Depression

"affective disorders"
"mood disorders"
(or whatever they're calling it these days)

Classification

- reactive vs. endogenous
  - reactive depressions are reactions to obviously stressful life events
  - endogenous depressions have no obvious environmental cause and are, therefore, assumed to be caused biologically
    - continuous or episodic endogenous depression
- unipolar vs. bipolar - noncycling depression vs. mood state cycling between depression and mania
- major depressive disorder vs. dysthymia (a person who is dysthymic is always mildly depressed)
- our discussion is restricted to unipolar MDD

Statistics

- one of the most common of psychological disorders
- figures on prevalence vary widely from 5% to 20%
- book says 3-7% (MDD); others say up to 20%
- about twice as prevalent in woman than in men (depending upon the diagnostic criteria used)
- bipolar disorder about equal between men and women (risk: 2-3%)

Major Depression

Definitions

Major depression is one of the most common mental disorders in the United States. For some individuals, major depression can result in severe impairments that interfere with or limit one's ability to carry out major life activities.

Additional information can be found on the NIMH Health Topics page on Depression.

The past year prevalence data presented here for **major depressive episode** are from the 2016 National Survey on Drug Use and Health (NSDUH). The NSDUH study definition of major depressive episode is based mainly on the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV):

- A period of two weeks or longer during which there is either depressed mood or loss of interest or pleasure, and at least four other symptoms that reflect a change in functioning, such as problems with sleep, eating, energy, concentration, self-image or recurrent thoughts of death or suicide.
- Unlike the definition in the DSM-IV, no exclusions were made for a major depressive episode caused by medical illness, bereavement, or substance use disorders.

Prevalence of Major Depressive Episode Among Adults

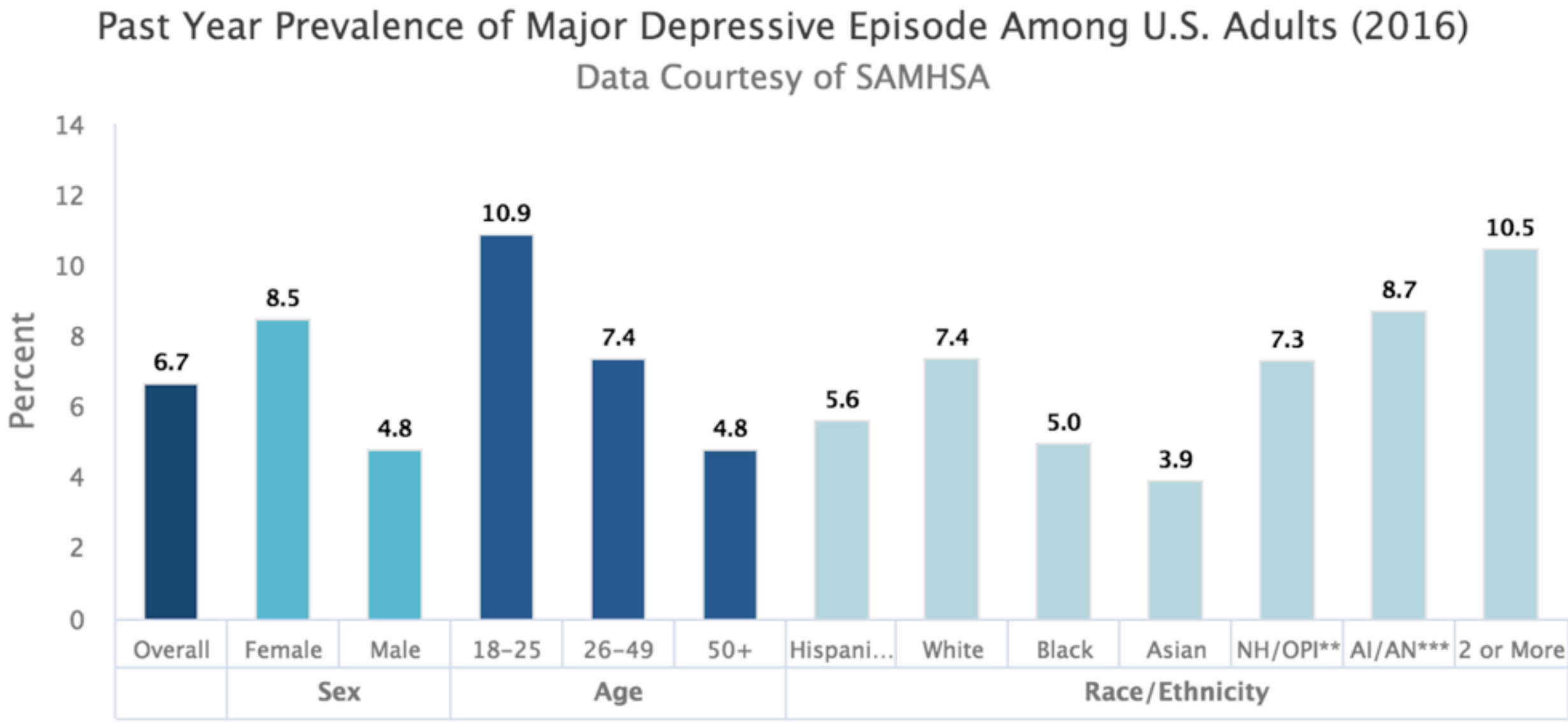
- Figure 1 shows the past year prevalence of major depressive episode among U.S. adults aged 18 or older in 2016.
  - An estimated 16.2 million adults in the United States had at least one major depressive episode. This number represented 6.7% of all U.S. adults.
  - The prevalence of major depressive episode was higher among adult females (8.5%) compared to males (4.8%).
  - The prevalence of adults with a major depressive episode was highest among individuals aged 18-25 (10.9%).
  - The prevalence of major depressive episode was highest among adults reporting two or races (10.5%).

This is what the NIMH says

https://www.nimh.nih.gov/health/statistics/major-depression.shtml

Figure 1 is on the next slide.

Figure 1.


Past Year Prevalence of Major Depressive Episode Among U.S. Adults (2016)
Data Courtesy of SAMHSA
Percent
14
12
10
8
6
4
2
0
6.7
8.5
4.8
10.9
7.4
4.8
5.6
7.4
5.0
3.9
7.3
8.7
10.5
Overall
Female
Male
18–25
26–49
50+
Hispani...
White
Black
Asian
NH/OPI**
AI/AN***
2 or More
Sex
Age
Race/Ethnicity

Symptoms

- it is probably useful to divide symptoms into cognitive, emotional, and somatic
  - cognitive: problems with memory, decision making, attention, concentration, initiating behavior, etc.
  - emotional: feelings of despair, guilt, unworthiness, hopelessness, apathy, anhedonia, amotivational state
  - somatic: changes in sleep cycle, appetite, etc.; stress response
- 15% attempt suicide (30% for bipolar)
- death from unnatural causes is 30 times the rate for matched control subjects

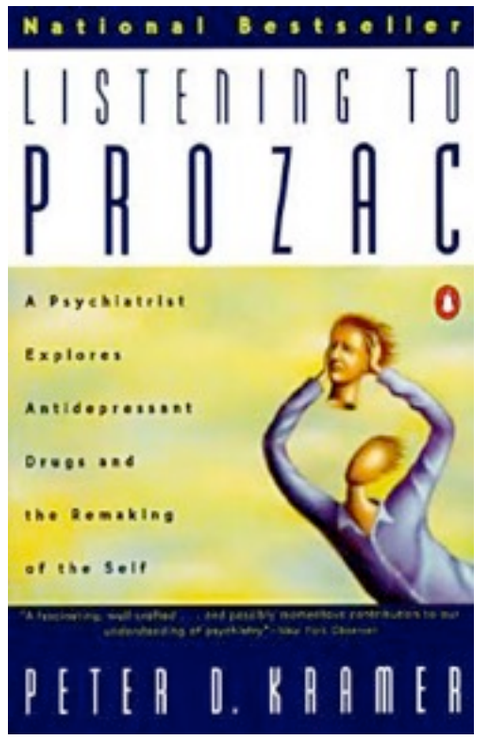
Heritability and Genetics

The patterns are similar to those that occur in schizophrenia.

- 69% of MZ twins with one index case were concordant
- 13% of DZ twins with one index case were concordant
- studies of biological relatives support the findings of the twin studies
- these days biological clock genes are the prime suspects

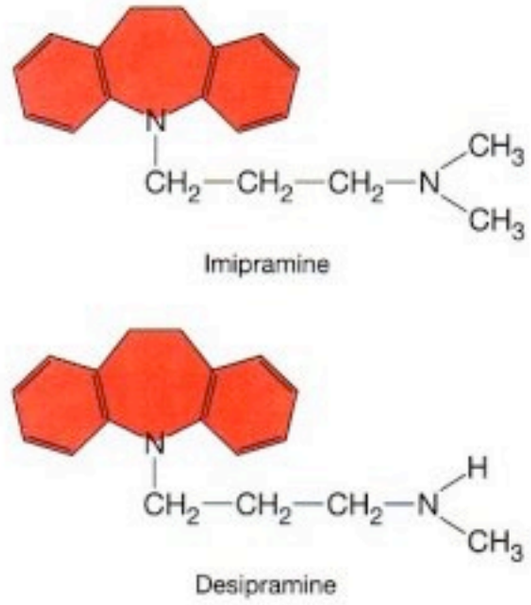
Effective Therapies

- traditional psychotherapy hasn't been very successful with endogenous depression
- effective biomedical treatments
  - MAO inhibitors (iproniazid)
  - tricyclic antidepressants - e.g., Elavil (1960s)
  - selective serotonin reuptake inhibitors (SSRIs) - e.g., Prozac (1986)
  - serotonin and norepinephrine reuptake inhibitors (SNRIs) - e.g., Cymbalta



1993

- lithium salts (lithium carbonate) - for bipolar depression
- electroconvulsive therapy (ECT)
- sleep deprivation
- phototherapy for seasonal affective disorder
- psychosurgery



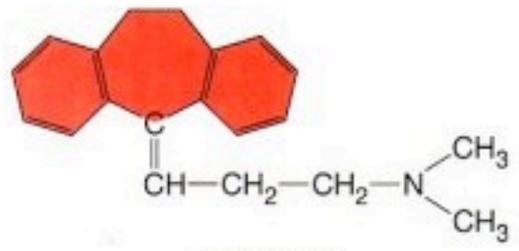
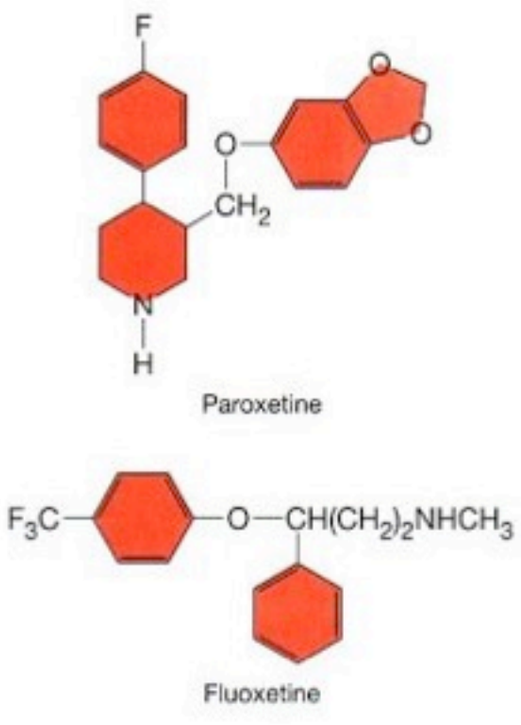


Figure 18–11 *Chemical Structures of Three Tricyclic Antidepressant Drugs.* The antidepressant efficacies of these drugs share a common theme of elevating extracellular monoamine concentrations, though a host of other neurochemical effects are observed. Adverse reactions to these drugs include, among other things, fine hand tremors, blurred vision, urinary retention, dry mouth, and constipation.



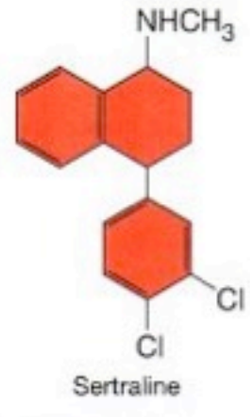
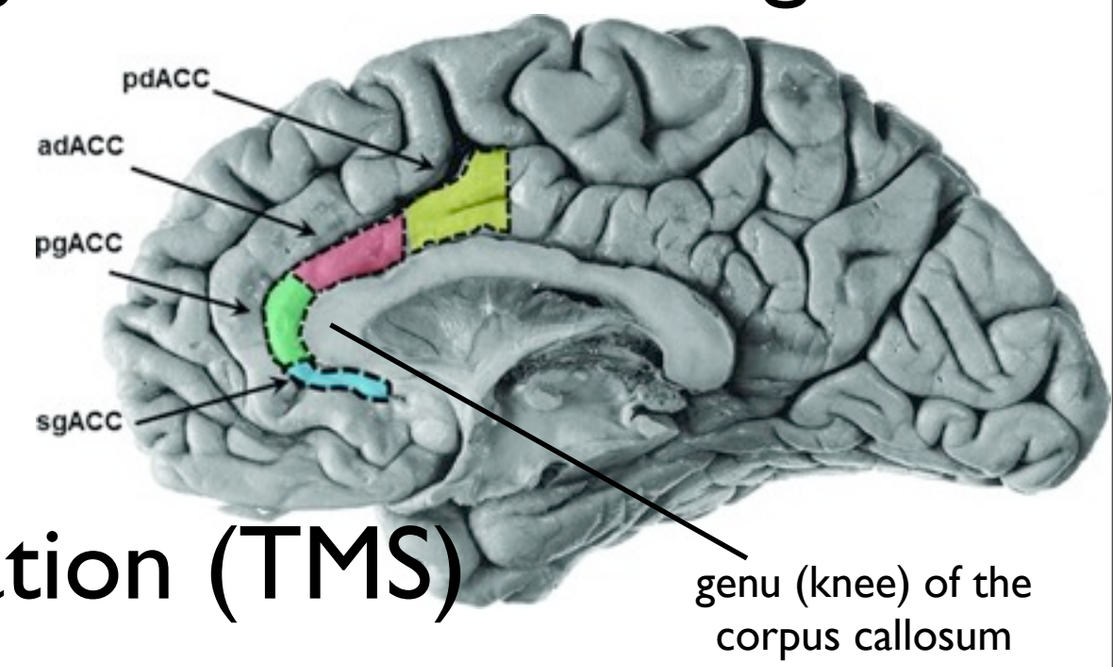


Figure 18–12 *The Chemical Structures of Three Selective Serotonin Re-uptake Inhibitors (SSRIs).* The antidepressant efficacy of these drugs is claimed to be related to their ability to block the re-uptake of serotonin, thereby increasing the serotonin concentrations in the synaptic cleft. While this increase in concentration is almost immediate, the therapeutic benefits take one to two weeks to develop. The success rate of SSRIs is around 85 percent and the SSRIs are generally better tolerated than traditional antidepressants. Some adverse reactions include anxiety, agitation, sleep disturbance, slight tremors, headaches, and sexual dysfunction (e.g., delayed ejaculation and impotence).

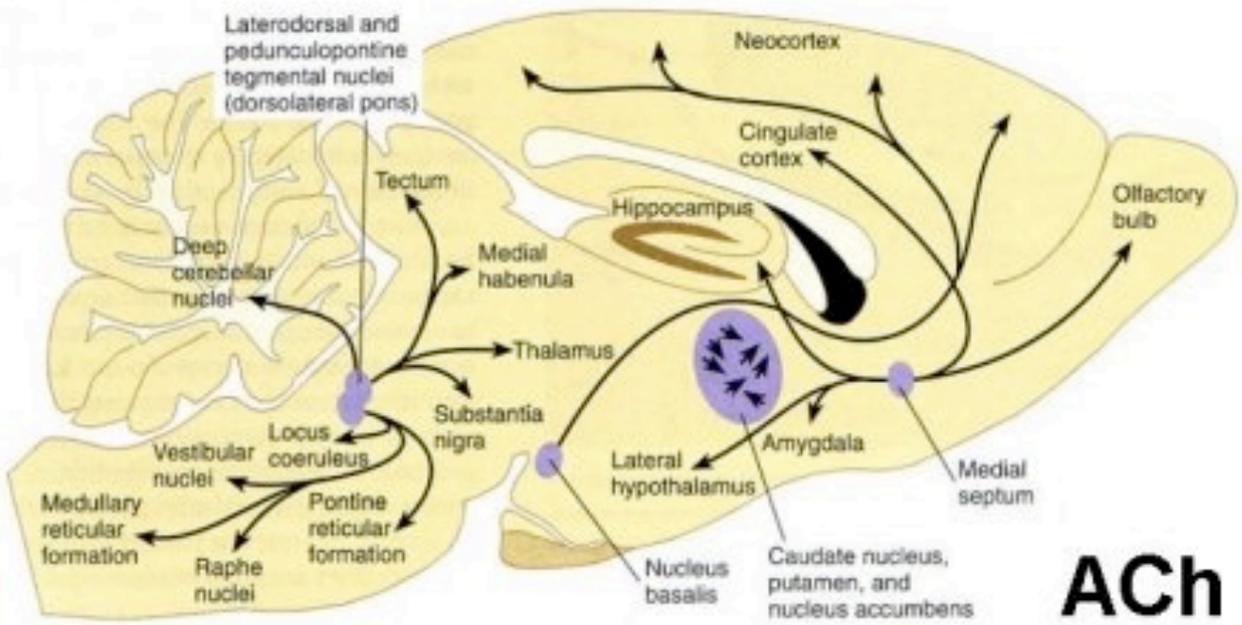
Depression

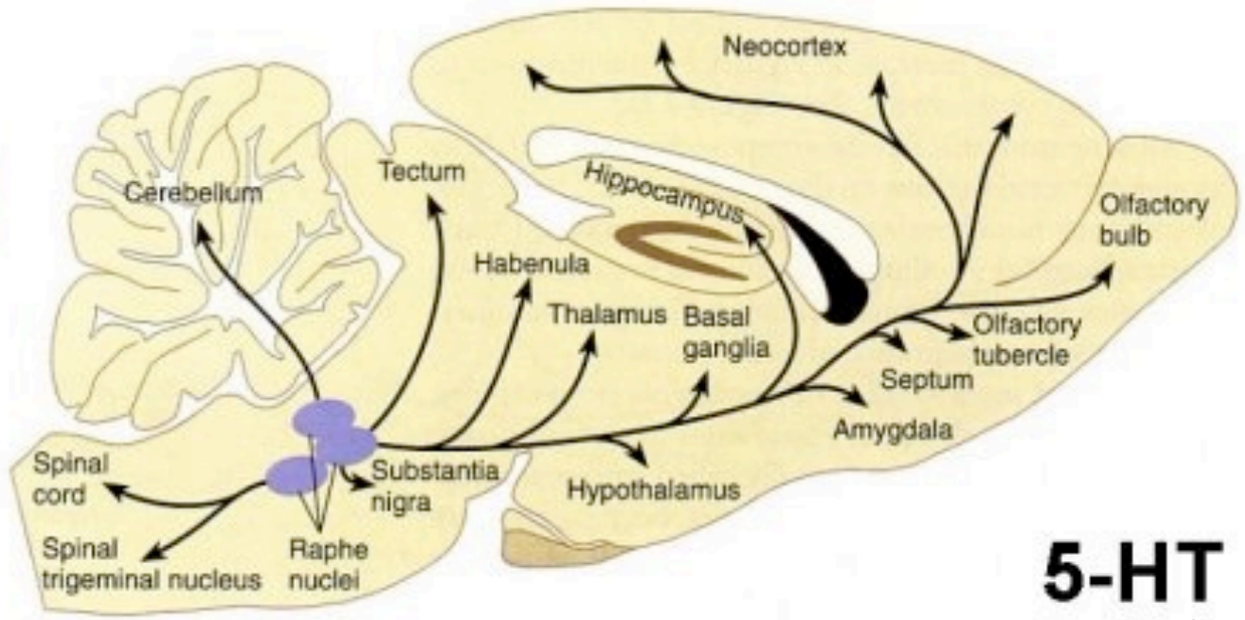
- 20-40% of patients are drug resistant
- electroconvulsive therapy (ECT) often helps these patients
- sleep deprivation is also often an effective (although temporary) treatment
- deep brain stimulation - subgenual anterior cingulate cortex (sgACC)
- vagus nerve stimulation- 10th cranial nerve (X)
- transcranial magnetic stimulation (TMS)

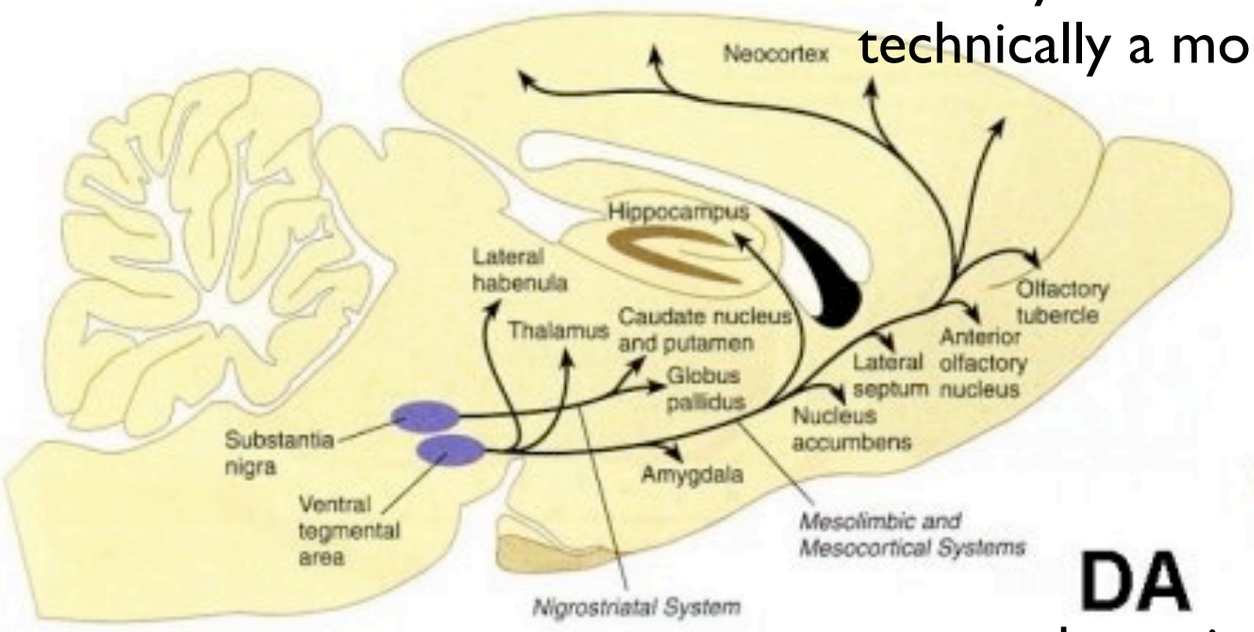


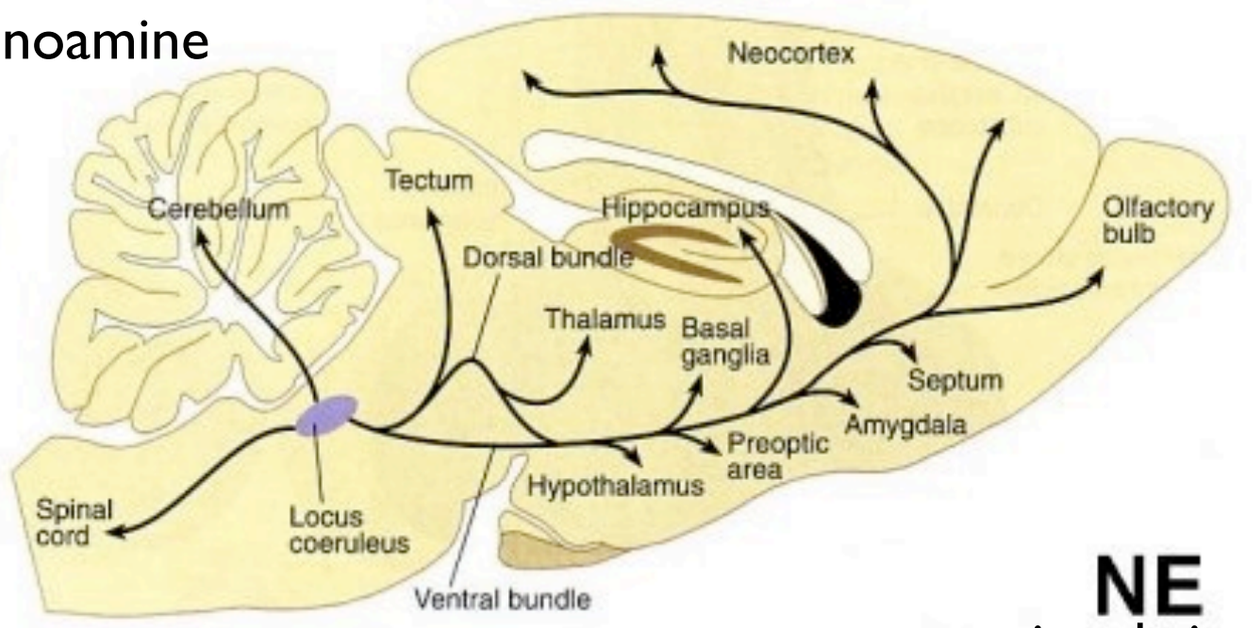
The Monoamine Theory

The monoamine neurotransmitter systems originate in the brainstem and project widely to the rest of the brain.









The Monoamine Theory

- this has been the most popular theory for decades (since before I was in grad school!)
- evidence supporting the monoamine theory
  - treatments that deplete the brain of MAs cause depression - reserpine, used to treat hypertension, has been found to cause severe (even suicidal) depression in up to 15% of those who use it

The Monoamine Theory

- evidence supporting the monoamine theory
  - suicidal depression is associated with abnormally low levels of 5-HIAA
    - a metabolite of serotonin (more 5-HIAA means more serotonin activity in the brain)
    - in one study, 5-HIAA was measured by spinal tap in depressed patients, and the patients were classified as having 5-HIAA levels above average or below average - those with below average 5-HIAA were much more likely to commit suicide

depressed patients	
5-HIAA above median	5-HIAA below median
no suicides	20% committed suicide

The Monoamine Theory

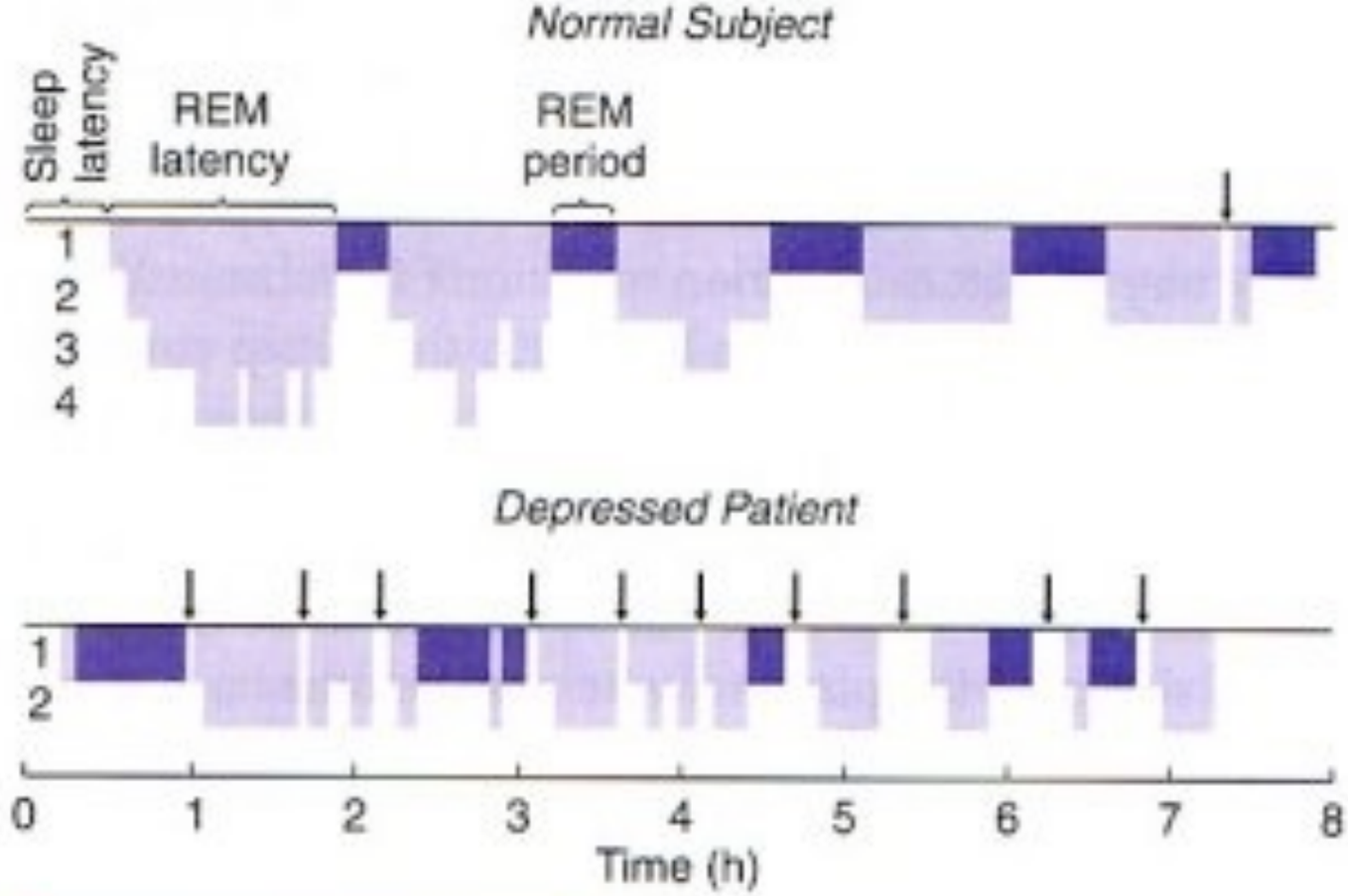
- evidence supporting the monoamine theory
  - drugs successful in alleviating depressive symptoms are MA agonists (increase MA activity in the brain)
  - diets that deplete serotonin cause relapse
    - tryptophan depletion procedure (1 day of low tryptophan diet followed by amino acid cocktail that is tryptophan-free) - brain tryptophan levels plummet and patients relapse
    - no effect on normal control subjects

The Monoamine Theory

- questions
  - is the DA reward system involved?
    - possibly - Wellbutrin is a DA agonist and is an effective antidepressant
  - why does it take antidepressant drugs 2-3 weeks to have a therapeutic effect?
    - there are a good many possibilities, but as yet there is no definite answer to this question
    - but it is not a fatal flaw in the MA theory

Depression & Circadian Rhythms

- seasonal affective disorder (SAD) - a form of depression suffered only in winter when exposure to daylight is at a minimum
- one of the most prominent symptoms of depression is disorganized sleep (next slide)

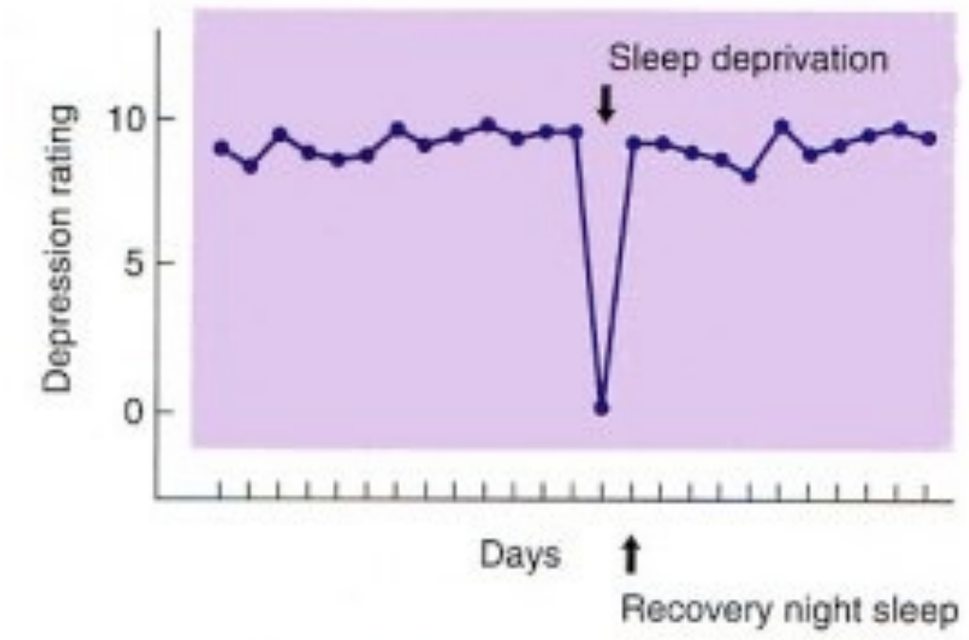


Patterns of the stages of sleep of a normal subject and of a patient with major depression. Note the reduced sleep latency, reduced REM latency, reduction in slow-wave sleep (stages 3 and 4), and general fragmentation of sleep (arrows) in the depressed patient.

(From Gillin, J. C., and Borbély, A. A. *Trends in Neurosciences,* 1985, *8,* 537–542. Reprinted with permission.)

Depression & Circadian Rhythms

- sleep deprivation is an effective treatment for depression
  - total sleep deprivation for one night has a temporary effect (see graph)
  - selective REM sleep deprivation takes several weeks to work but may result in long-term improvement even after treatment is discontinued
- almost all antidepressant drugs suppress REM sleep
- and all drugs that suppress REM sleep act as antidepressants



Changes in the depression rating of a depressed patient produced by a single night's total sleep deprivation.
(From Wu, J. C., and Bunney, W. E. *American Journal of Psychiatry*, Vol. 147, pp. 14–21, 1990. Copyright 1990, the American Psychiatric Association. Reprinted by permission.)

Depression & Circadian Rhythms

- the Wu and Bunney theory

Am J Psychiatry 1990; 147:14-21

REVIEW OF REPORTED CASES

The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis

JC Wu and WE Bunney
Department of Psychiatry and Human Behavior, University of California, Irvine 92717.

Sixty-one papers involving over 1,700 subjects have documented that over half of depressed patients experience an antidepressant response to sleep deprivation. Eighty-three percent of unmedicated depressed patients who had an antidepressant response to sleep deprivation relapsed after one night of sleep. Short naps can also activate severe relapses. The authors suggest that these phenomenological observations concerning relapse with a night of sleep or with naps after successful sleep deprivation would be compatible with the existence of a sleep- associated depressogenic process.

- the Wu and Bunney theory

  - they noted that total sleep deprivation causes an immediate (but temporary) remission of depression

  - suggested that a depressogenic substance is produced in the brain during sleep that is gradually broken down during waking

  - this is consistent with the well known fact that depressed patients often feel worst in the mornings, but their mood gradually improves during the day (endogenous depression; tends to be the reverse in reactive depression)

  - not everyone has a good response to sleep deprivation - but there are differences in the brain scans of responders and nonresponders (next slide)

These PET scans show differences in brain activity between people how respond to sleep deprivation and those who don't.

DEPRESSION AND ANXIETY 14:37–49 (2001)

SLEEP DEPRIVATION AS A MODEL EXPERIMENTAL ANTIDEPRESSANT TREATMENT: FINDINGS FROM FUNCTIONAL BRAIN IMAGING

J. Christian Gillin, M.D.,[1*] Monte Buchsbaum, M.D.,[2] Joseph Wu, M.D.,[2] Camellia Clark , M.D.,[1] and William Bunney, Jr., M.D.[1]

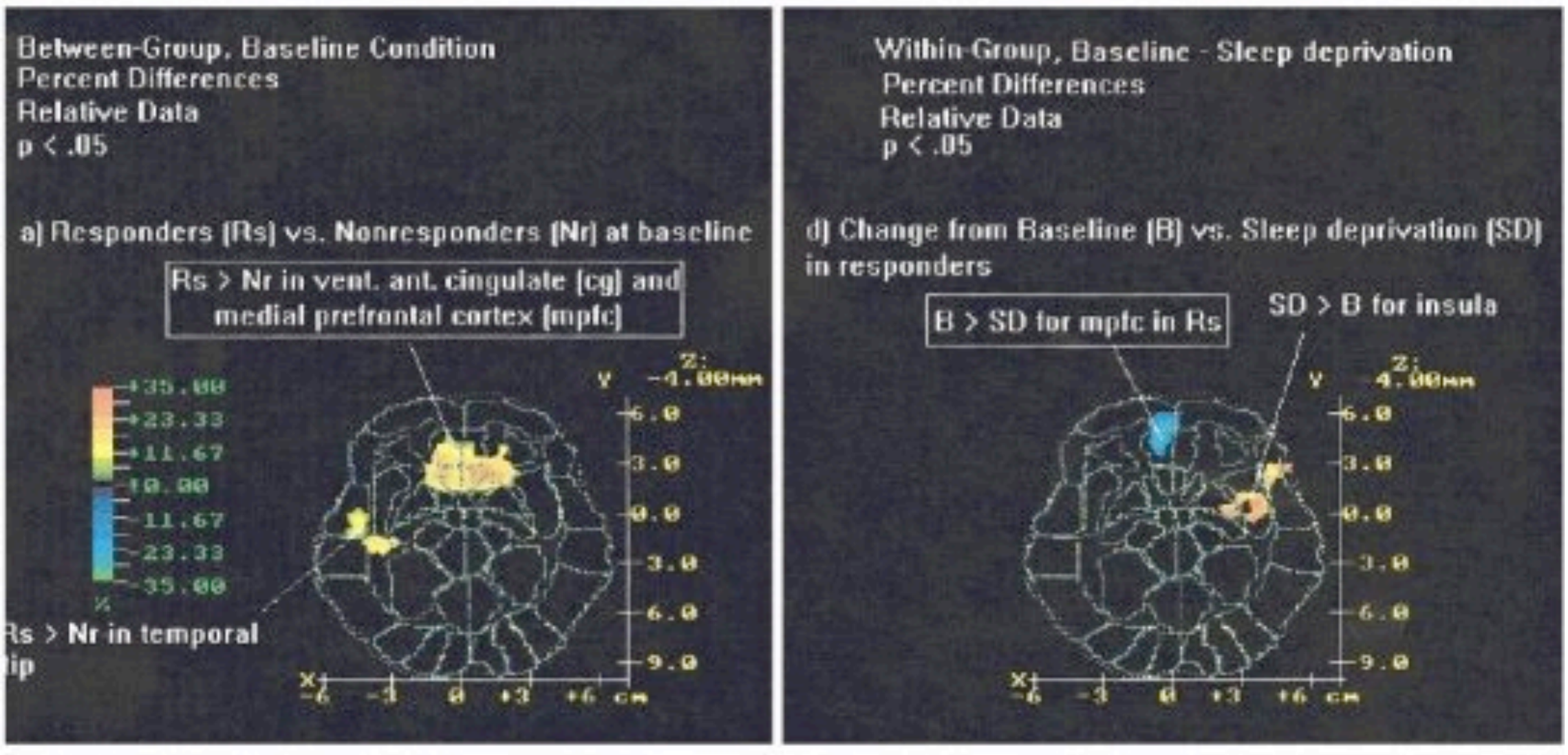


Figure 1. Clinical antidepressant response is significantly correlated with reduction in relative local cerebral glucose metabolic rate responders following total sleep deprivation for one night in unmedicated depressed patients [Wu et al., 1999].

The Resilience Theory

- We all suffer psychological stress and even mild depression from time to time.
- These result in the brain being "flooded" with stress hormones (glucocorticoids).
- Too much stress hormones can damage brain cells, esp. in the hippocampus.
- Most of us can repair this damage -- our brains are "resilient."
- But for one reason or another, some people can't -- their brains are not "resilient."

The Resilience Theory

- Once sufficient damage occurs, the person becomes prone to serious depression.
- Antidepressants may work because they promote resilience in the brain.

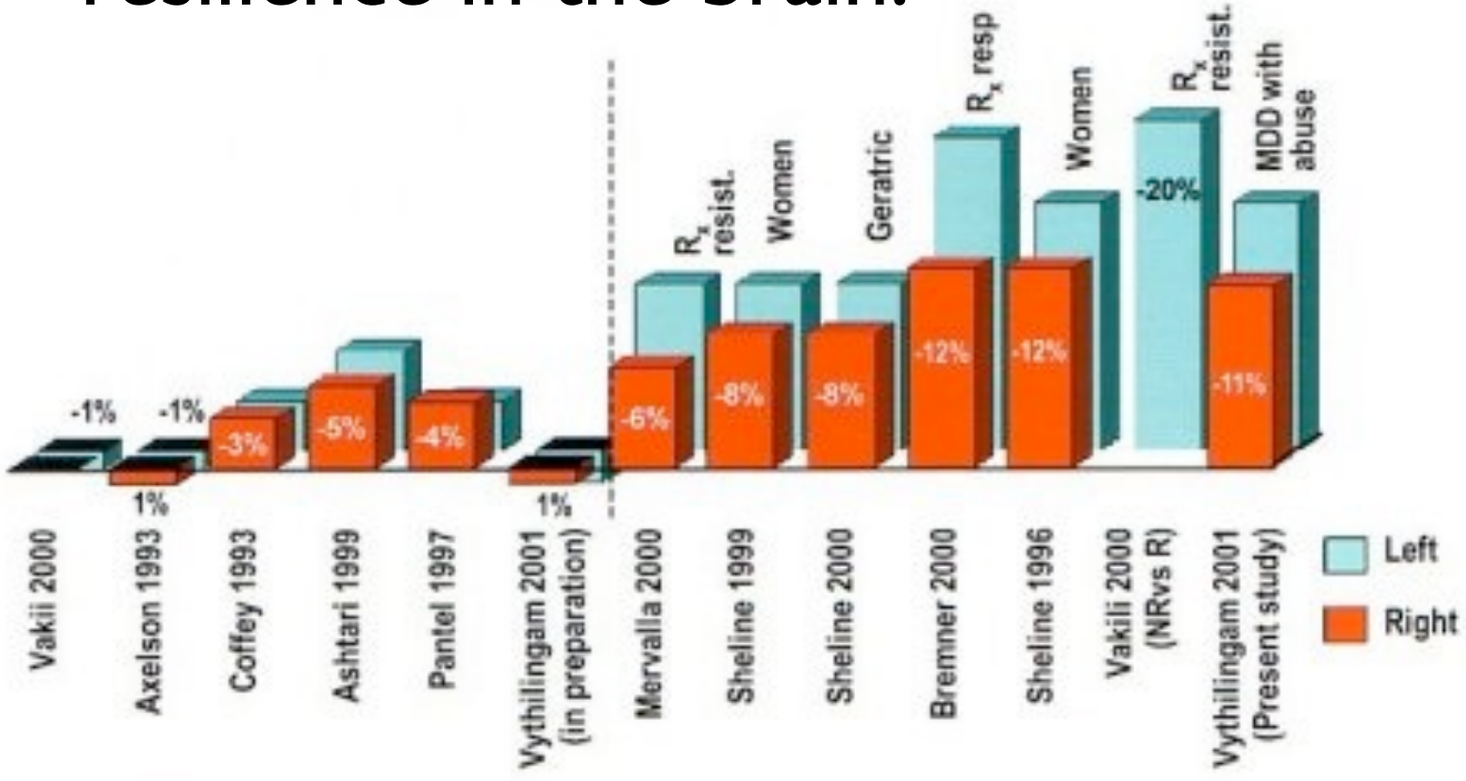
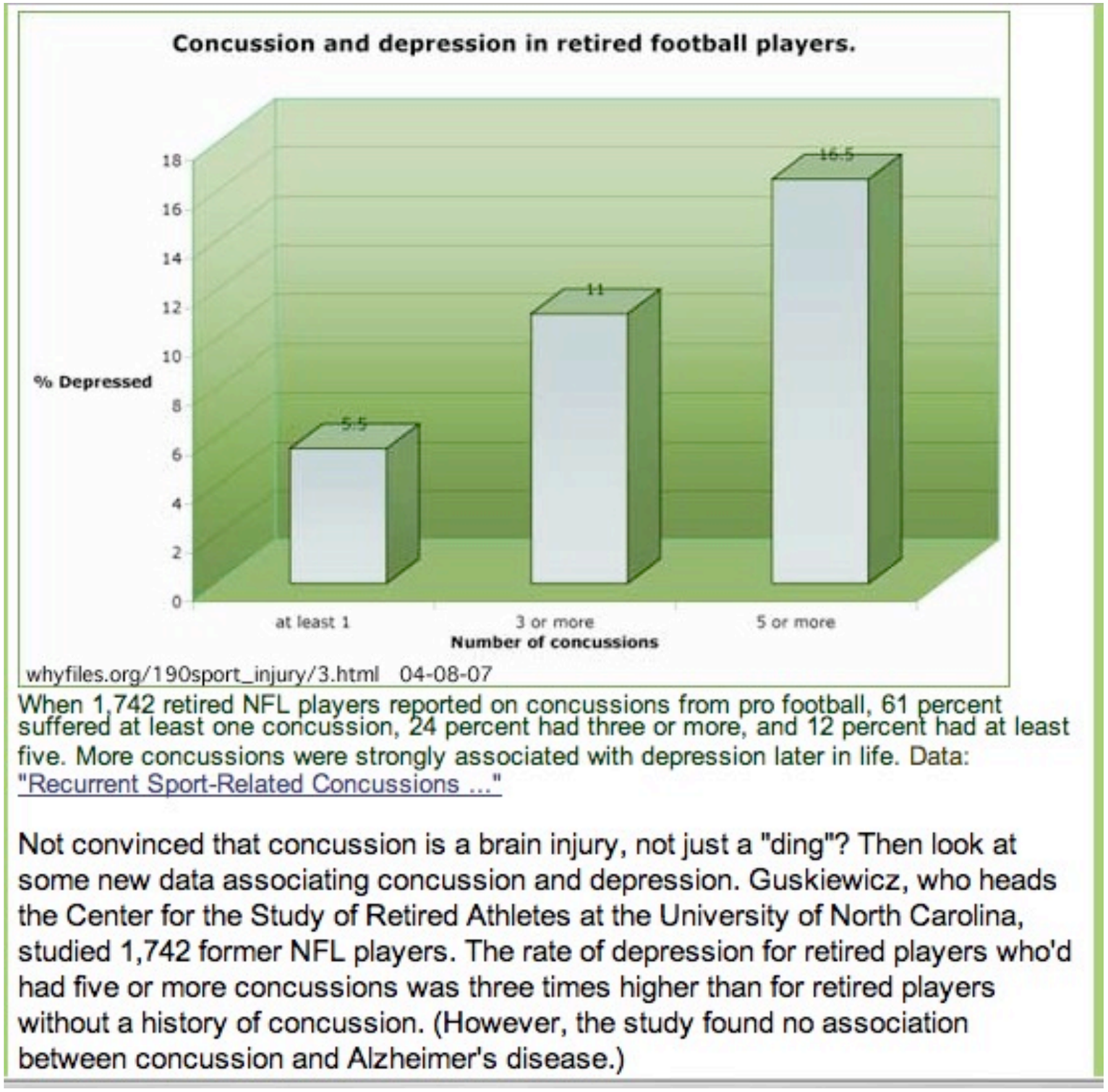


Fig. 6.1. Hippocampal volume in depression. Studies either showed no change (left of dotted line) or a reduction in hippocampal volume in depression. Factors that may contribute to smaller volume include chronicity of disease, treatment resistance, and early trauma.

Source: Bremner (2005)

7 out of 13 studies showed significantly reduced hippocampal volume in depressed patients, especially in the left hemisphere.

Further evidence of a relationship between brain damage and depression



When 1,742 retired NFL players reported on concussions from pro football, 61 percent suffered at least one concussion, 24 percent had three or more, and 12 percent had at least five. More concussions were strongly associated with depression later in life. Data: "Recurrent Sport-Related Concussions ..."

Not convinced that concussion is a brain injury, not just a "ding"? Then look at some new data associating concussion and depression. Guskiewicz, who heads the Center for the Study of Retired Athletes at the University of North Carolina, studied 1,742 former NFL players. The rate of depression for retired players who'd had five or more concussions was three times higher than for retired players without a history of concussion. (However, the study found no association between concussion and Alzheimer's disease.)

Resilience Theory (concluded)

- antidepressant drugs and ECT increase neurogenesis in the hippocampus (and related structures)
  - takes about 2-3 wks. for the new neurons to mature (same as delay in drug response)
  - if neurogenesis is suppressed with x-rays, antidepressant drugs are ineffective
  - exercise increases blood flow in this region and is an effective treatment for depression - also promotes neurogenesis, provided...

The Journal of Neuroscience
The Official Journal of the Society for Neuroscience

Expand

Serotonin Is Required for Exercise-Induced Adult Hippocampal Neurogenesis

Friederike Klempin[1,*], Daniel Beis[1,*], Valentina Mosienko[1], Gerd Kempermann[2,3], Michael Bader[1], and Natalia Alenina[1]

Author Affiliations

Author contributions: F.K., D.B., and N.A. designed research; F.K., D.B., and V.M. performed research; F.K. and D.B. analyzed data; F.K., G.K., M.B., and N.A. wrote the paper.

*F.K and D.B contributed equally to this work.

The Journal of Neuroscience, 8 May 2013, 33(19): 8270-8275; doi: 10.1523/JNEUROSCI.5855-12.2013

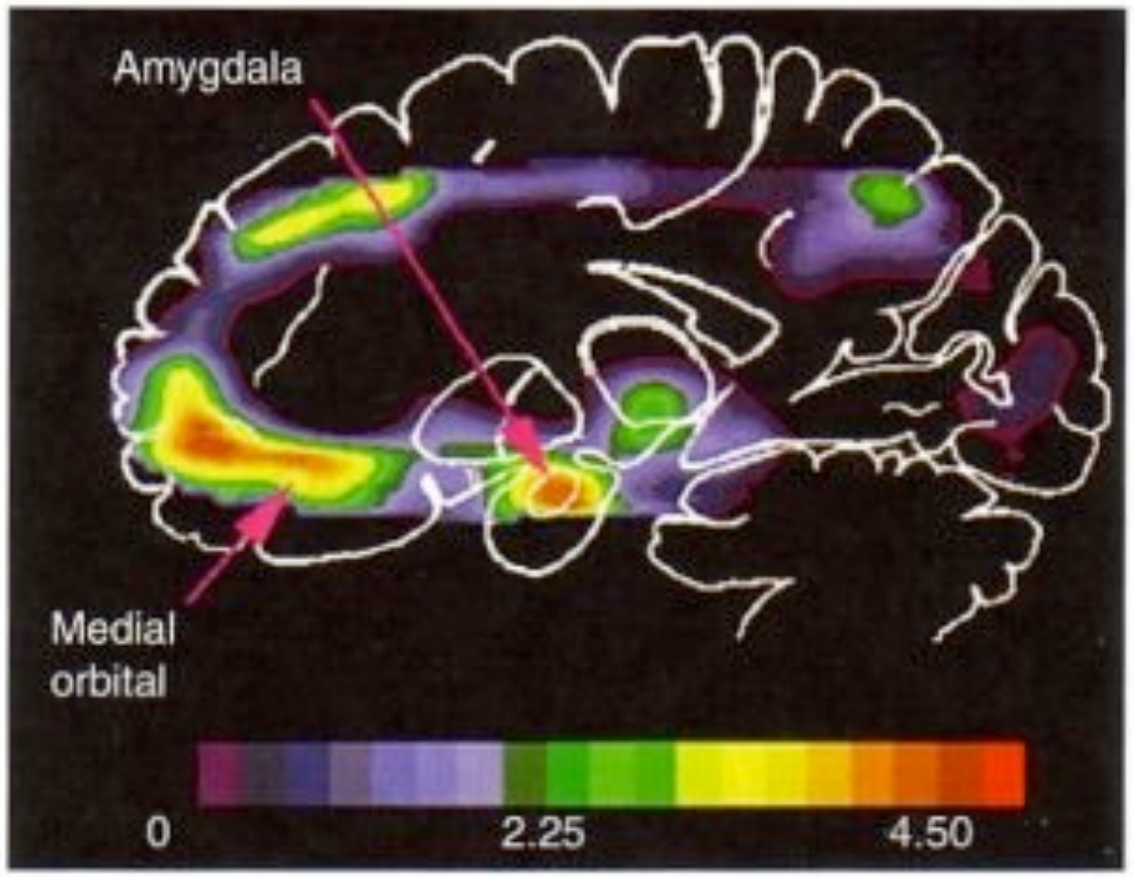
Abstract

Voluntary wheel running has long been known to induce precursor cell proliferation in adult hippocampal neurogenesis in rodents. However, mechanisms that couple activity with the promitotic effect are not yet fully understood. Using tryptophan hydroxylase (TPH) 2 deficient (*Tph2*-deficient) mice that lack brain serotonin, we explored the relationship between serotonin signaling and exercise-induced neurogenesis. Surprisingly, *Tph2*-deficient mice exhibit normal baseline hippocampal neurogenesis but impaired activity-induced proliferation. Our data demonstrate that the proproliferative effect of running requires the release of central serotonin in young-adult and aged mice. Lack of brain serotonin further results in alterations at the stage of Sox2-positive precursor cells, suggesting physiological adaptations to changes in serotonin supply to maintain homeostasis in the neurogenic niche. We conclude that serotonin plays a direct and acute regulatory role in activity-dependent hippocampal neurogenesis. The understanding of exercise-induced neurogenesis might offer preventive but also therapeutic opportunities in depression and age-related cognitive decline.

Received December 21, 2012.
Revision received March 27, 2013.
Accepted April 3, 2013.

PET and fMRI Studies

- Drug-free depressives, both those actively depressed and those in remission, show increased activity in the amygdala.
  - 50-75% increase in blood flow
  - correlated with severity of depression
- In addition, those in an active depressive episode show decreased activity in the dorso-lateral prefrontal cortex.
- The subgenual anterior cingulate cx (medial PFC) is also another area of interest - increased activation in depressed patients.



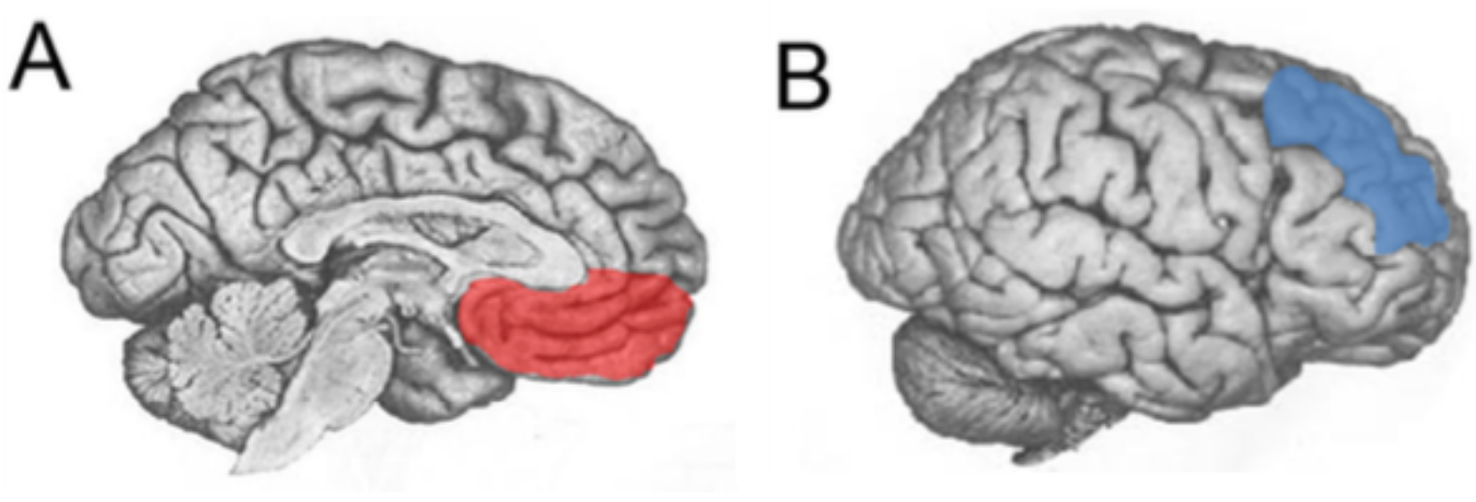
Composite fMRI image showing increased metabolic rate in the amygdala and medial orbitofrontal cortex of patients with unipolar depression.
(From Drevets, W. C., *Current Opinion in Neurobiology*, 2001, *11*, 240–249.)

Depression and the Frontal Lobes

- the old view
  - right PFC mediates negative emotions
  - left PFC mediates positive emotions
  - damage to the left PFC results in "pseudodepression"
- executive functions again - esp. management of mood and emotion
- however, depressed people also have problems with memory, decisions making, initiating behavior, etc.

Depression and the Frontal Lobes

- the new view - two areas of the prefrontal cortex seem to be important
  - ventromedial prefrontal cortex (which includes the subgenual cingulate gyrus) - see A in diagram
  - dorsolateral prefrontal cortex - see B in diagram



Depression and the Frontal Lobes

- the new view
  - ventromedial prefrontal cortex - too active
  - dorsolateral prefrontal cortex - not active enough
    - although can be activated by appropriate tasks like working memory tasks
    - so unlike in schizophrenia, evidence suggests no damage or degeneration here
    - although some studies do find decreased volume

Depression and the Frontal Lobes

- the new view - scans and stimulation
  - scans of depressed people show increased activity in VMPFC and decreased activity in DLPFC (compared to normal controls)
  - scans of people who have recovered from depression (for any reason) show increased activity in the DLPFC and decreased activity in the VMPFC (compared to their depressed state)
  - activation of DLPFC by transcranial magnetic stimulation or inhibition of VMPFC by deep brain stimulation seems to have therapeutic benefit in many cases

Depression and the Frontal Lobes

- the new view - lesion studies
  - people who have sustained lesions bilaterally in the DLPFC are more likely to be depressed
  - people who have sustained lesions bilaterally in the VMPFC are less likely to be depressed
  - one seriously depressed woman who attempted suicide by gunshot to the head managed to destroy most of the ventral part of her prefrontal cortex (and survived) - her depression was markedly diminished and she reported an absence of sadness and suicidal ideation

Depression and the Frontal Lobes

- the new view - DLPFC
  - connected to posterior association cortices, thalamus, basal ganglia, and hippocampus
  - involved in executive functions, working memory, planning, abstract reasoning, and cognitive flexibility such as task switching and ability to think about multiple concepts simultaneously
  - matures late - increasing input from dopamine pathways
  - may be damaged by episodes of severe stress or circulating stress hormones

Depression and the Frontal Lobes

- the new view - VMPFC
  - connected to amygdala, hippocampus, hypothalamus, cingulate cortex, dorsomedial thalamus, ventral tegmental area, and ventromedial reward network
  - involved in emotional regulation and personal and emotional decision making (perhaps also guilt, sadness, self-dislike, and rumination)
  - develops rapidly during adolescence and young adulthood
  - heavy reciprocal interconnections with the amygdala (but this is functionally somewhat confusing)

Depression

- in summary
  - something biological is clearly going on in people with major depressive disorder
  - 50 years of research into what that might be has not led to any breakthroughs
  - however, the resilience theory is hot
  - abnormal functioning in the prefrontal cortex seems clearly to be involved
  - as of now, drug therapy, cognitive-behavioral therapy, and ECT are the best we have to offer