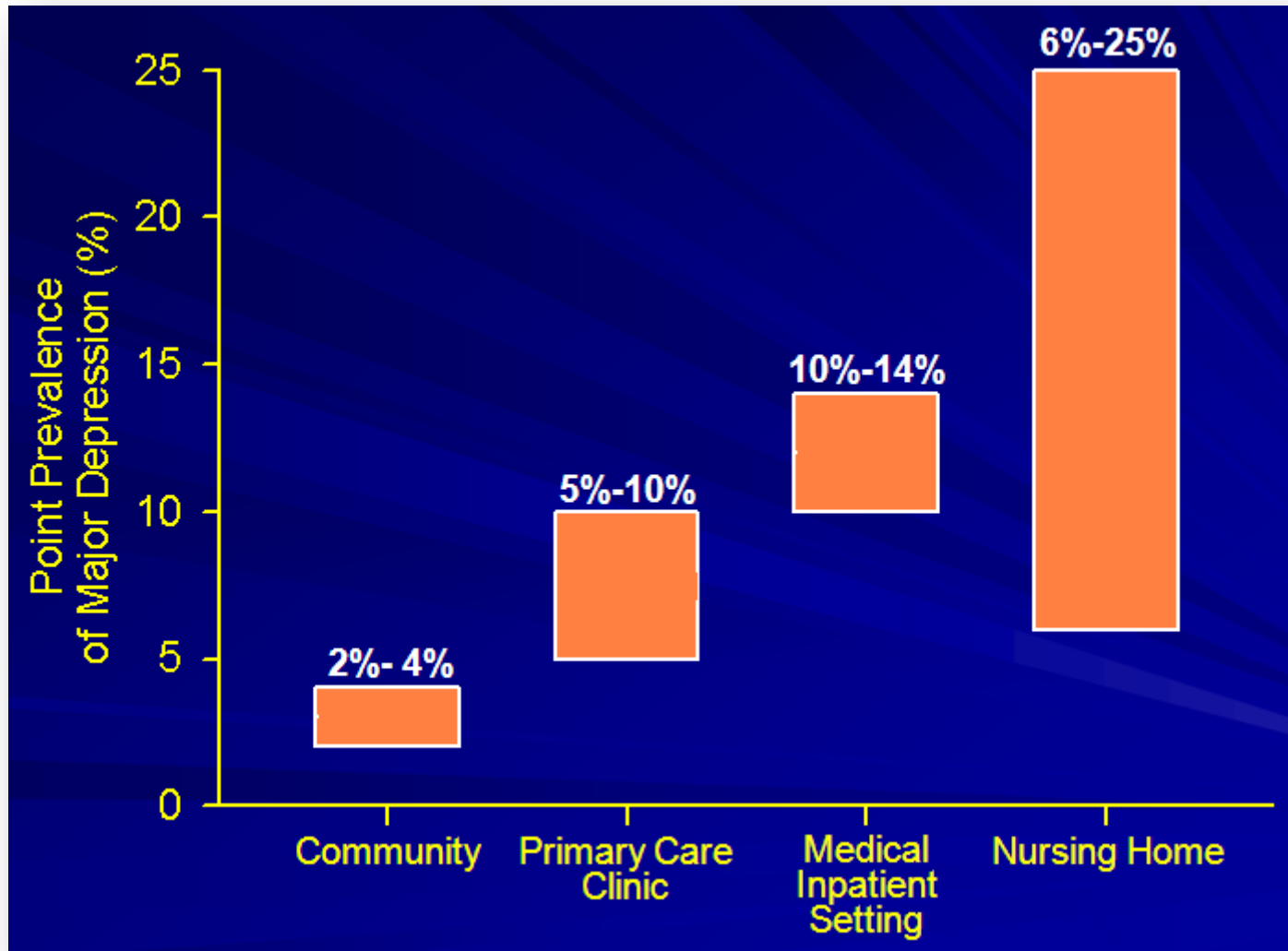
Major Depressive Episode: DSM-IV Diagnostic Criteria

- Characterized by clinically significant distress and/or impairment in social, occupational, or other important areas of functioning
- Symptoms must persist for most of day, nearly every day, for ≥ 2 consecutive weeks

DSM-IV Diagnostic Criteria for Major Depression

- ≥ 5 symptoms including depressed mood and/or anhedonia
 - Other symptoms may include:
 - Significant weight change
 - Psychomotor agitation/retardation
 - Pervasive loss of energy/fatigue
 - Feelings of worthlessness/excessive or inappropriate guilt
 - Difficulty concentrating
 - Sleep disturbance
 - Recurrent thoughts of death/suicide
- Symptoms present for ≥ 2 weeks

Prevalence of Depression in United States



Katon W. Schulberg H. Gen Hosp Psychiatry. 1992; 14: 237-247

Depression—A Major Cause of Disability Worldwide

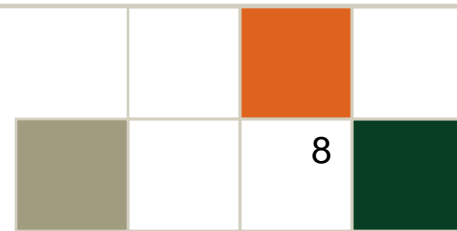
DALYs—2000 and 2020

<u>Rank</u>	<u>2000¹</u>	<u>2020 (Estimated)²</u>
1	Lower respiratory infections	Ischemic heart disease
2	Perinatal conditions	Unipolar major depression
3	HIV/AIDS	Road traffic accidents
4	Unipolar major depression	Cerebrovascular disease
5	Diarrheal diseases	Chronic obstructive pulmonary disease

1. World Health Report 2001. *Mental Health: New Understanding, New Hope*. Geneva, World Health Organization, 2001.

2. Murray CJL, Lopez AD, eds. *The Global Burden of Disease*. Boston: Harvard University Press; 1996.

DALYs=disability-adjusted life-years.



Depression is Often Under Diagnosed and Inadequately Treated

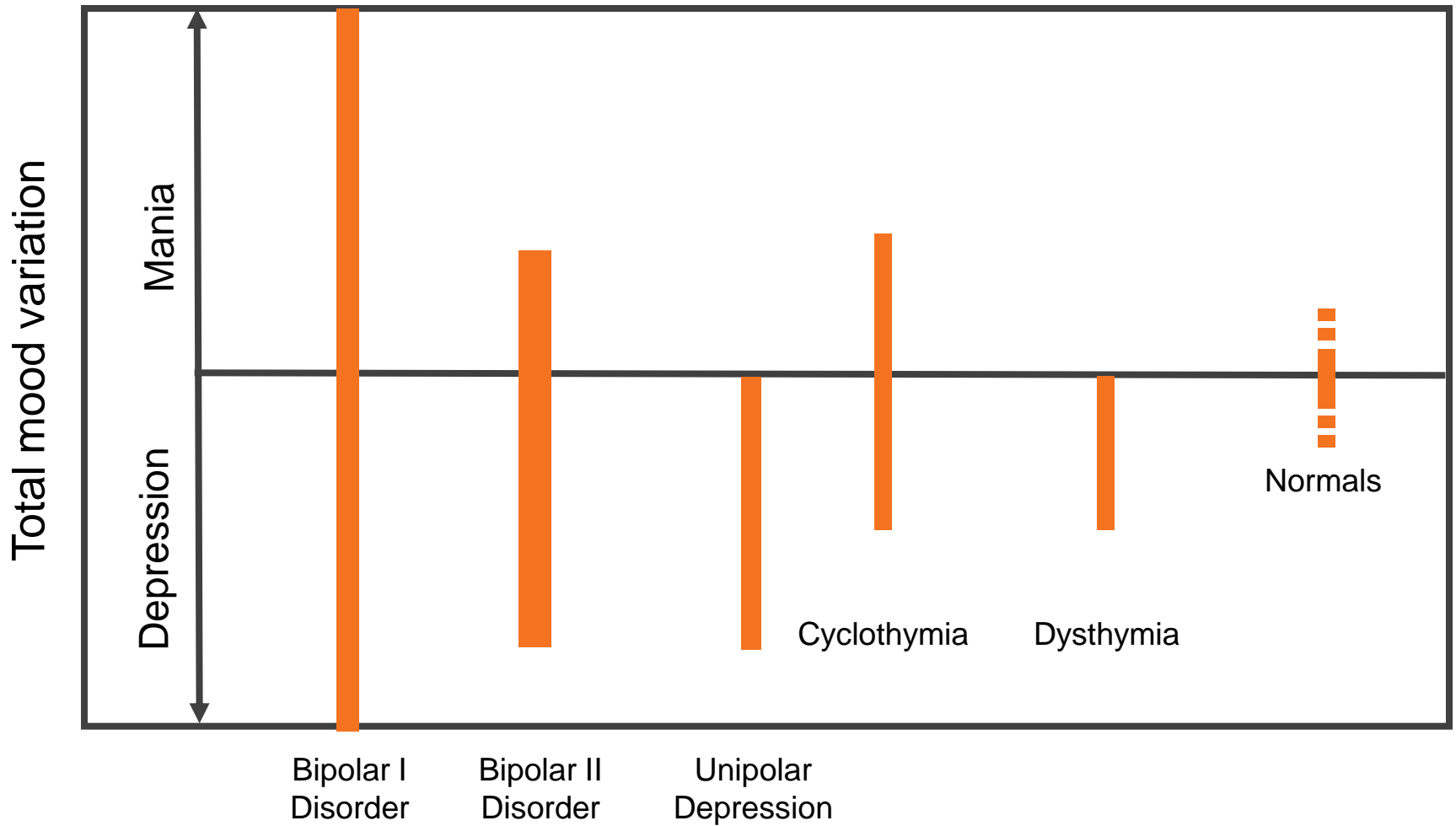
- Less than 1/2 of patients with major depression are explicitly recognized as being depressed¹
- Only about 1/2 of all depressed patients receive some form of therapy for their illness²
- Only about 1/4 of depressed patients receive an adequate dose and duration of antidepressant treatment³

1. AHCPR. Rockville, Md: US Dept of Health and Human Services; 1993. Publication 93-0550.

2. Lepine JP, et al. *Int Clin Psychopharmacol.* 1997;12(1):19-29.

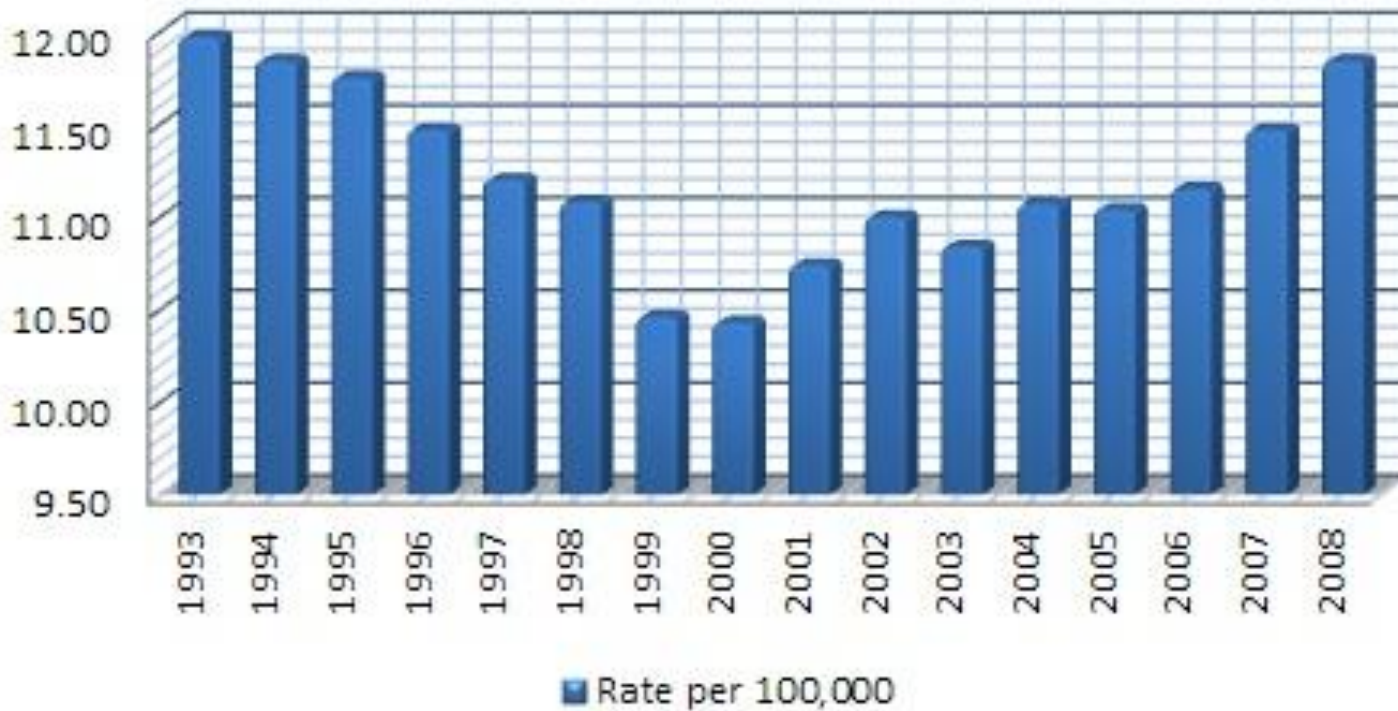
3. Katon W, et al. *Med Care.* 1992;30(1):67-76.

The Mood-Disorders Spectrum



FACING THE FACTS...

Suicide Rate over 15 Years

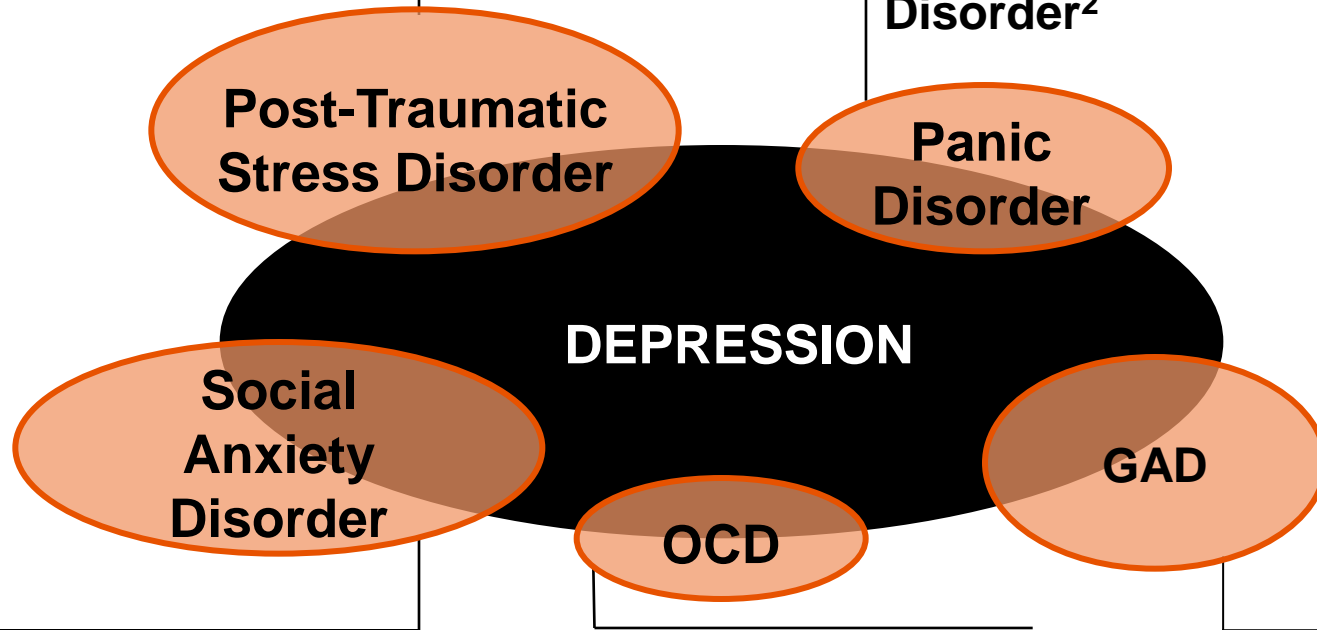


Comorbidity

Lifetime comorbidity of mood and anxiety disorders

48% of patients with PTSD¹

Up to 65% of patients with Panic Disorder²



Up to 70% of patients with Social Anxiety Disorder⁵

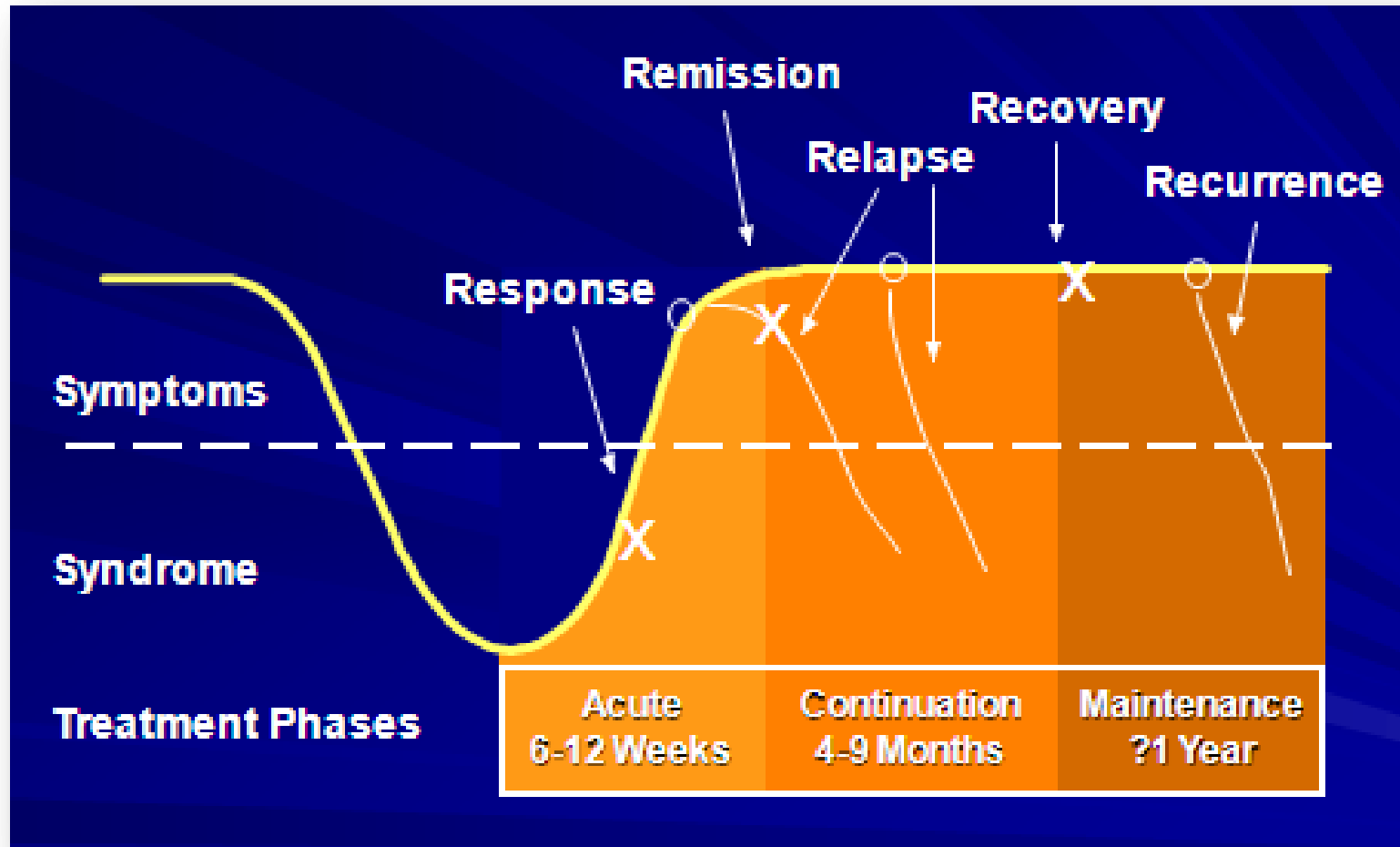
67% of patients with Obsessive-Compulsive Disorder⁴

42% of patients with Generalised Anxiety Disorder³

Kessler et al. Arch Gen Psychiatry 1995; DSM-IV-TR™ 2000; Brawman-Mintzer et al. Am J Psychiatry 1993; Rasmussen et al. J Clin Psychiatry 1992 ; Dunner, Depression and Anxiety 2001

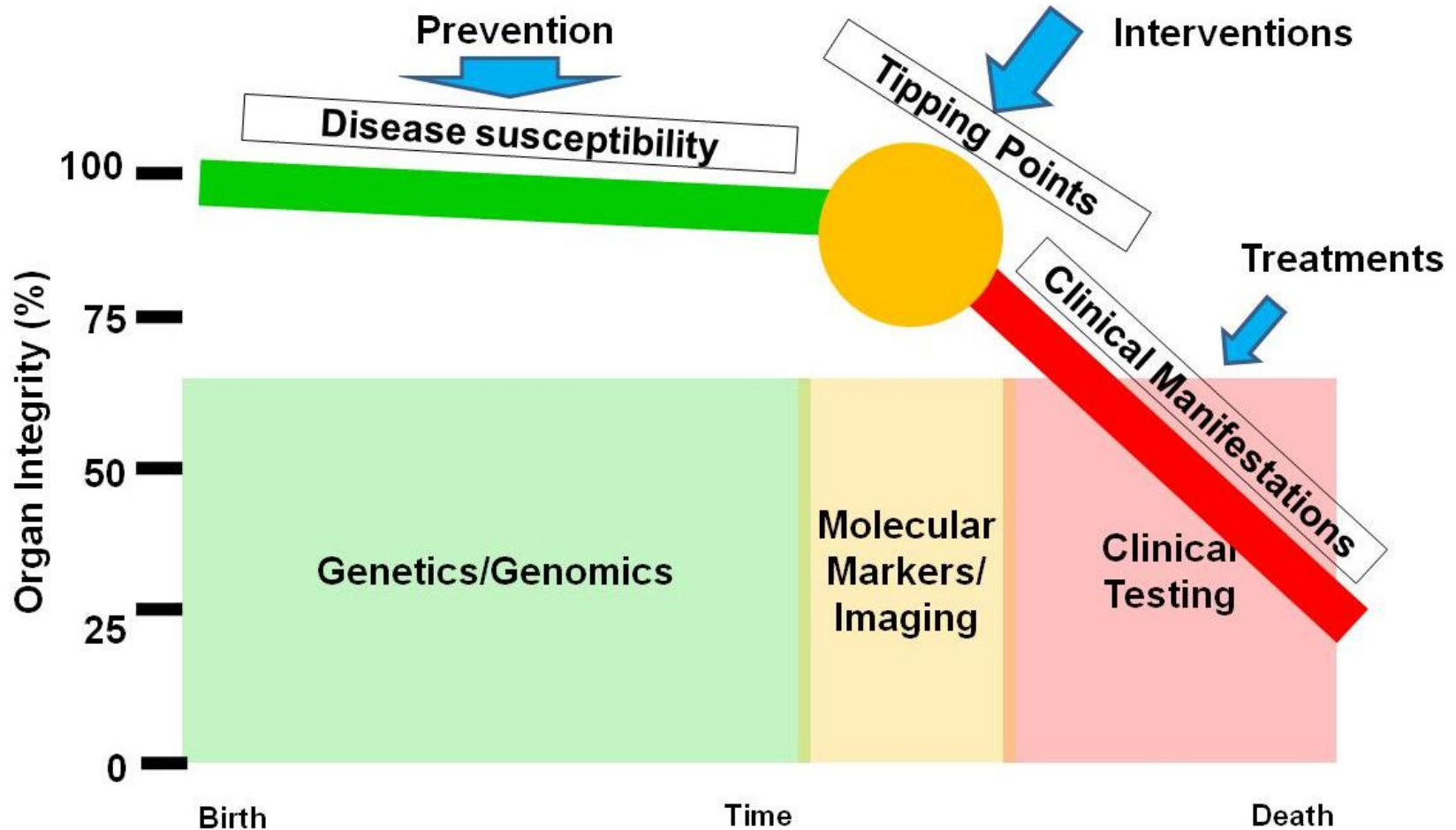
Outcome of Depression Treatment

The Five Rs



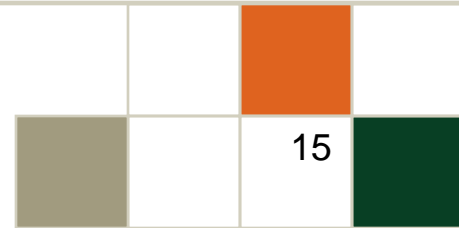
Reproduced with permission from Kupfer DJ. J Clin Psychiatry. 1991;52(suppl 5):28-34. Copyright 2002, Physicians Postgraduate Press.

21st Century Medicine



Etiology of Major Depression

- Over a third of the liability for developing MDD comes from genetic factors
- Genes likely mediate risk as well as resilience
- Environmental stressors interact with genes to influence the likelihood of developing MDD



Genetics and Environmental Factors

- Studies of identical twins have revealed that some conditions, such as psoriasis, have a strong genetic component and are less influenced by environmental and lifestyle factors—identical twins are more likely to share these diseases; but other conditions, such as MS, are only weakly influenced by genetic makeup and therefore twins may show differences depending on their exposure to various environmental factors
- “We used to think our fate was in our stars. Now we know, in large measure, our fate is in our genes.”

—J. D. Watson



Strong
Genetic
Influence

Psoriasis

Bipolar disorder

Schizophrenia

Neurotic/
extrovert

Diabetes

Cardiac
conditions

Multiple
sclerosis

MDD

IQ

Asthma

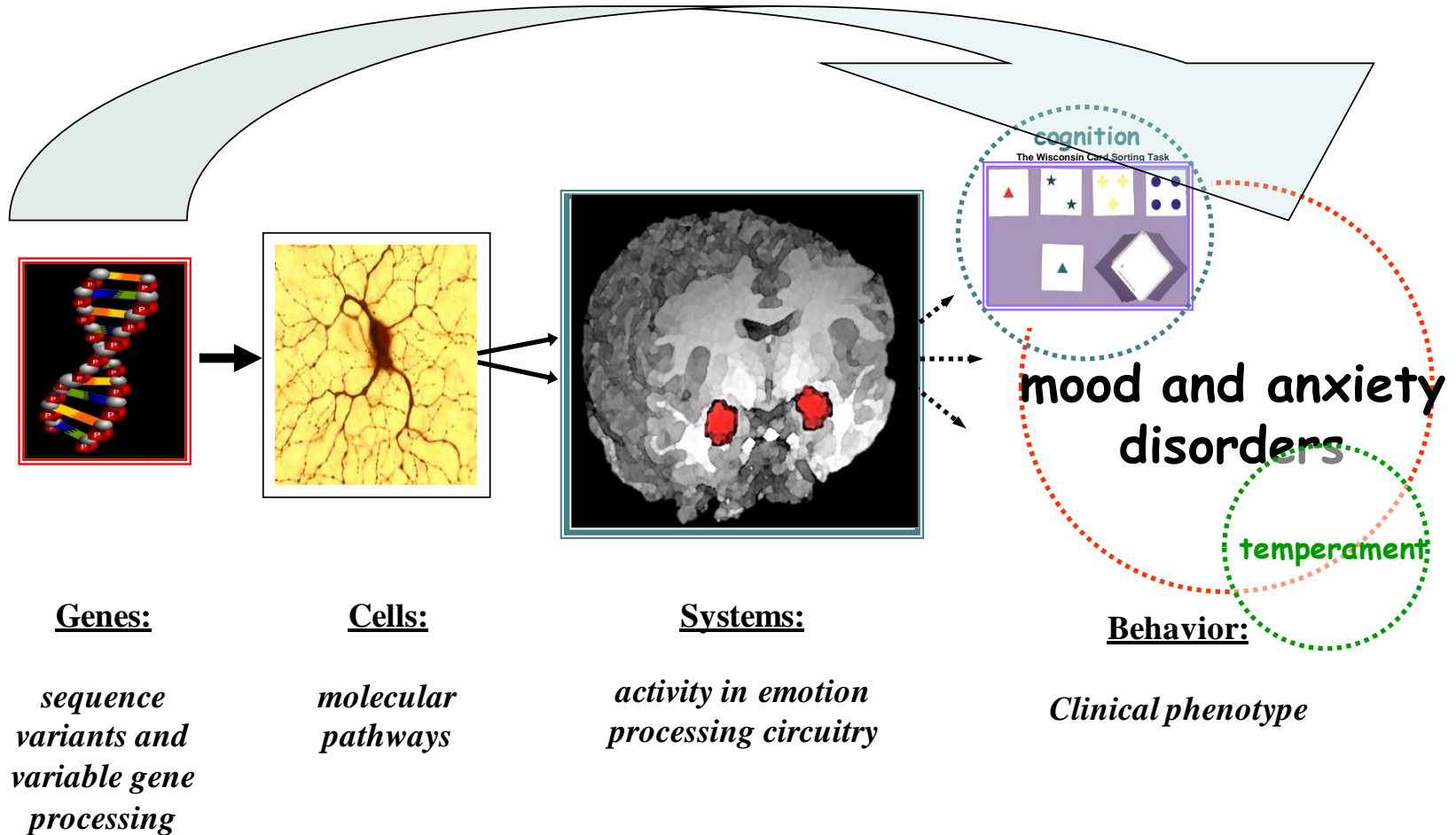
Cancers



Weak Genetic
Influence

16

Depression and anxiety are ultimately about how the brain responds to the environment



Risk Factors for Depressive Disorders

- **Family History of depressive disorders**
- **Prior personal history of a depressive disorder**
- **Female gender**
- **Life stressor (eg, bereavement, chronic financial problems)**
- **Certain personality traits**
- **Loss of parents at an early age**
- **Childhood abuse**
- **Alcohol or drug abuse**
- **Anxiety disorders**
- **Neurologic disorders (eg, Parkinson's, Alzheimer's, stroke)**
- **Primary sleep disorders**

*Hirschfeld RMA, Goodwin FK. In: The American Psychiatric Press Textbook of Psychiatry. 1987: 403-441
Depression Guideline Panel. Depression in Primary Care: Volume 1. Detection and Diagnosis. 1993: 1-65*

Depressive Disorders: The Essentials

Stress is an important risk factor for depression

Early life stress is an important risk factor

Genes account for a substantial variation in risk

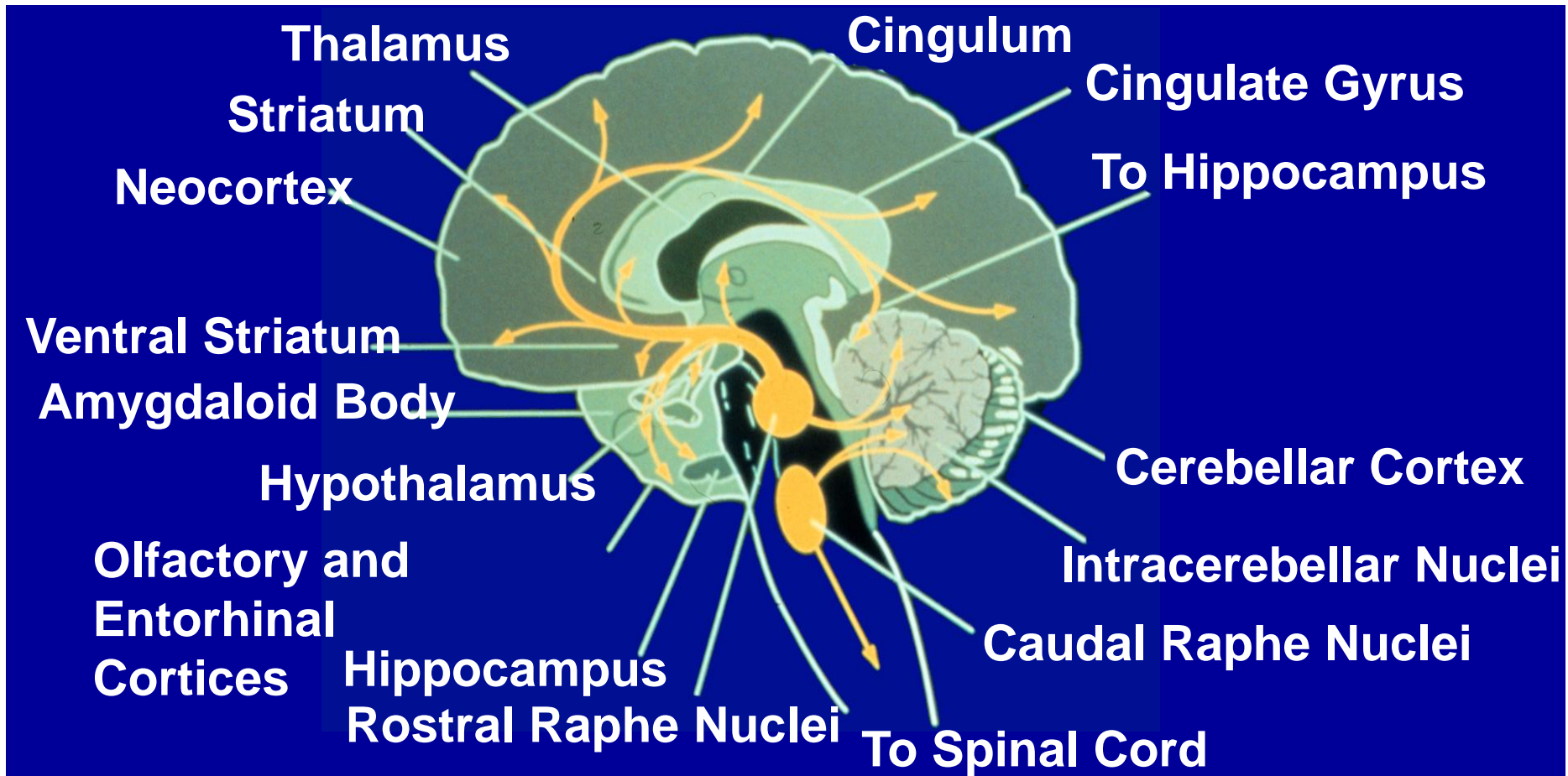
Brain systems related to the regulation of emotion are functionally impaired during an episode

Monoaminergic drugs are therapeutic

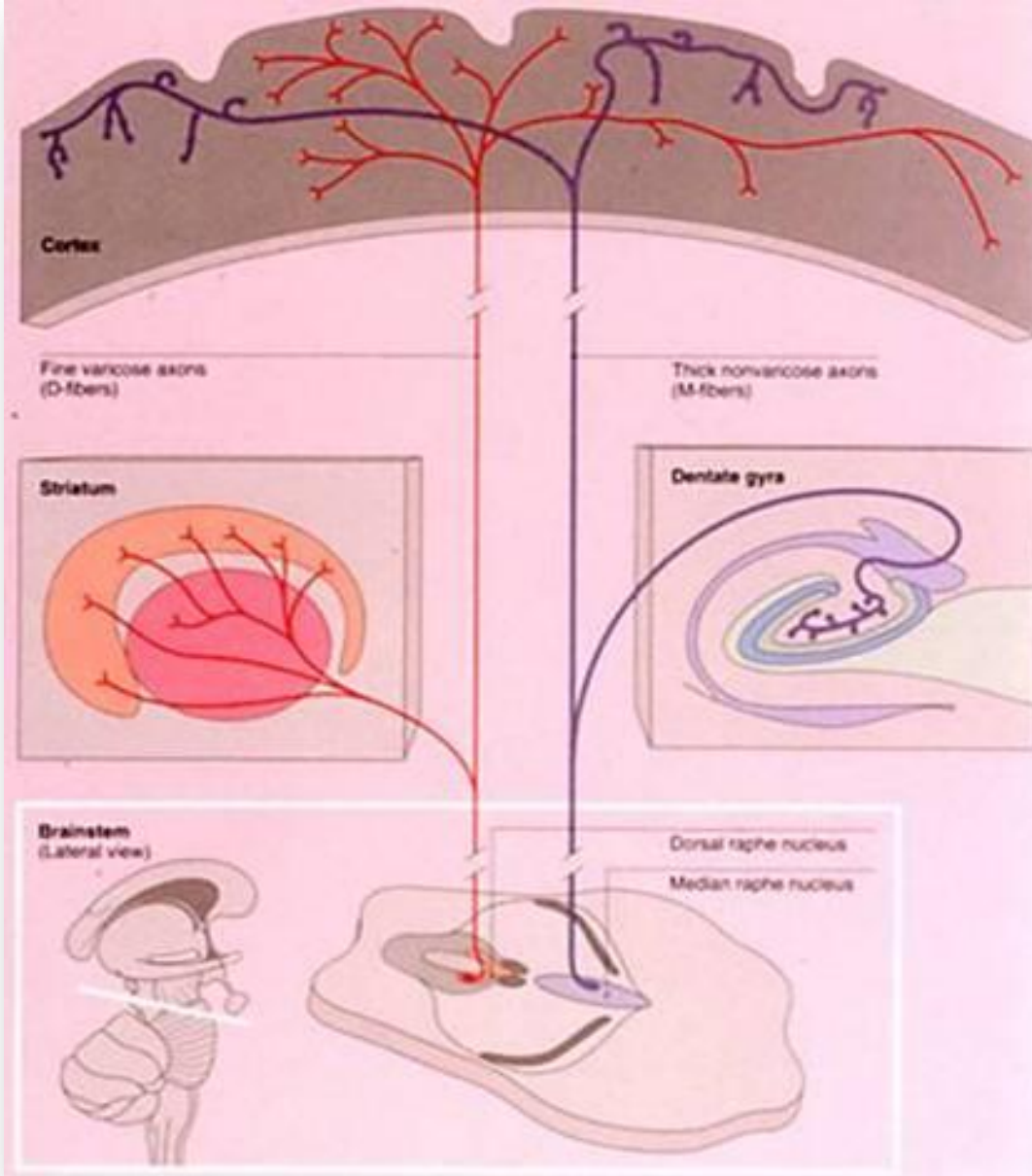
Neurotransmitters and Depression

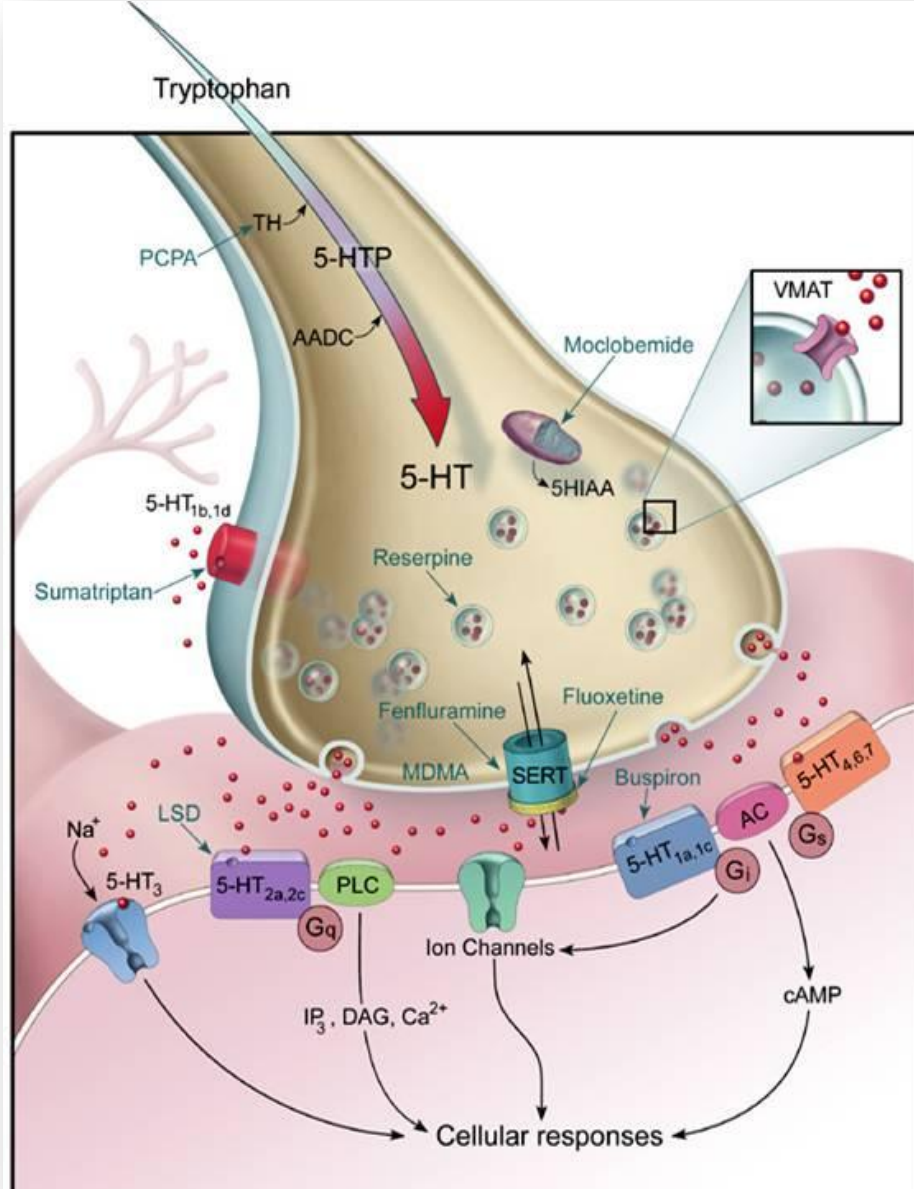
- There are disturbances in the monoamine systems
 - Serotonin (5-hydroxytryptamine, 5-HT)
 - Norepinephrine (NE)
 - Dopamine (DA)??
- There are also disturbances in other neurotransmitter systems (e.g., corticotropin-releasing factor [CRF] and substance P)
- Serotonin and norepinephrine have been the most extensively studied in the clinical setting

Axon Terminals of Serotonergic Neurons Project to Virtually All Portions of the Brain

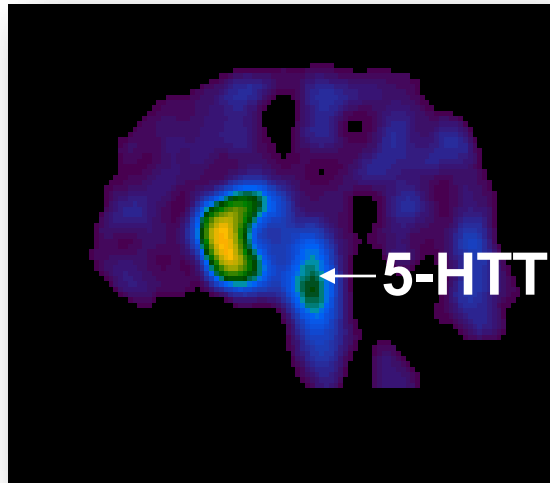


Kaplan HI, Sadock BJ (1991), *Synopsis of Psychiatry: Behavioral Sciences, Clinical Psychiatry*, 6th ed. New York: Lippincott Williams & Wilkins

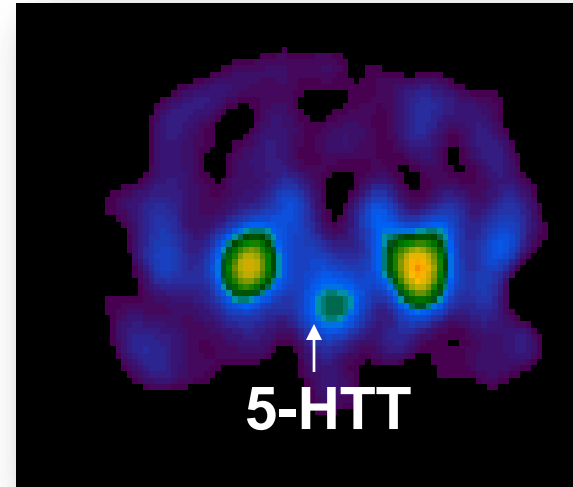




Serotonin Transporters Measured With ^{123}I β -CIT and SPECT



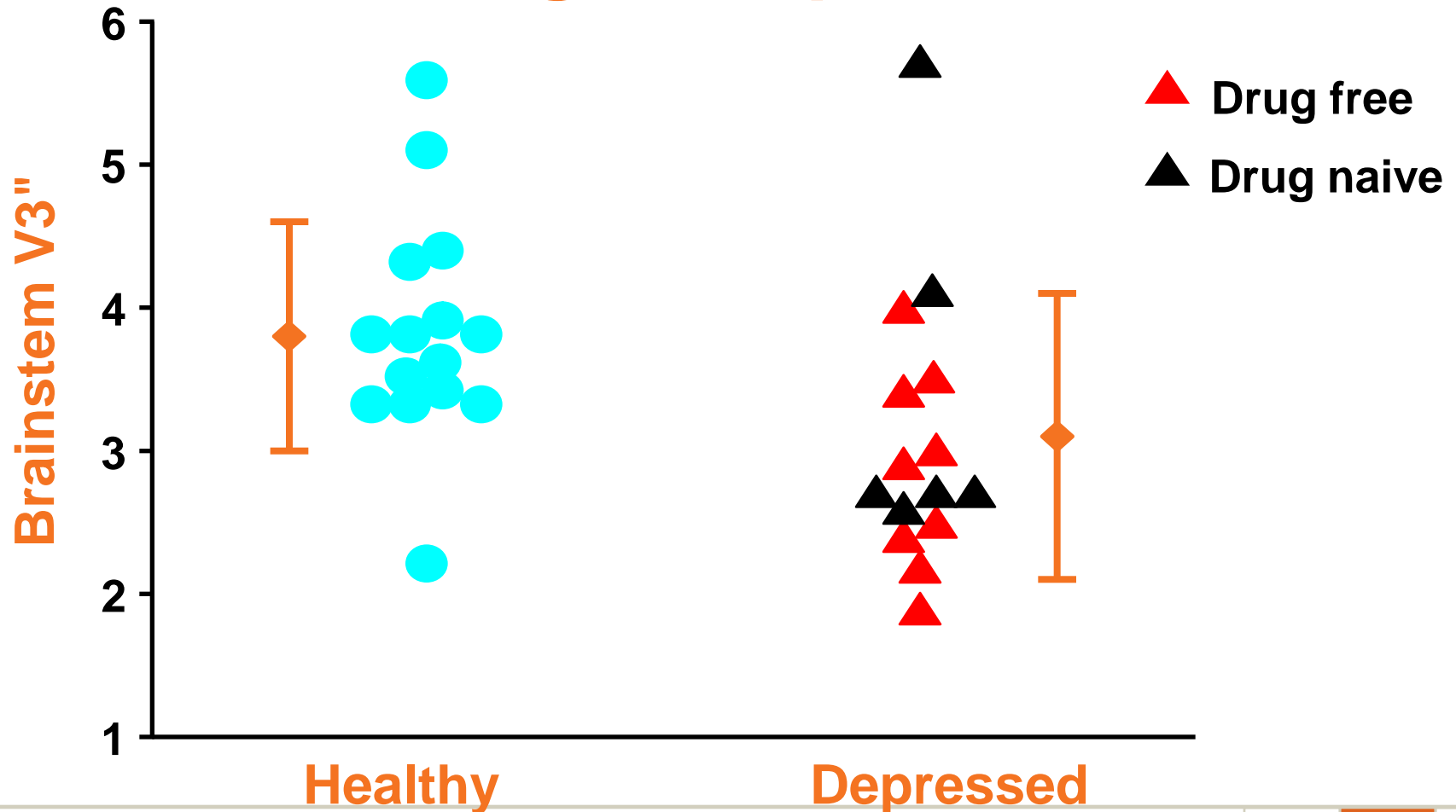
**Sagittal Image Through
Brainstem and Basal
Ganglia**



Coronal Image

SPECT = single photon emission-computed tomography

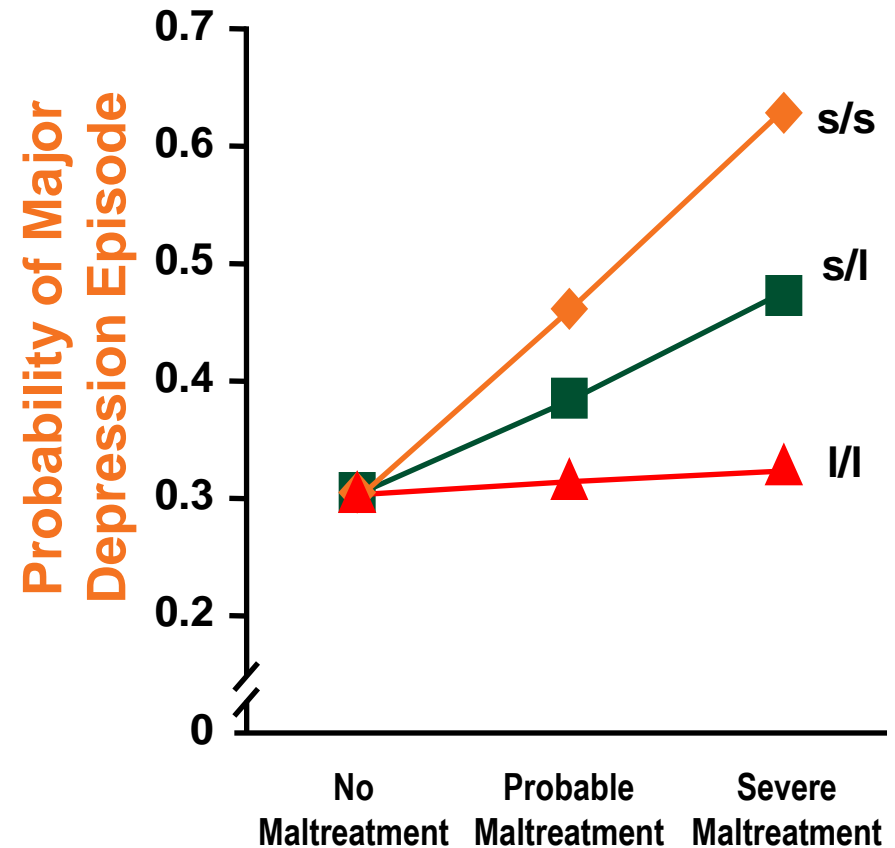
Reduced Brainstem [¹²³I]β-CIT Binding in Depression



*p=0.02; V3'' = [brainstem-occipital]/occipital; Malison RT et al. (1998), Biol Psychiatry 44(11):1090-1098

Influence of Life Stress on Depression

- Results of regression analysis estimating the association between childhood maltreatment (between the ages of 3-11) and adult depression (ages 18-26), as a function of 5-HTT genotype



Caspi A et al. (2003), Science 301(5631):386-389

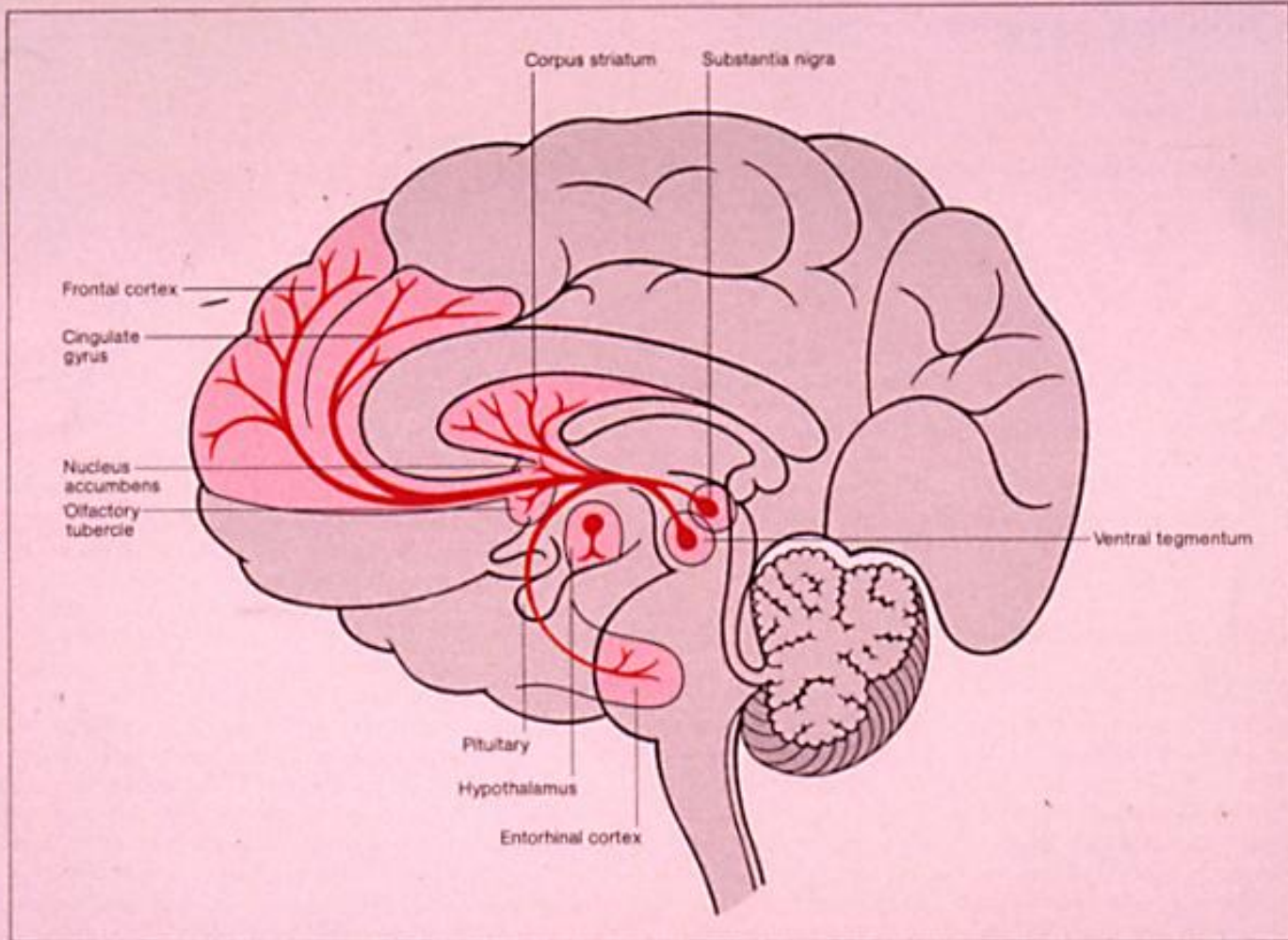


Fig. 1. The major dopamine pathways in the human brain. The dopamine cell bodies in the substantia nigra project to the corpus striatum, and a deficiency of dopamine in the striatum is associated with Parkinson's disease. The ventral tegmental dopamine cell bodies form the mesocortical and mesolimbic dopamine pathways, which project respectively to the frontal cortex and to a variety of limbic forebrain structures including the nucleus accumbens, the olfactory tubercle, the amygdala and the entorhinal cortex. The short dopamine pathway in the hypothalamus regulates hormone release from the pituitary gland; most importantly, dopamine inhibits prolactin release

Dopamine and Depression

- Role of dopamine neurons in behavioral and physiological areas altered in depression
- High rate of comorbidity of Parkinson's disease and depression
- Pathophysiological involvement of DA systems in depression

Imaging Studies

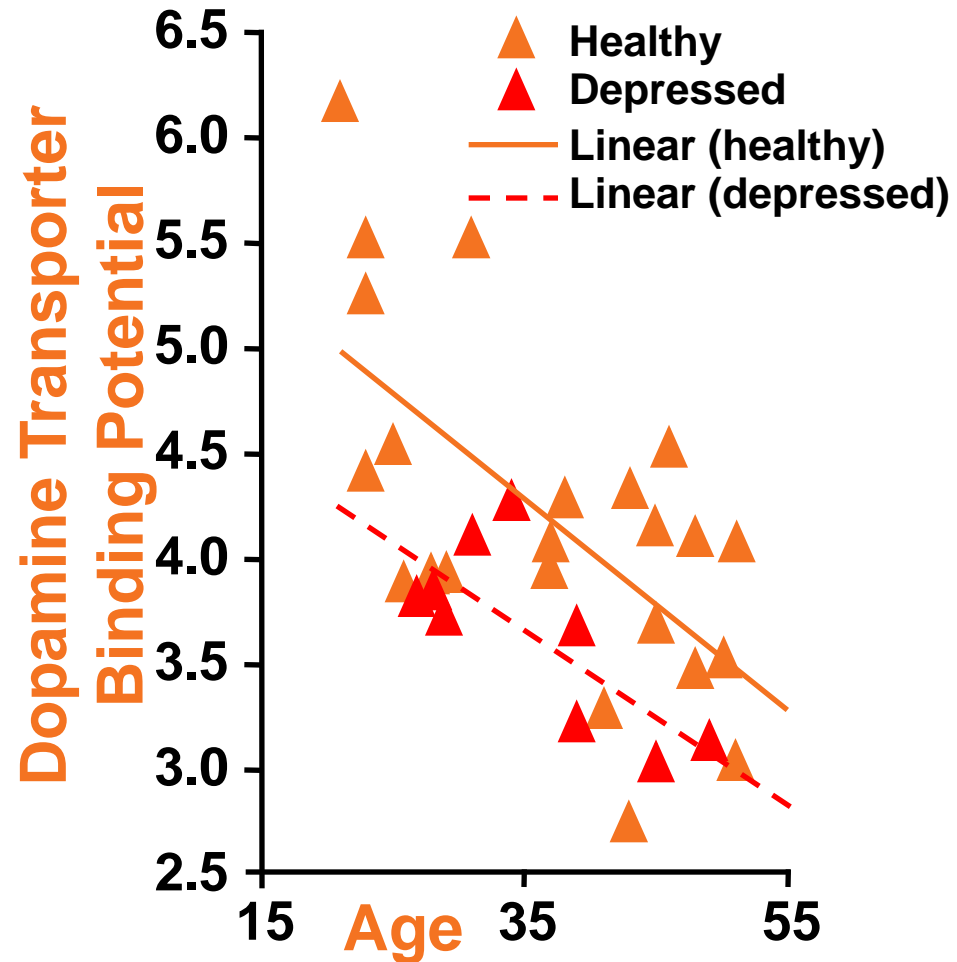
Postmortem Studies
Fluids Studies

Biological

- Role of DA circuits in the actions of antidepressants
 - MAOIs
 - Effects on the DA transporter

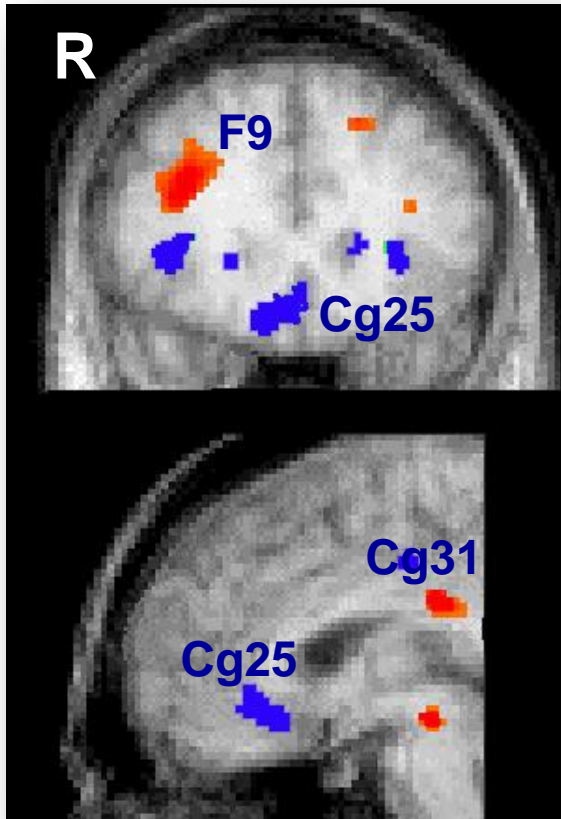
Dopamine Transporter Binding Potential in Depression

- Dopamine transporter binding potential in bilateral striatum is lower in depressed patients. Data was analyzed using analysis of covariance with age as a covariate, examining effect of diagnosis (effect of diagnosis: $F_{1,29} = 7.1$, $p=0.01$)



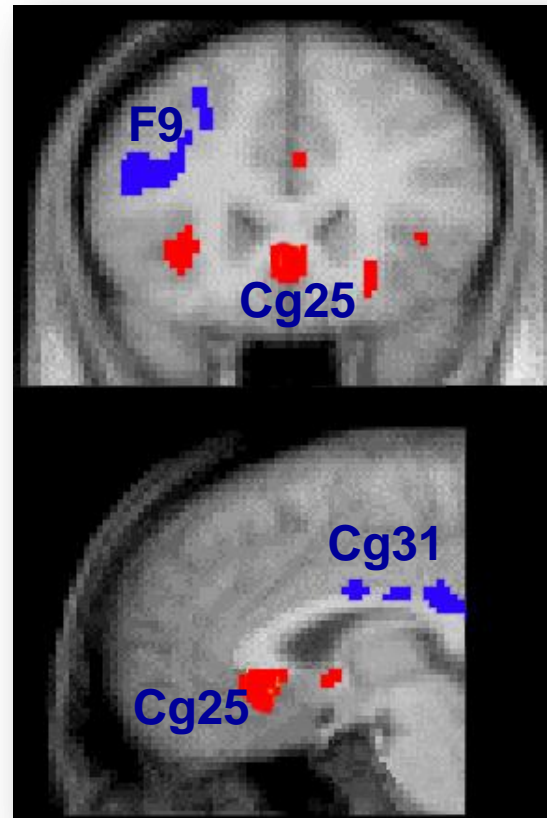
Cg25-Frontal Interactions in Negative Mood Regulation

Recovery With SSRI
FDG PET

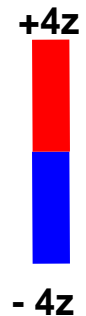


Depressed Patients

Transient Sadness
CBF PET



Healthy Volunteers



Mapping Treatment Effects: Isolate Potentially Most Relevant Regions

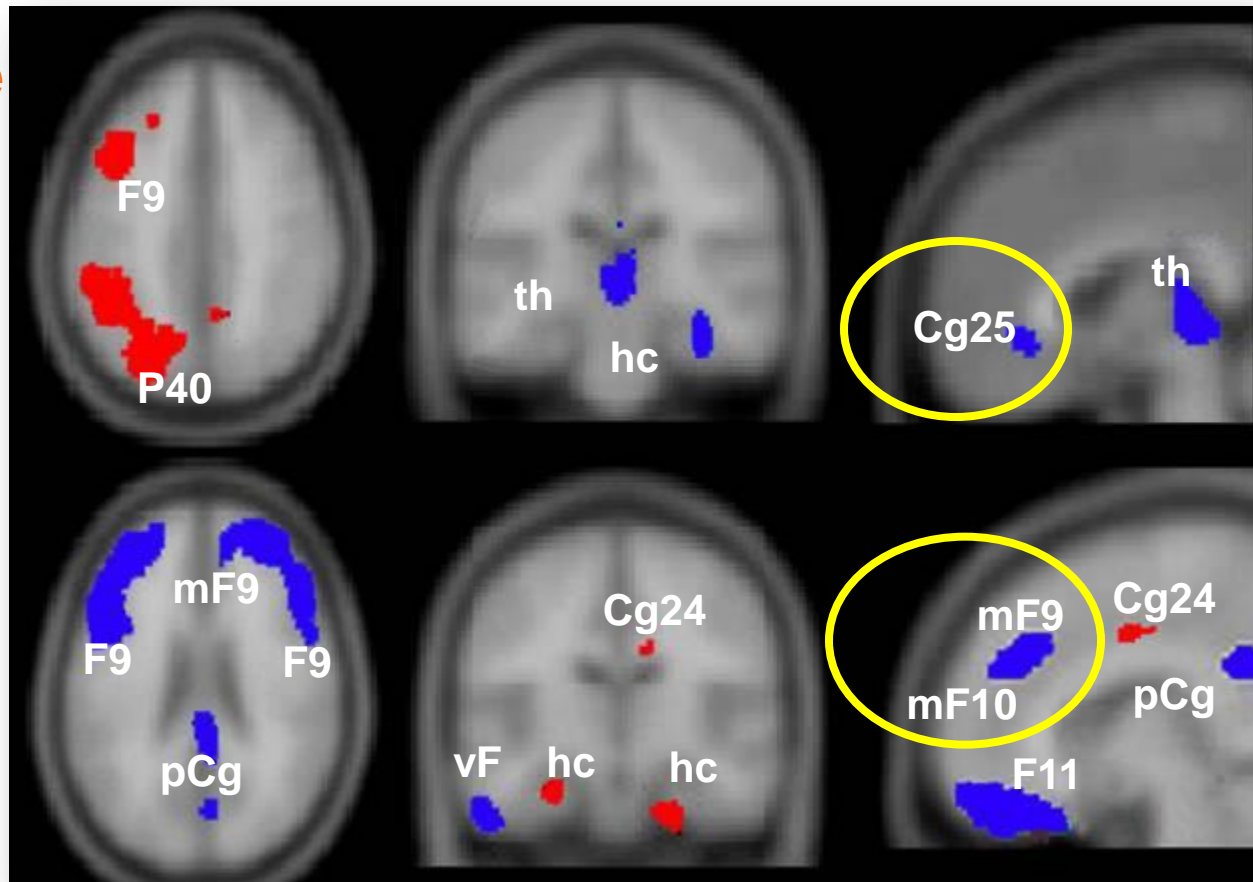
Paroxetine (Paxil)

N=13

Age 36 ± 10

HAM 22 ± 3

post 6 ± 4



CBT

N=14

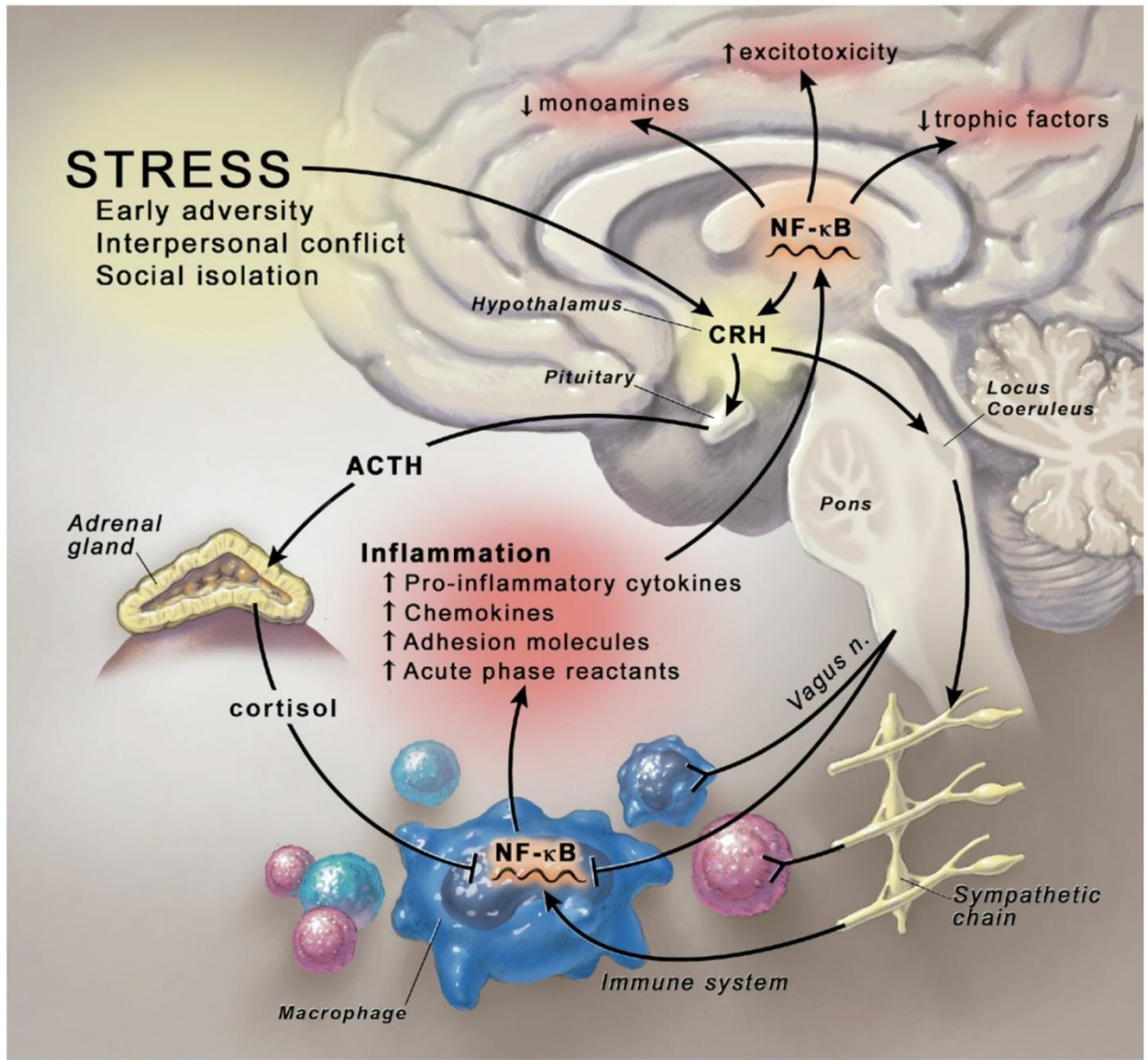
Age 41 ± 9

HAM 20 ± 3

post 6.7 ± 4

Different Treatments; Different Targets

HAM = HAM-D Score; P = inferior parietal; th = thalamus; hc = hippocampus; pCg = posterior cingulate; mF = medial frontal; vF = ventral prefrontal; Goldapple K et al. (2004), Arch Gen Psychiatry 61(1):34-41



Current Treatment Options for Depression

Goal = reduce symptoms of depression and return patient to full, active life

Nonpharmacologic

- Psychotherapy
 - Cognitive behavioral therapy
 - Interpersonal therapy
 - Psychodynamic therapy
- Electroconvulsive therapy
- Phototherapy

Pharmacologic

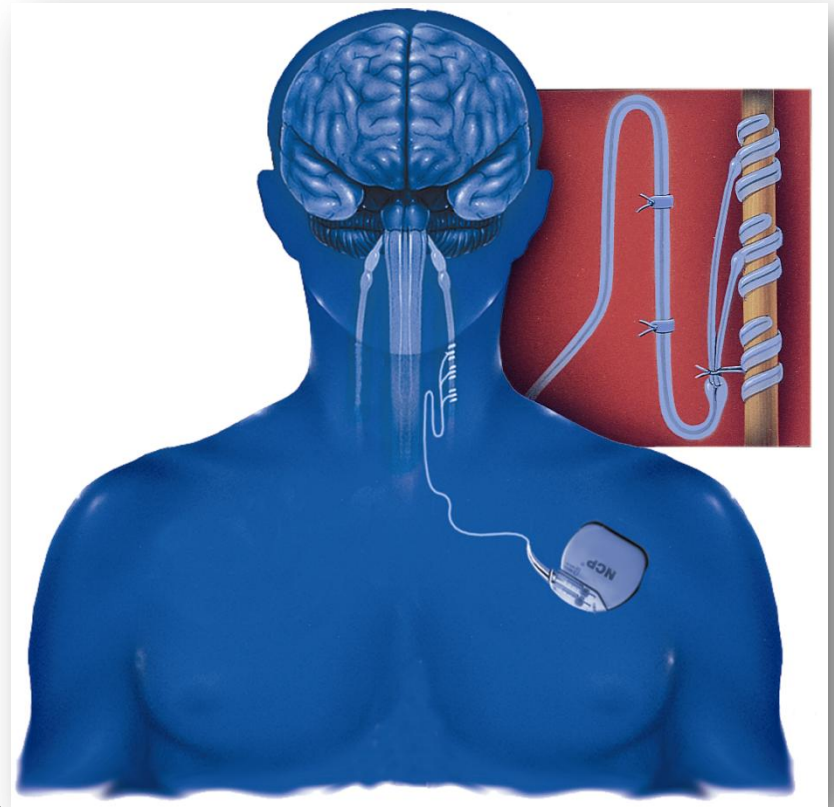
- Antidepressant medications

Optimizing current treatments

- ECT effective for depression¹
 - Limitations include side effects and high relapse rate (even with continuation ECT)²
 - Increasingly focal ECT may be efficacious with fewer side effects^{3,4}
- Magnetic seizure therapy
 - Convulsive therapy with a very focal initial stimulation
 - Preliminary efficacy suggested with fewer cognitive side effects than ECT^{5,6}

Vagus Nerve Stimulation (VNS)

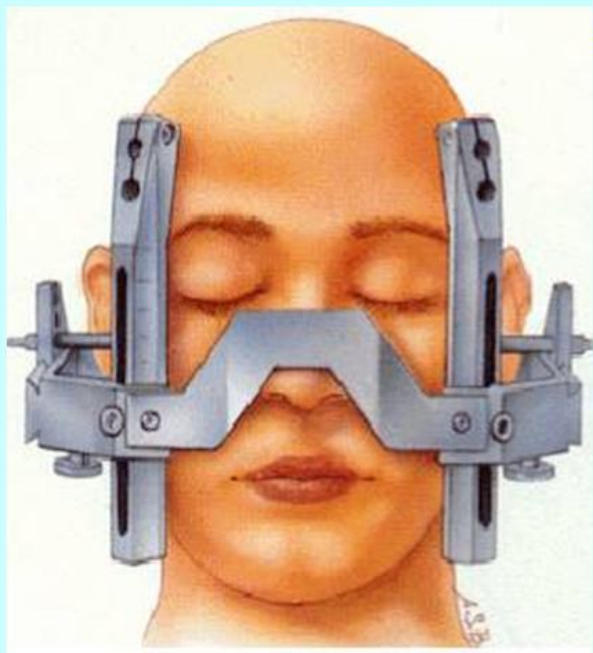
- FDA-approved (1997) for treatment of medication-refractory epilepsy
- FDA-approved (2005) for treatment of depression that has not responded to four or more medications
- Achieved by implanting a pulse generator attached to (usually) the left vagus nerve



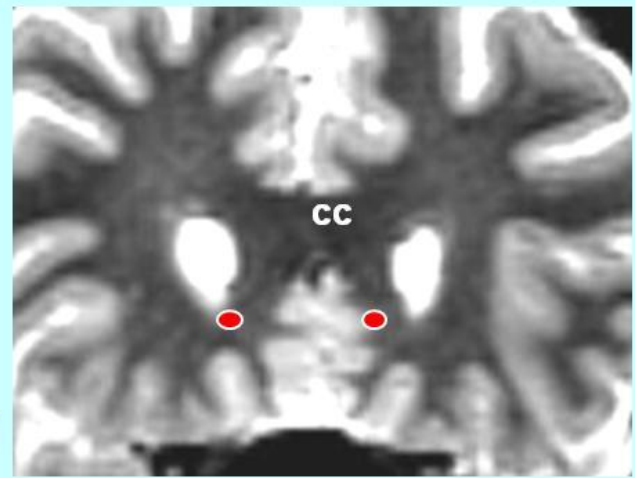
rTMS

- Studied for treatment of depression since 1993
 - Multiple open and sham-controlled studies have been performed; meta-analyses support antidepressant effects for high frequency left-sided rTMS^{1,2}
 - Some studies have suggested a favorable comparison to ECT, but data are mixed^{3,4}
 - Low frequency right-sided rTMS may also have antidepressant effects^{5,6}
- Side effects are generally mild; serious adverse events (seizures) from TMS performed within current safety guidelines are very rare⁷

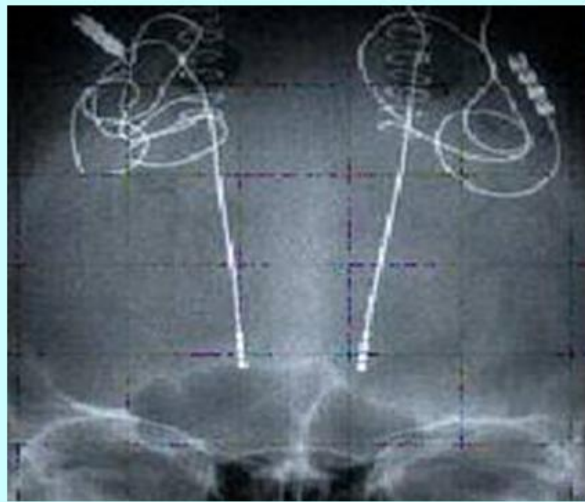
1Holtzheimer et al., Psychopharm Bull, 2001; 2Kozel et al., Journal of Psychiatric Practice, 2002; 3Grunhaus et al., Biol Psychiatry, 2000; 4Eranti et al., Am J Psychiatry, 2007; 5Fitzgerald et al., Arch Gen Psychiatry, 2003; 6Januel et al., Prog Neuropsychopharmacol Biol Psychiatry, 2006; 7Wassermann, Electroencephalogr Clin Neurophysiol, 1998



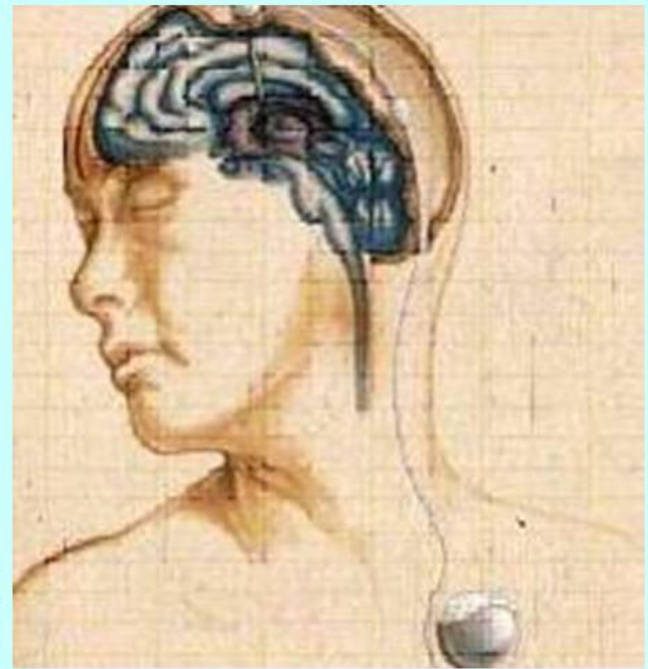
FRAME



TARGET



IMPLANTS



ENTIRE SYSTEM

