

Anxiety Disorders

Classification

- panic disorder
- generalized anxiety disorder (GAD)
- phobic anxiety
- social anxiety
 - social phobia (social anxiety disorder)
 - avoidant personality disorder (Axis II)
- obsessive-compulsive disorder (OCD)
- post-traumatic stress disorder (PTSD)

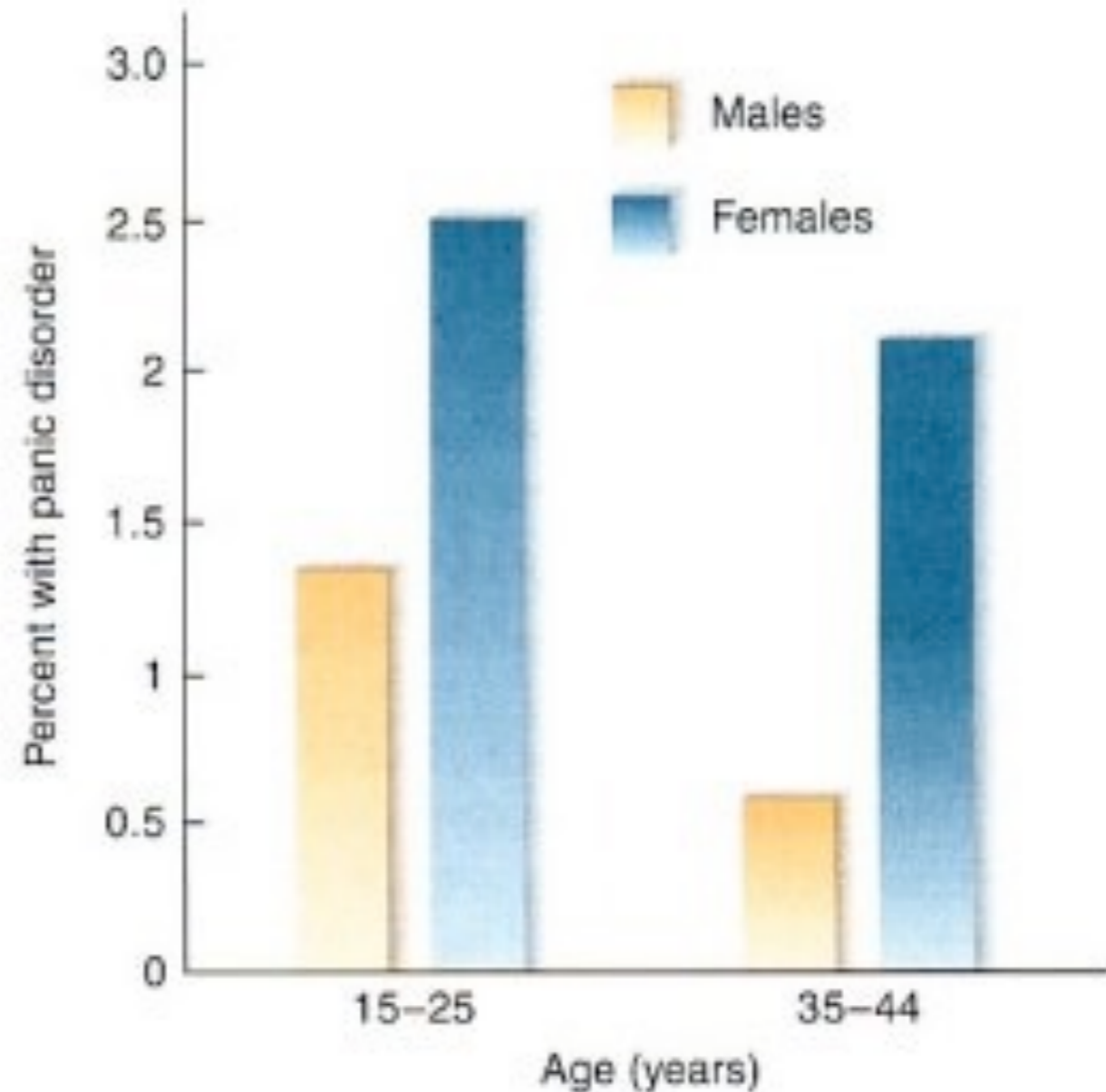
Issues

- Is this a homogeneous group of disorders? (Do OCD, PTSD, and panic disorder all belong in the same group, for example.)
- Are the disorders biological vs. psychological? (They appear to be a bit of both.)
- What is their relationship to other disorders?
 - e.g., OCD and Tourette's Syndrome appear to be related in some way
 - phobic vs. panic anxiety (Do they work the same in the brain?)
 - comorbidity with depression (Anxiety and depression have an overlapping set of symptoms.)
- overdiagnosis (and contamination of subject pools)
 - “sexy” disorders - It's almost “cool” to have an anxiety disorder, especially social anxiety.
 - insurance issues - The doc has to diagnose you with something or else he ain't gonna get paid!

Panic Disorder (PD)

- characterized by panic (anxiety) attacks - severe, incapacitating, and unpredictable attacks of panic
 - shortness of breath
 - clammy sweat
 - dizziness, faintness
 - feelings of unreality
 - sometimes mistaken for a heart attack
- anticipatory anxiety - the fear of an impending attack
- associated with secondary agoraphobia - the person is afraid to go out in public for fear of having an attack.
- lifetime risk - about 2% with usual onset in young adulthood, twice as common in women

gender and PD
(later in life the
ratio appears to be
closer to 3 to 1)

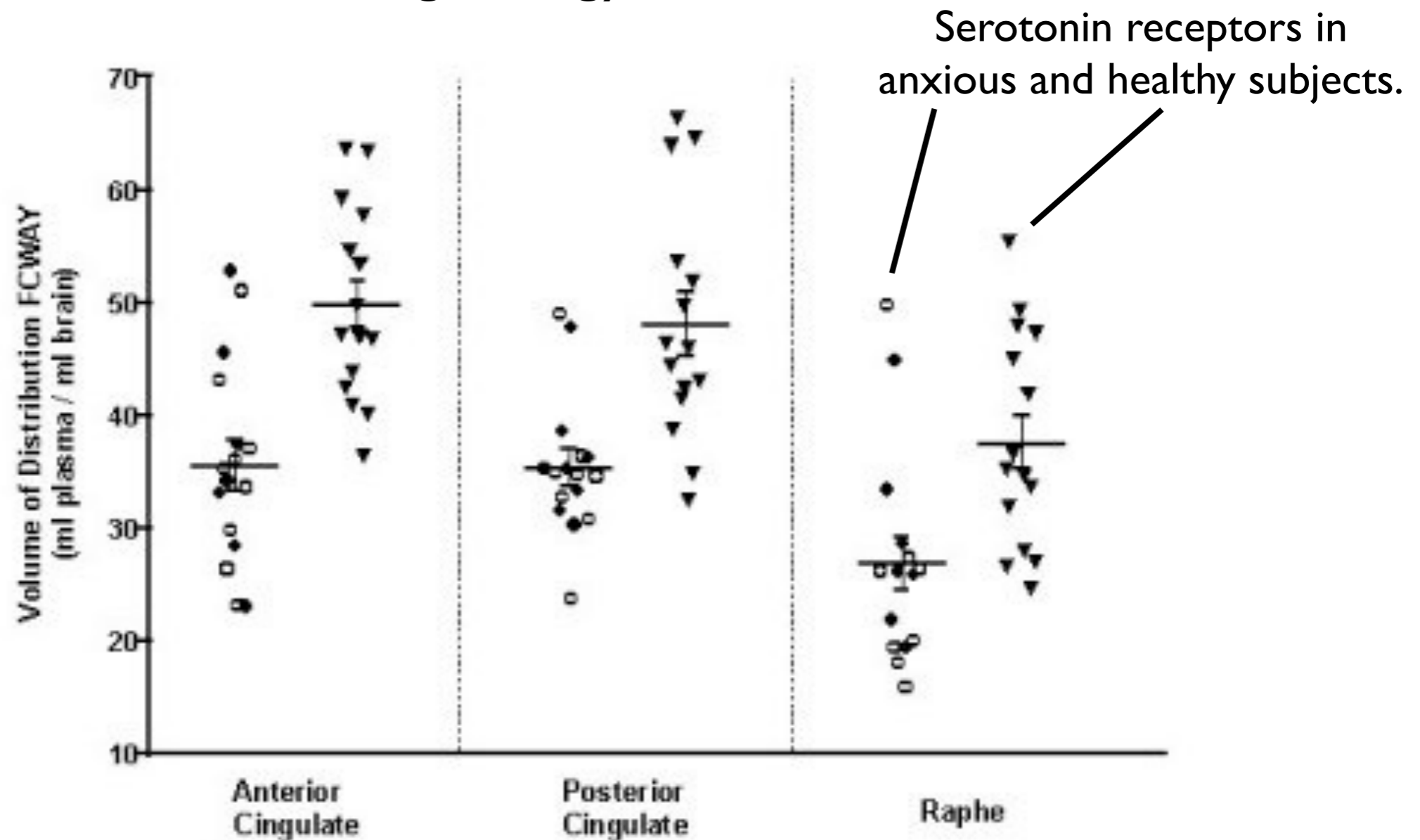


Percentage of men and women who receive a diagnosis of panic disorder earlier and later in life.

(Based on data from Eaton, W. W., Kessler, R. C., Wittchen, H. U., and Magee, W. J. *American Journal of Psychiatry*, 1994, 151, 413-420.)

- there is good evidence for a genetic predisposition in PD - some studies suggest a single, dominant gene
- PET scanning studies
 - How do you catch a panic attack in a PET scanner???
 - Panic attacks can be induced by injection of lactic acid or inhalation of carbon dioxide in people who are prone to them.
 - the temporal poles “light up” - dramatically increased blood flow and glucose utilization just before and during an attack
 - the amygdala has been implicated (the amygdala is located in the temporal pole (the anterior end of the temporal lobe)
 - decreased activation in the anterior cingulate cortex and orbitofrontal cortex has also been observed

- more PET scanning studies
- lately, studies have been looking at deficiency of serotonin receptors in areas such as the cingulate gyrus

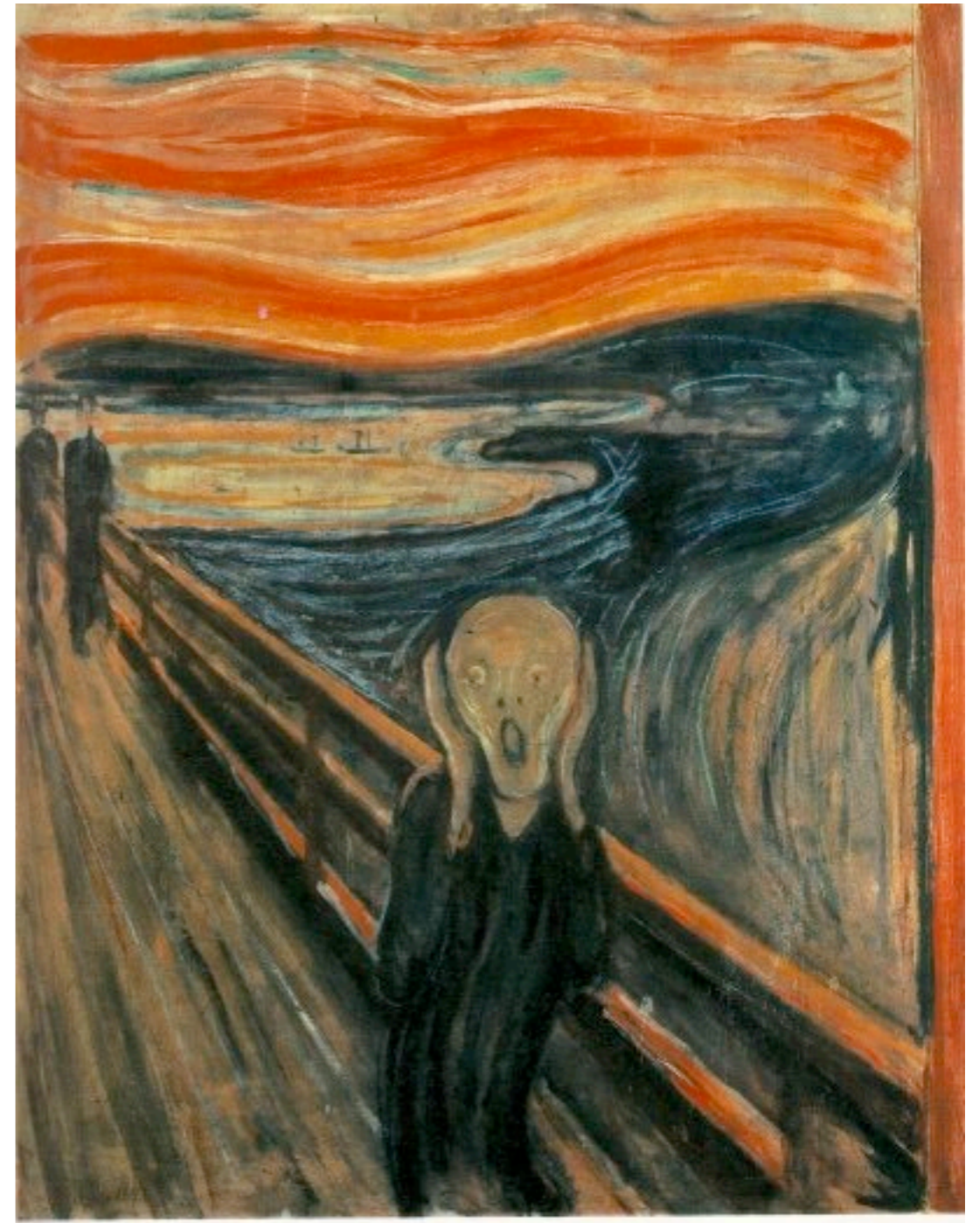


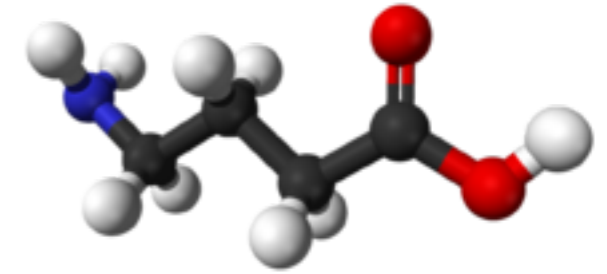
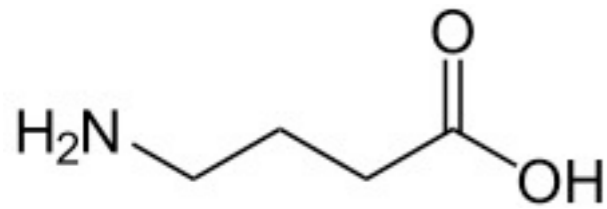
PET scans revealed that 16 panic disorder patients (circles), including 7 with comorbid depression (dots), averaged nearly a third fewer serotonin 5-HT_{1A} receptors in three key brain areas, compared with 15 healthy controls (triangles).

Source: NIMH Mood and Anxiety Disorders Program, 2004

Generalized Anxiety Disorder (GAD)

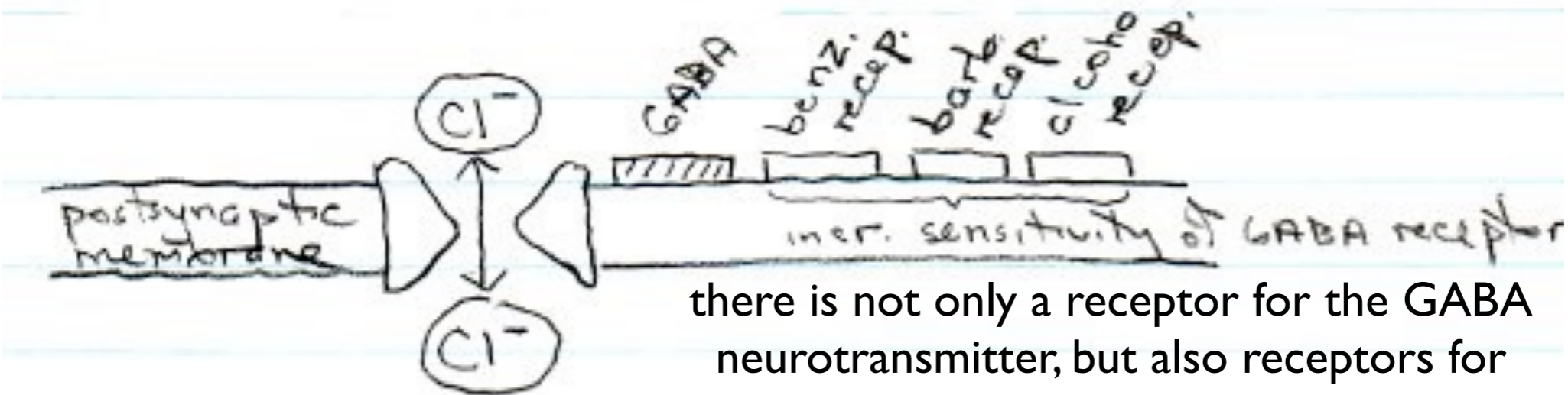
- characterized by free-floating anxiety, worry, and dread (anxiety that is always present and not attached to any specific circumstances)
- risk - about 3%
- about twice as common in women as men





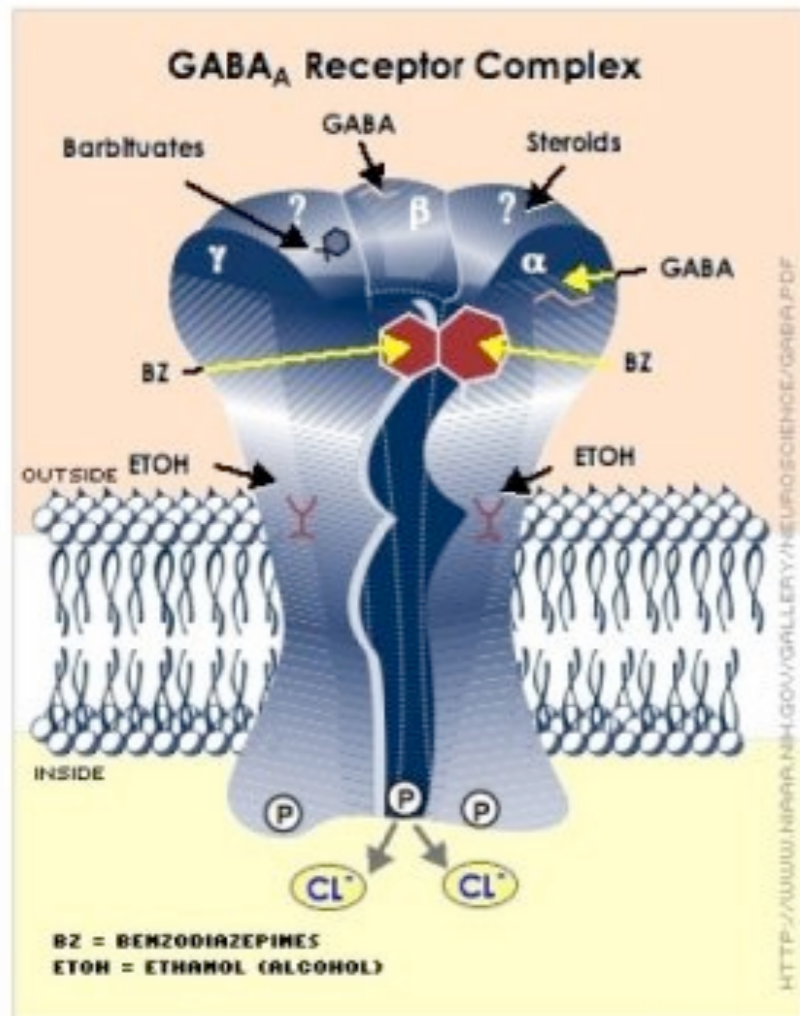
- the role of GABA in regulating anxiety
- traditional anxiolytic drugs (tranquilizers) are all GABA agonists (activate the GABA-A receptor or make it more sensitive to other ligands)
- barbiturates - "old school" depressants (once commonly prescribed as "sleeping pills")
- benzodiazepines - 20% of all prescriptions for controlled substances (e.g., Valium, Xanax)
- alcohol - often self-prescribed for social anxiety!

- the GABA-A receptor complex



there is not only a receptor for the GABA neurotransmitter, but also receptors for benzodiazepines, barbiturates, and alcohol

gates (opens and closes) a chloride channel

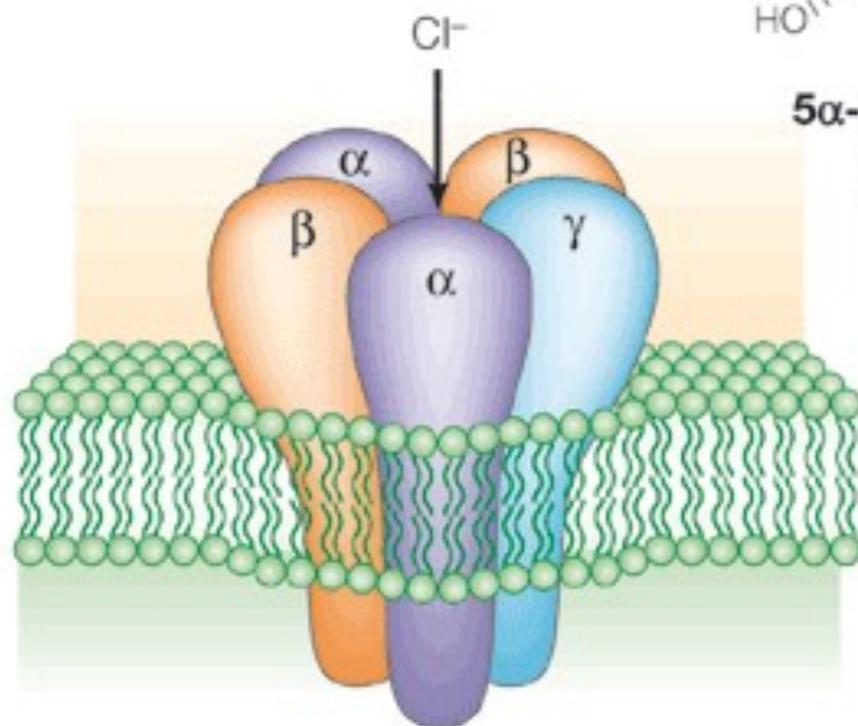
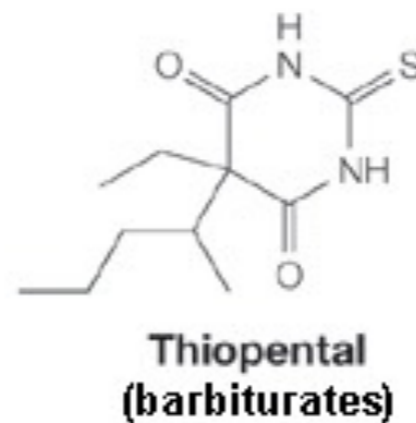
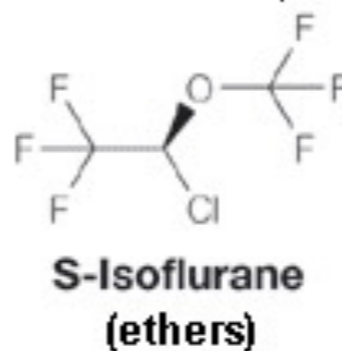
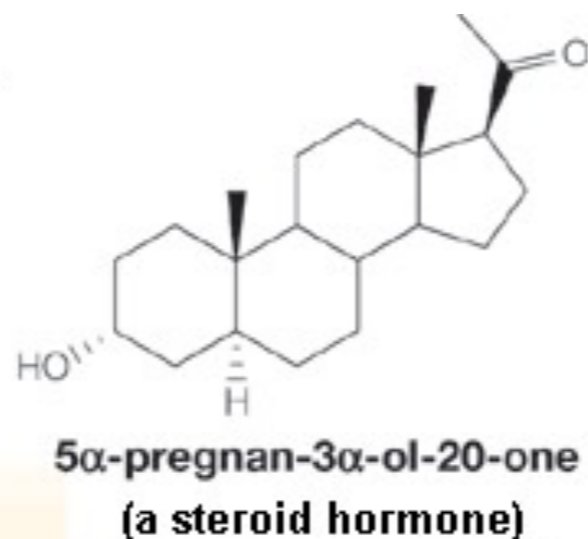
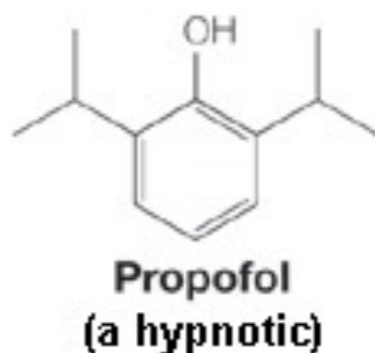
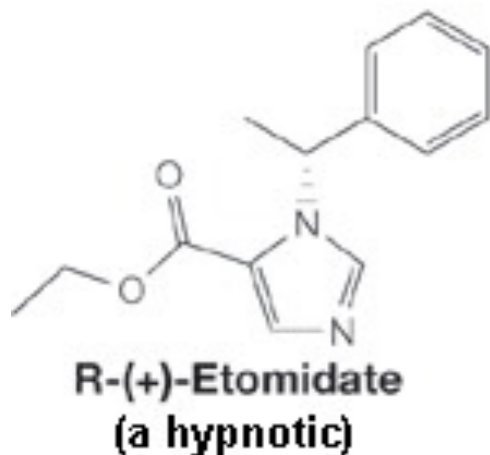
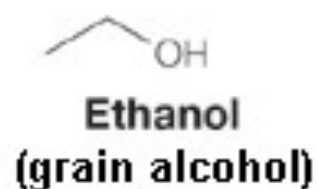
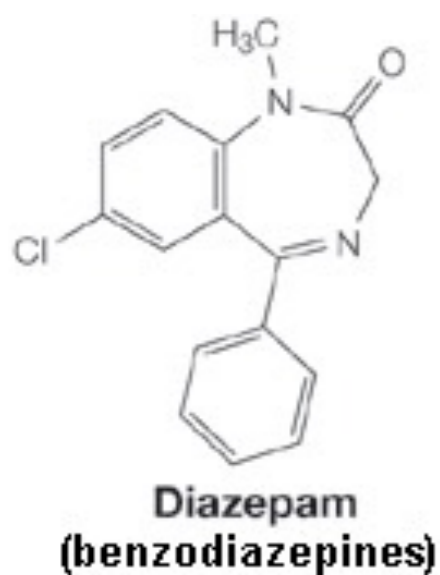


activation of the GABA-A receptor gates a chloride channel and tends to return the membrane to resting potential (an inhibitory action)

50% of inhibitory synapses in the brain are mediated by GABA (it is the primary inhibitory neurotransmitter in the brain)

- the GABA-A receptor complex (another view)

The GABA-A Receptor



The most common form is 2A-2B-1G, but other forms exist. Different ligands bind to different subunits. Thus, how the receptor responds to drugs depends upon what subunits are present. (The subunits are the individual proteins that make up the receptor complex.)

Neurosteroids: endogenous regulators of the GABA_A receptor
 Delia Belelli & Jeremy J. Lambert
 Nature Reviews Neuroscience 6, 565-575 (July 2005)

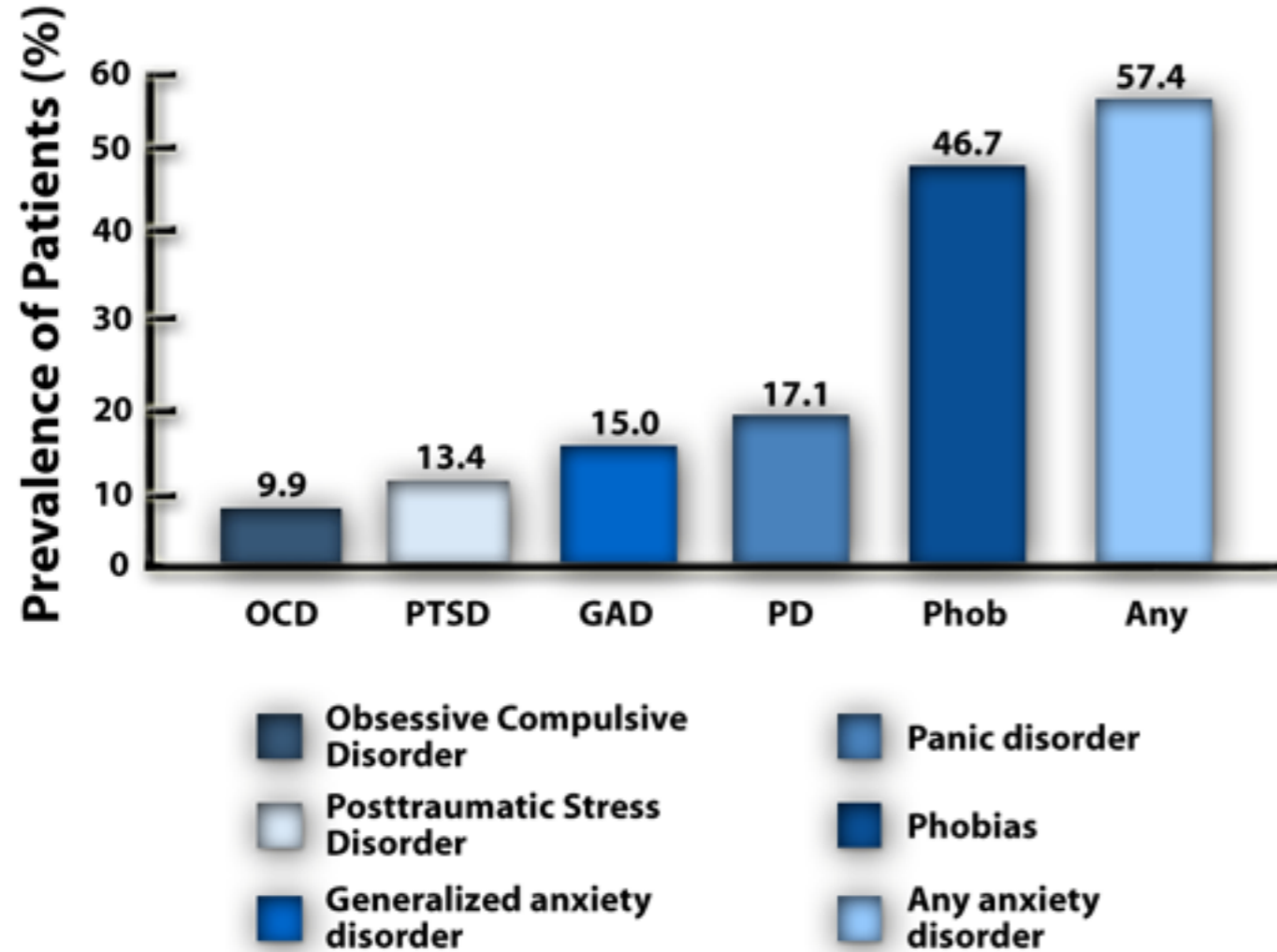
- anxiety may be the result of decreased “sensitivity” of GABA-A receptors
- certain anxiety disorders (GAD?) may result from chronic decreased sensitivity of GABA-A receptors (due to a decreased number of benzodiazepine receptors?)
- an experiment with cats
 - pregnant cats were given diazepam to expose the kittens to it prenatally
 - this produced anxious, fearful kittens with reduced numbers of benzodiazepine receptors in the CNS

- role of the amygdala in the GABA-A story
 - there is a high concentration of GABA-A receptors in the amygdala
 - local infusion of benzodiazepines produce anxiolytic effects in animals (it is sufficient for the drug to get to the amygdala to have its anxiolytic effect)
 - local infusion of GABA antagonists prevents the anxiolytic effects of systemically administered benzodiazepines in animals (it is necessary for the drug to get to the amygdala to have its anxiolytic effect)
 - necessary and sufficient - this is strong evidence that anxiety is being produced in the amygdala (or that the amygdala is essential to anxiety) and that it has something to do with GABA)

- a spanner in the works of the GABA theory
- buspirone (Buspar) is a serotonin agonist
- anxiolytic but not sedating or ataxigenic (it does not produce ataxia, i.e., clumsiness and lack of coordination; drunk people are ataxic, for example)
- acts at the 5-HT_{1A} receptor (a subtype of the serotonin receptor)
- drugs of choice lately for the treatment of anxiety disorders are serotonin agonists - SSRIs (e.g., Prozac and Zoloft)
- benzodiazepines and barbiturates cannot be given long term anyway as they are addicting and have a medically dangerous withdrawal syndrome
- cognitive-behavioral therapy is also useful

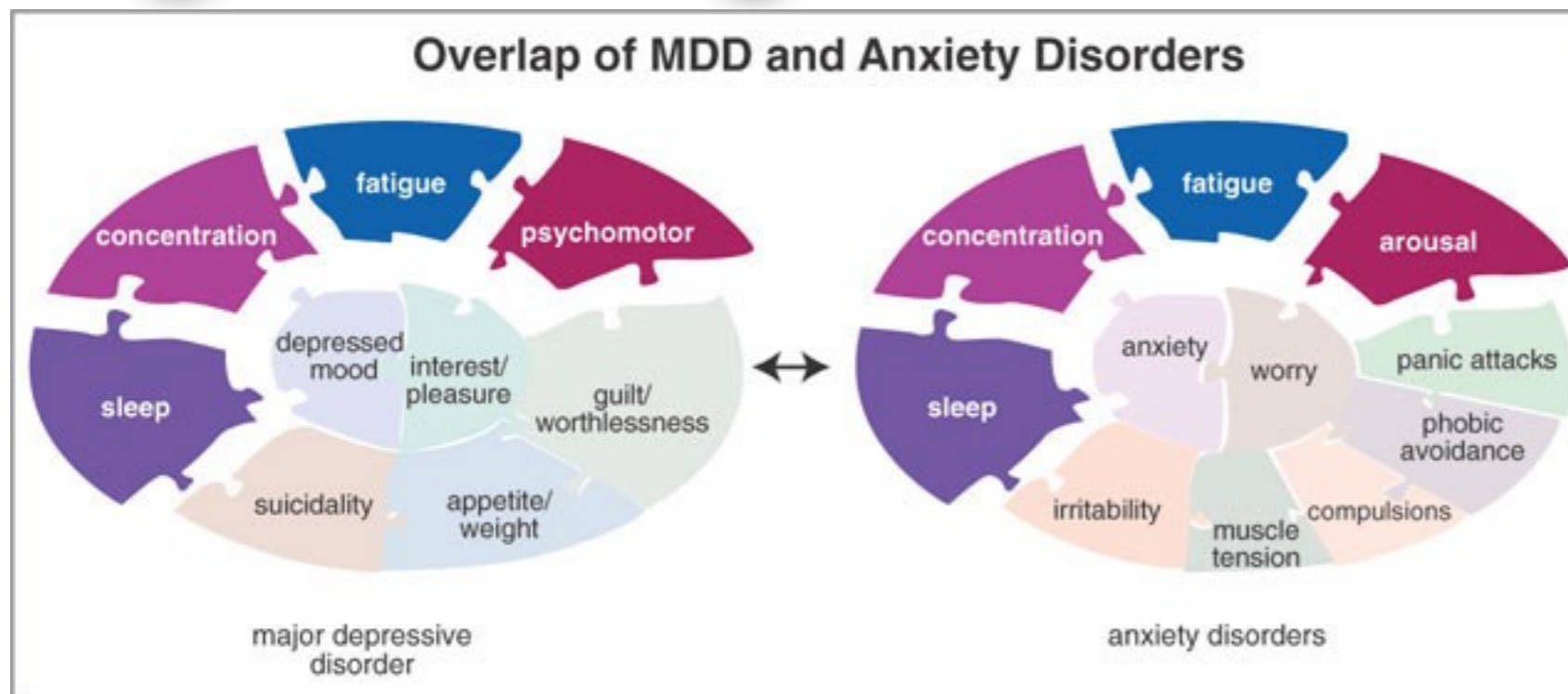
Figure 6. Percentage of Outpatients With Depression Who Had Comorbid Anxiety Disorders

(Zimmerman et al., 2002)



comorbid means they both occur together in the same person

anxiety disorders are often comorbid with depression, and the symptoms overlap



Social Anxiety Disorder (Social Phobia)

- the latest “sexy” disorder

If this guy had genuine social anxiety disorder, the LAST thing he would want is to have people asking him about it!



(This button is my favorite. My people will get this! :)

- excessive fear of being exposed to public scrutiny
- intense anxiety and distress during unavoidable social situations
- risk - about 5%
- equally common in men and women
- there is probably a genetic predisposition
- also associated with cold, authoritarian fathers and overprotective mothers
- cognitive-behavioral therapy is the best treatment
- can also be treated with SSRIs

Obsessive-Compulsive Disorder (OCD)

- obsessions - persistent, irresistible, and disturbing thoughts
- compulsions - same except with behaviors
- lifetime risk - about 1-2%, esp. in young adults, women slightly more than men
- some interesting parallels
 - amphetamine-induced stereotypy in rats
 - “punding” and “tweaking” in amphetamine addicts

- OCD is associated with Tourette's syndrome
- characterized by muscular and vocal tics, facial grimaces, pacing, twirling, barking, sniffing, coughing, grunting, repeating specific words (often obscenities), echolalia
- a tic disorder that begins in childhood (age 5-7 is typical)
- thought to be inherited - exact mode of inheritance unknown, and no gene has been identified
- environmental factors also play a role
 - streptococcal infections
 - autoimmune reactions against the brain
- prefrontal cortex, basal ganglia, cingulate cx, and thalamic circuits have been implicated
- OCD may be an alternate expression of the Tourette's genotype
- some people now want to classify OCD as a tic disorder

- **PET scanning studies**

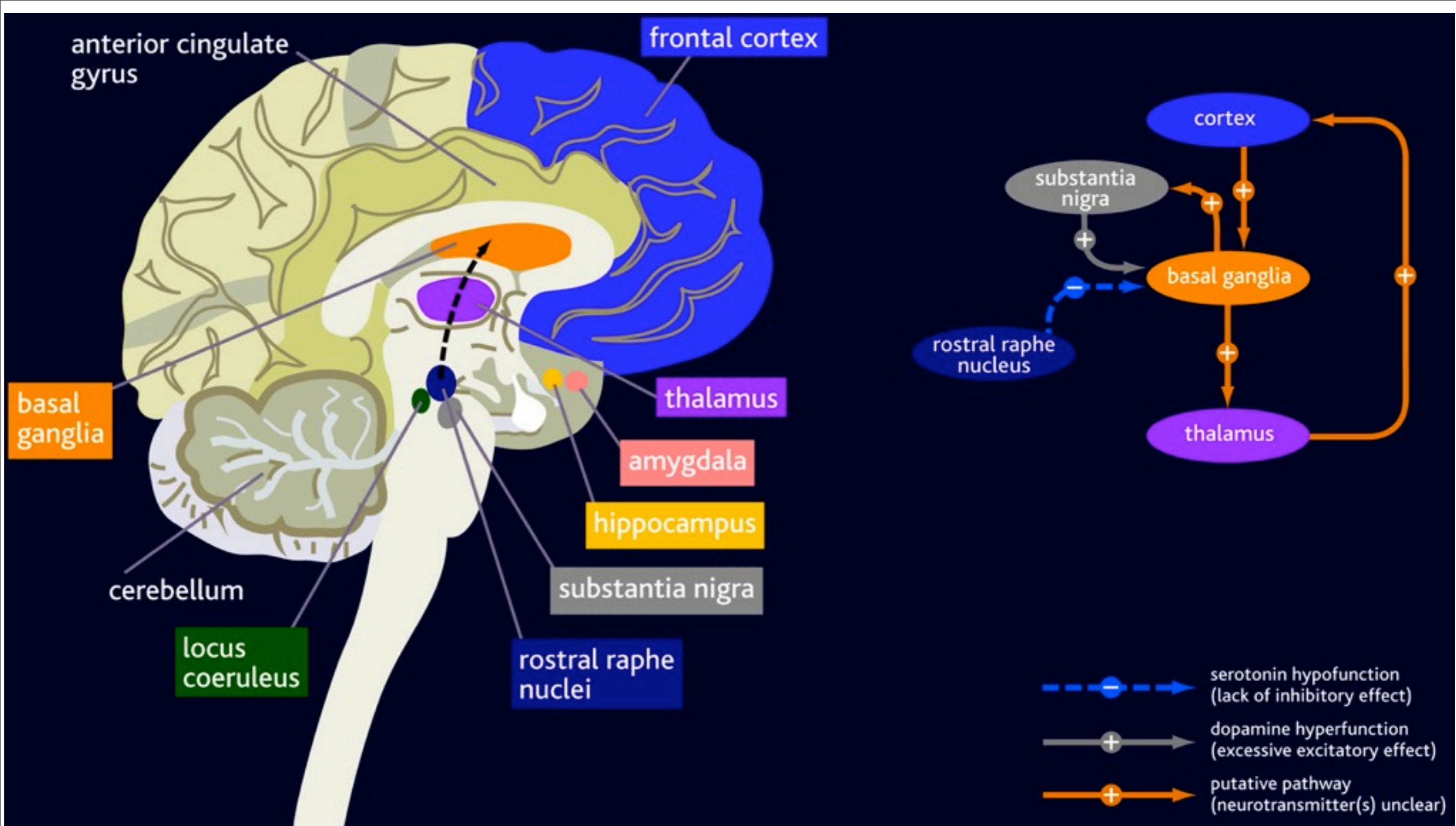
- have implicated the following areas (i.e., increased glucose utilization during active episodes of OCD has been found in...)

- caudate nucleus

- cingulate gyrus

- orbitofrontal cortex

- after successful behavior therapy or drug treatment - substantial drops in glucose utilization are seen in the caudate and orbitofrontal cx.



A possible biology of OCD: There is an excitatory loop from cortex to basal ganglia to thalamus and back to cortex. The breaks are normally put on this circuit by serotonin neurons, the cell bodies of which are in the rostral raphe nucleus. If serotonin is deficient (or there are not enough receptors), the feedback loop becomes a “runaway train” resulting in obsessions and compulsions.

- possible role of the output pathways of the neostriatum (caudate and putamen) via the globus pallidus - there are two output pathways from the globus pallidus
- direct (excitatory) pathway - rapid execution of automatic behaviors
- indirect (inhibitory) pathway - suppressing automatic behaviors permitting a switch to other adaptive patterns of behavior
- theory - OCD is due to an imbalance between these two pathways (Saxena)
- role of the orbitofrontal cx - recognizes situations that have personal significance and activates the excitatory loop of neostriatal output, or inhibits this pathway when the automatic behaviors are inappropriate

- treatment
 - prefrontal leukotomy - disconnecting prefrontal cortex and cingulate cortex from limbic system by cutting tracts between the two (side effects: loss of initiative, loss of motivation, frontal lobe syndrome)
 - deep brain stimulation has worked in some patients
 - drugs - serotonin agonists
 - clomipramine - a tricyclic antidepressant that is fairly 5-HT specific
 - fluoxetine (Prozac, an SSRI)
 - fluvoxamine (Luvox, an SSRI)

