

Round 14:
Disorders of Mood
Bipolar & Anxiety

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Disorder of Mood: Bipolar Disorder

- 1851 Jean-Pierre Falret published an article on “circular insanity”
 - Noted connection between mania and depression & genetic connection
- Emil Kraepelin 1921
 - Separated bipolar from schizophrenia



Disorder of Mood: Bipolar Disorder

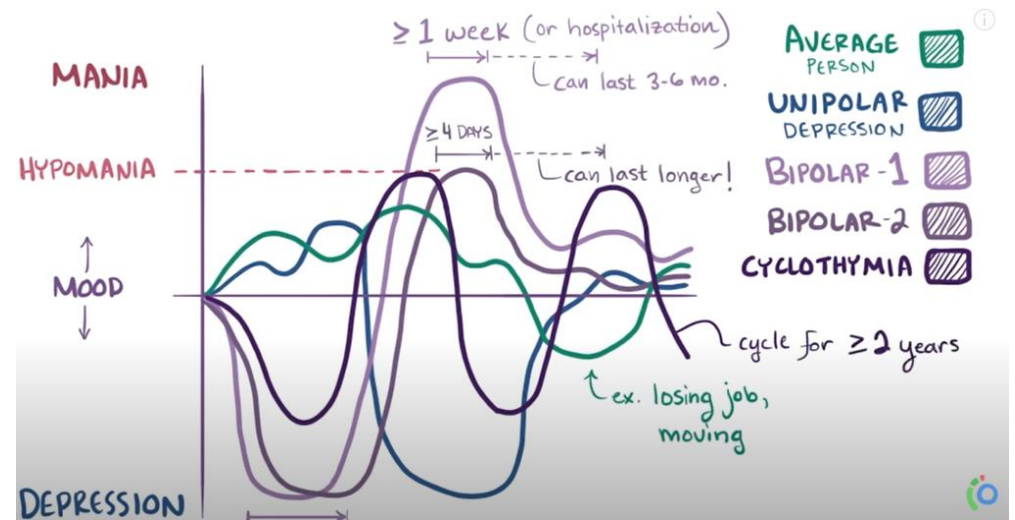
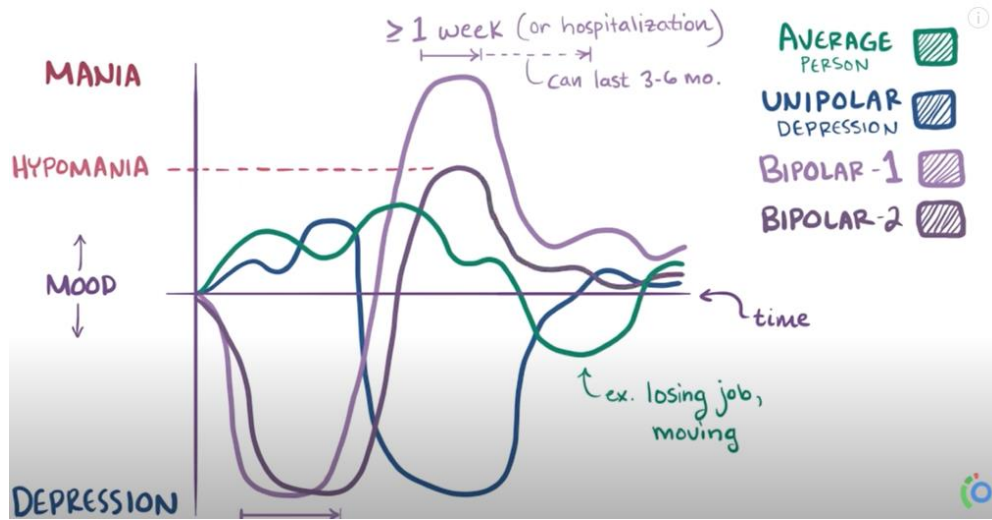
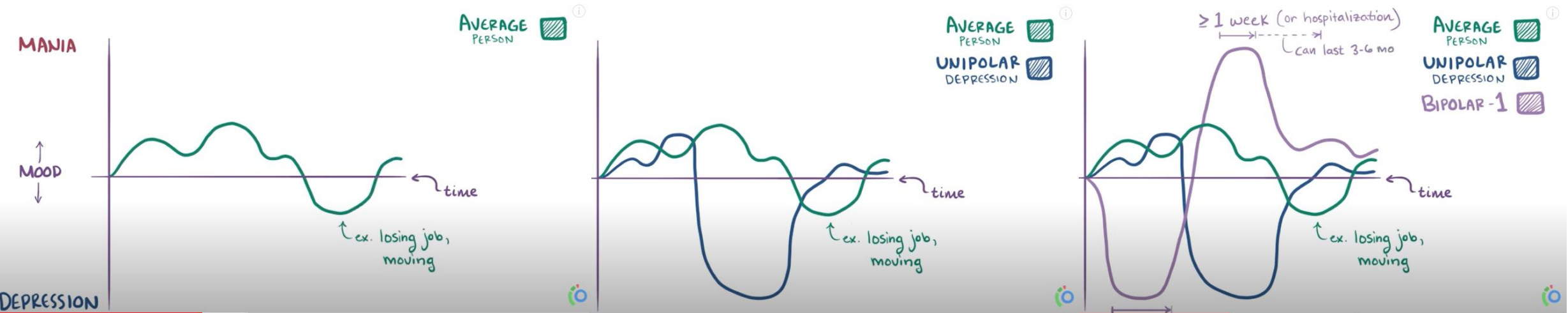
- ~4.5% of population in US
- Affects men and women equally
- Onset occurs around 20

- Depressive episodes are much like unipolar

- Manic episodes
 - Elevated or irritable mood lasting 1 week
 - Overactivity, overtalkativeness, social intrusiveness, increased energy/libido, grandiosity, distractibility, decreased need for sleep, reckless behavior
 - Delusions, hallucinations

- Recurrent
- Can cycle rapidly sometimes manner of minutes

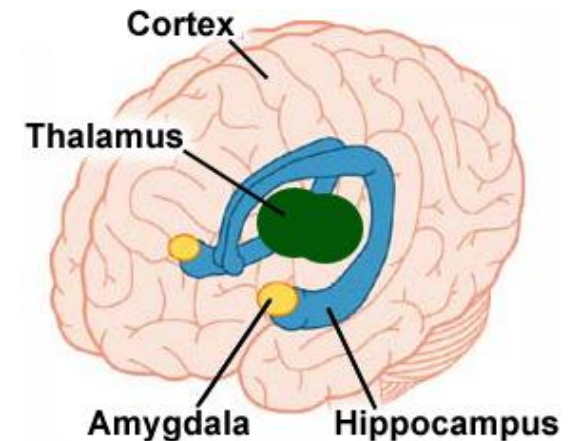
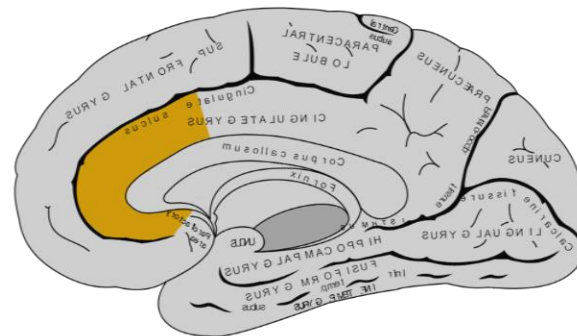
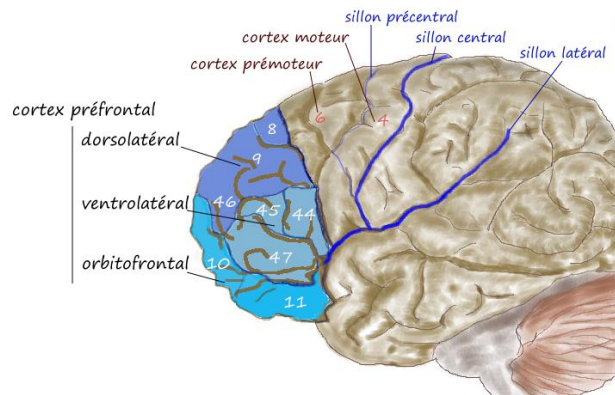
Disorder of Mood: Bipolar Disorder



Disorder of Mood: Bipolar Disorder

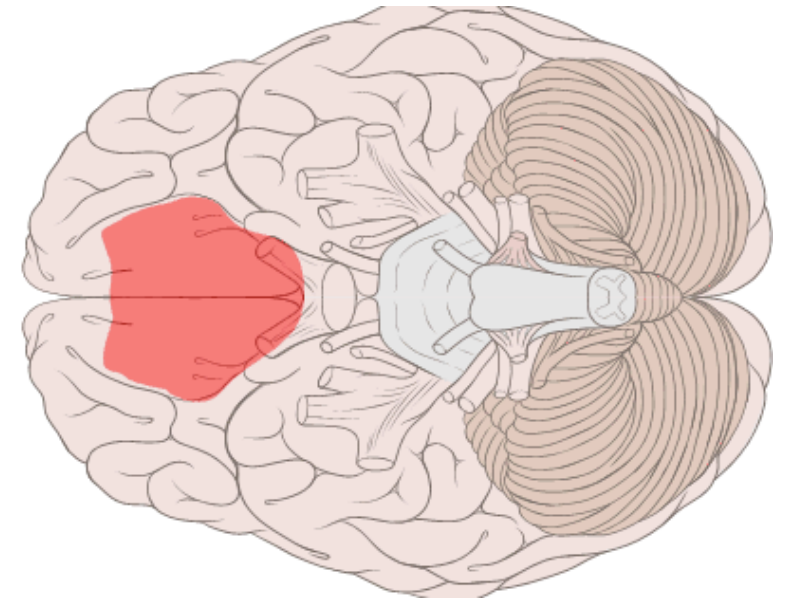
Overall view of brain dysfunction:

- Decreased prefrontal activity & relative hyperactivity of subcortical limbic structures
- Thinner cortical gray matter in frontal, temporal and parietal regions of both brain hemispheres.
 - Reduced cortical surface area -> history of psychosis
- Deficits in three core domains: Attention, executive function, and emotional processing.
 - Pathophysiology in distributed neural circuitry that includes the prefrontal and anterior cingulate cortices, subcortical limbic structures including the amygdala and the ventral striatum



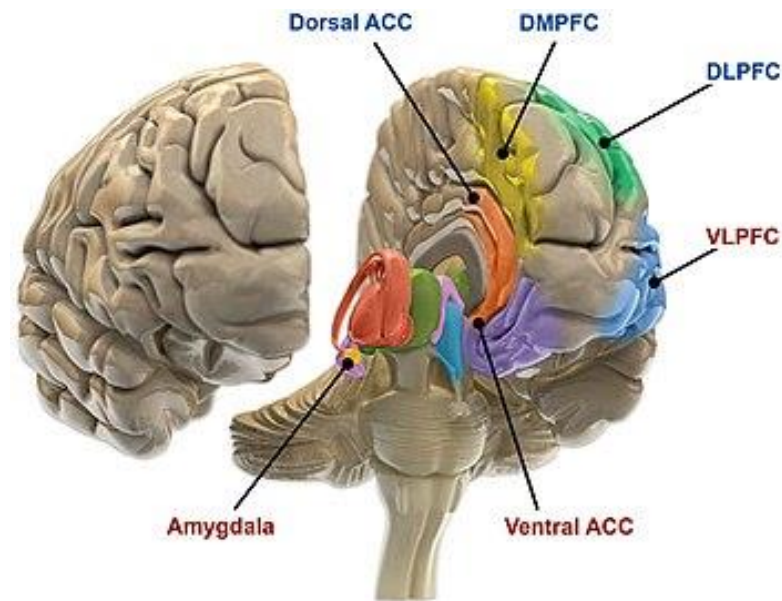
Ventral Prefrontal Cortex

- Plays a crucial role in the ability to rapidly adapt behavior to positive and negative environmental contingencies
- Injury to VPFC ->
 - Can articulate the optimal behavior given a particular situation
 - Cannot adaptively regulate behavior within an emotionally- or motivationally-charged situation.
- Impaired VPFC regulation of behavior -> manic-type behaviors
 - Excessive hedonically-driven activities (e.g., sexual indiscretions, gambling, and excessive spending)
- Integrates motivational relevance of environmental stimuli with internal state & provides regulatory feedback via amygdala and hypothalamus
 - Processing of facial expressions (VPFC -> amygdala) disrupted
 - Misinterpret social cues, alter responses to social situations
 - Difficulties in emotional regulation, adaptive behavioral regulation, and social behavior



Prefrontal Cortex

- Correlation between vulnerability/ number of cycles & smaller VPFC volumes
 - Direction unclear
 - Cycle because of low VPFC volume, or
 - VPFC volume decreases with each cycle
- Decreased neuron density & glial enlargement in DLPFC & OrbitoPFC
 - Decreased blood flow to orbitofrontal
 - Decreased right prefrontal cortical flow
 - Decreased ventral prefrontal activation



DLPFC: Dorsolateral prefrontal cortex DMPFC: Dorsomedial prefrontal cortex
VPFC: Ventrolateral prefrontal cortex ACC: Anterior cingulate cortex

- Manic cases

- Dysregulation of medial and ventral prefrontal circuitry during risky decision-making
- Blunted activation of the right lateral orbitofrontal cortex -> inhibitory control

- Remitted bipolar patients

- Deactivation in orbital and medial prefrontal cortex during the incongruent Stroop blocks
 - also seen in manic and depressed bipolar groups, suggesting a trait marker of pathophysiology in the orbitofrontal cortex.
- Emotional tasks (e.g., recognition of emotional facial expressions) -> abnormally increased subcortical limbic activity
- Limbic hyperactivity has also been reported during nonemotional tasks (e.g., sustained attention task, serial reaction time task)
- Underactive PFC (e.g., cognitive control/impulse control) & Overactive limbic (e.g., emotional responses)

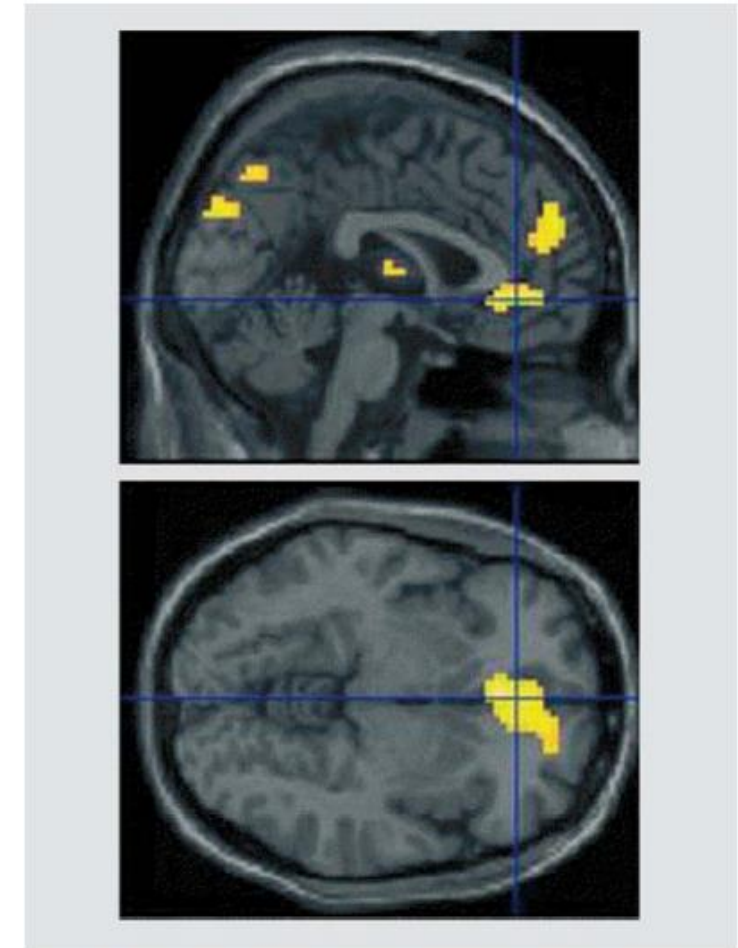
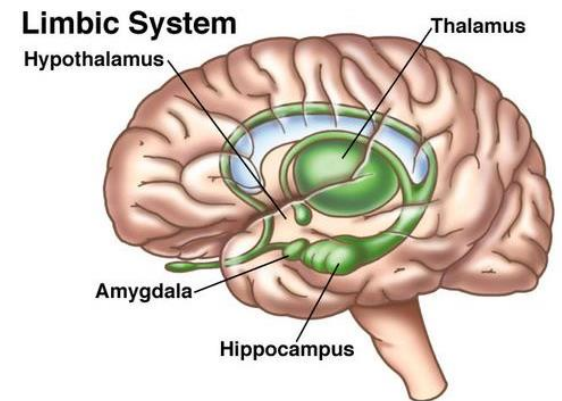
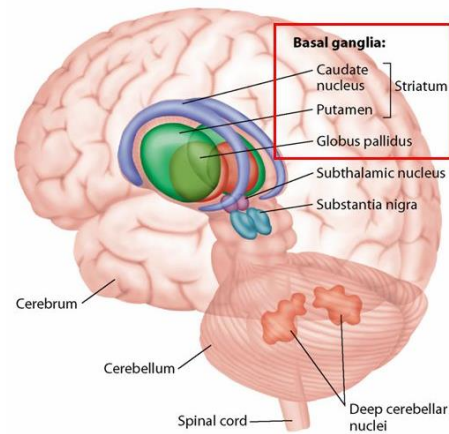
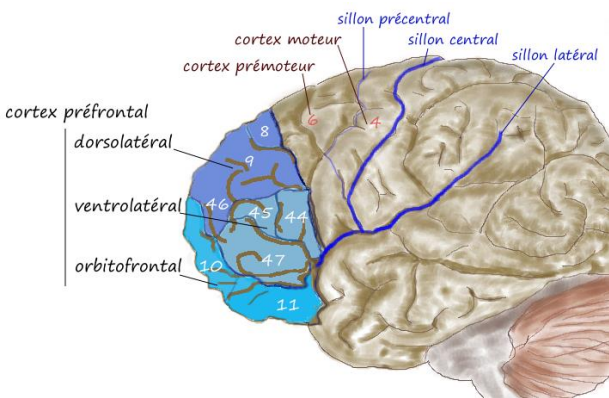


Figure 2. Brain responses during the affective Go No Go task in patients with mania and healthy controls. This section shows areas of increased activity in patients relative to controls, in blocks when positive (happy) words were distracters compared with blocks where neutral valenced words were distracters, consistent with increased brain activity to mood-congruent, task-irrelevant information.



Networks

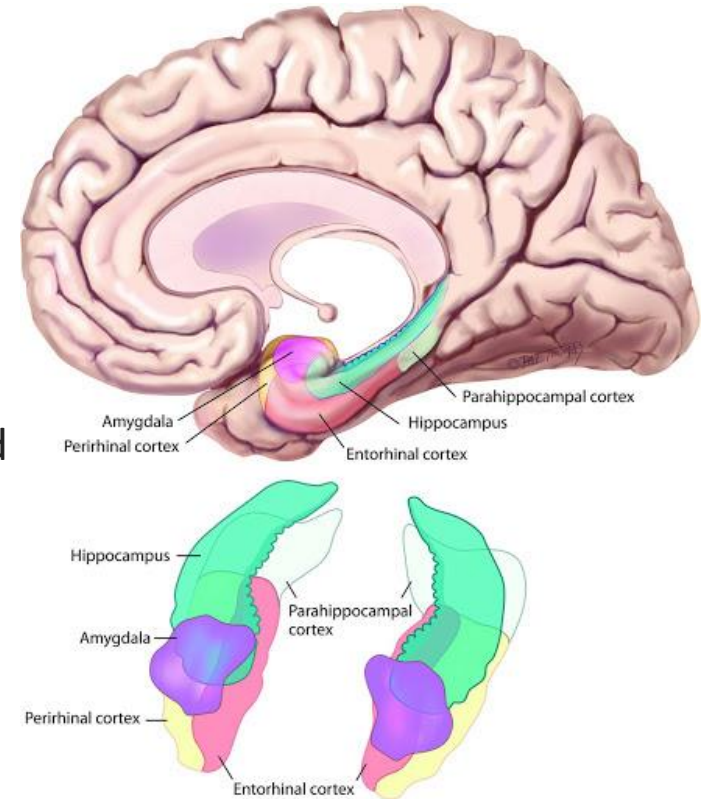
- Prefrontal – Striatal – Thalamic loops
 - Modulate emotional, cognitive, and social behavior
 - Sample incoming information to modulate behavior

- Striatum & Thalamus – role in motivation
 - Mania -> Motivationally driven behaviors in mania
 - Depression -> Amotivation



Medial Temporal

- Loss of prefrontal modulation of subcortical and medial temporal limbic structures 
- Dysfunction of limbic areas may disrupt the function of cortical regions associated with mood and cognitive function (e.g., anterior cingulate, dorsolateral prefrontal cortex) 
- Excessive activity in medial temporal structures (e.g., amygdala)
- Overactivation of emotional brain regions (e.g., ventrolateral prefrontal cortex, parahippocampus/amygdala) during non-emotional tasks -> vulnerability to mood episodes
- Amygdala enlargement in adults but not adolescents
 - may be a result of abnormal development

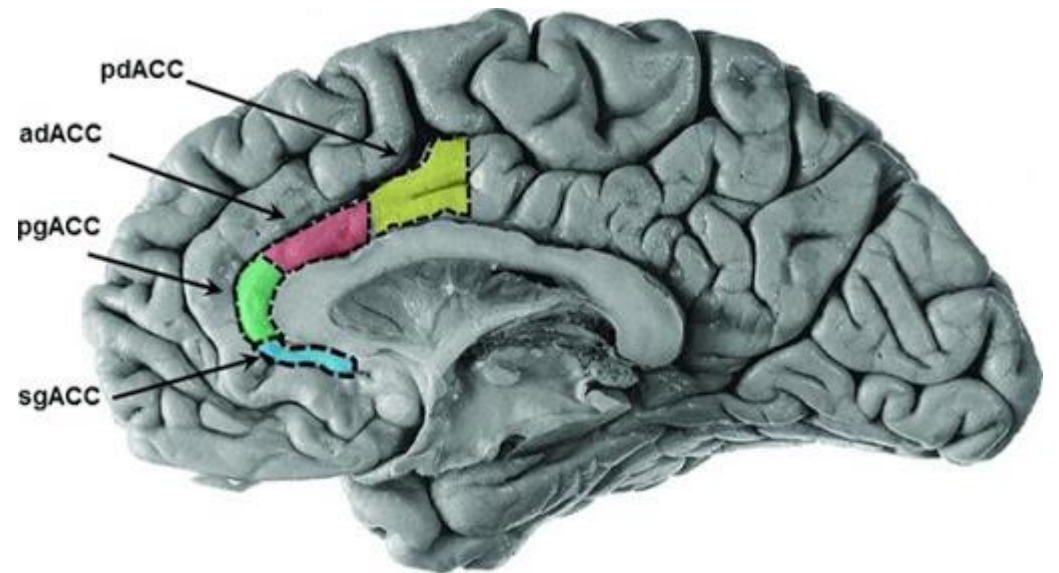


- Subgenual Prefrontal Cortex

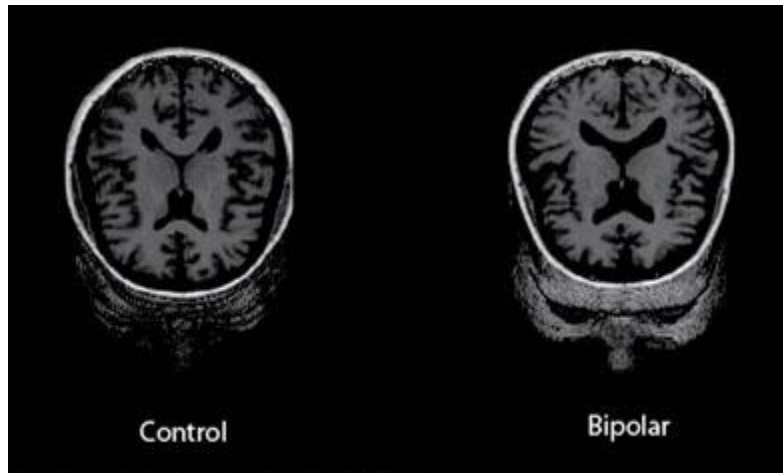
- Portion of the anterior cingulate inferior to the genu of the corpus collosum
- Modulates human mood states
- Integrates cognitive & emotional information
- Smaller left SGPFPC volume
- Decreased blood flow & metabolism in depressive state, increases to normal during manic

- Corpus Collosum

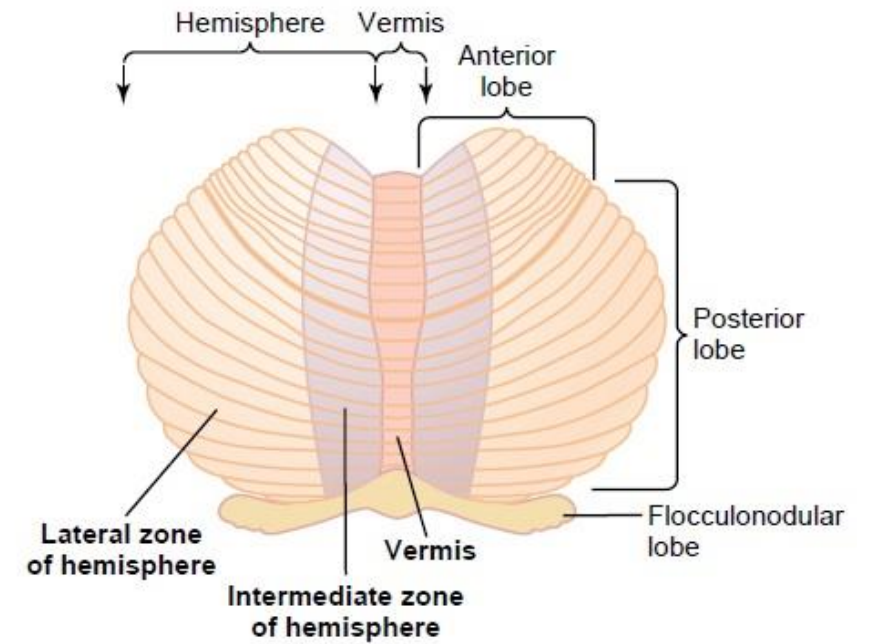
- Decreased white matter tracts & abnormal connections



- Cerebellar Vermis
 - Connected to limbic regions
 - Decreased volume -> number of episodes
 - Consequence of recurrent mood episodes
- Ventricle size correlated with number of manic episodes



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- Latter half of the 20th century, studies in patients with seizure disorders demonstrating BD-type symptoms
 - Excessive activity in medial temporal lobe structures might contribute to mood symptomatology in BD
 - Left-side foci: Humorlessness, fear, and paranoia
 - Depression associated with left-sided ventral frontal increases & dorsal decreases
 - Right-side foci: Elation, emotionality, fluctuating mood
 - Mania associated with right-sided VPFC decreases

Treatments

- Psychotherapy
- ECT
- TMS
- NFB
 - Depressive phase (left)
 - Manic phase (right)
- Medications
 - Antipsychotics
 - Zyprexa, Risperdal, Seroquel, Abilify, Geodon, Latuda
 - Anticonvulsants
 - Valproate, Lamotrigine
 - Restoring balance of excitatory glutamate & inhibitory GABA in the amygdala
 - Birth defects (e.g., spina bifida, heart abnormalities, cleft lip), developmental problems (e.g., intellectual abilities, poor verbal production & comprehension, memory problems, ASD, delayed walking & talking)
 - Mood Stabilizers
 - Depakote, Lamictal, Lithium

- Lithium

- Ancient Greece
 - bath salts used calm manic behavior and lift the spirits of depressed people
- 19th century
 - Treatment for gout b/c it dissolves uric acid
 - Used to treat mania in “brain gout”
- Early 1900s
 - Used as replacement for table salt b/c of high blood pressure
 - Side effects
 - Kidney disease and affect thyroid
 - Death -> Lithium toxicity
- 1949 Australian John Cade discovered lithium salts in treating mania in rodents bc it calmed them used as a tranquilizer
- Used in 7-up “Bib-Label Lithiated Lemon-Lime Soda”
 - launched 2 weeks before stock market crash in 1929
 - banned in 1948



Disorder of Mood: Anxiety

- Frequent symptoms:
 - Fear
 - Restlessness
 - Heightened responsiveness/awareness
 - Sweat
 - Heart racing
 - Increased blood pressure
 - Avoidance behavior
- Is adaptive in healthy individuals -> avoid danger
- Pathological -> excessive & persistent, no longer serves to signal/respond to actual danger
- Most common psychiatric disorder
 - 10-15% of general population

Disorder of Mood: Anxiety Disorders

- Generalized Anxiety Disorder
- Panic Disorder
- Post-Traumatic Stress Disorder
- Obsessive-Compulsive Disorder
- Specific Phobia
- Selective Mutism
- Social Anxiety Disorder
- Separation Anxiety

Anxiety Disorders

Generalized Anxiety

- Unrealistic, excessive worry lasting 6 months or longer
- Motor tension (e.g., trembling, muscle aches, restlessness)
- Autonomic hyperactivity (e.g., shortness of breath, palpitations, increased heart rate, sweating cold hands)
- Vigilance & Scanning (e.g., feeling on-edge, exaggerated startle reflex, difficulty concentrating)

Panic Disorder

- Brief, recurrent, spontaneous episodes of terror without a clearly identifiable cause
- Last 15-30 mins
- Sense of impending disaster accompanied by intense overactivity of sympathetic nervous system
- Onset in 20s
- Recur over months to years - Experienced several times a week

Anxiety Disorders

Post-Traumatic Stress Disorder

- Exposure to an event that involved threat of death or serious injury causing intense fear, helplessness, horror
- Re-experience traumatic event
 - Intrusive thoughts, nightmares, flashbacks
 - Physiological reactivity to reminders of event, exaggerated startle reflex, hyperarousal, difficult sleeping, concentrating, hypervigilance

Obsessive-Compulsive Disorder

- Obsessions - Unwanted, recurrent intrusive thoughts that cause anxiety
 - Fear of contamination
 - Needing things to be orderly/symmetrical
- Compulsions - Repetitive behaviors pt feels driven to perform in order to relieve anxiety “structural event complex”
 - Washing/Cleaning
 - Checking
 - Counting
 - Strict routine

Selective Mutism

- Usually seen in children
- Inability to speak or communicate in select social settings
- Often co-morbid with social anxiety and/or separation anxiety
- May have Sensory Processing Disorder
 - Sensitive to sound, lights, touch, taste, and smells
 - Misinterpret social cues
- May have language abnormalities or auditory processing disorder

Social Anxiety

- Everyday interactions cause significant anxiety, fear, self-consciousness, fear of being judged
- Children may manifest in crying, temper tantrums, clinging to parents, refusing to speak
- Blushing, fast heartrate, trembling, sweating, upset stomach, lightheadedness/dizziness, muscle tension
- Low self-esteem & negative self-talk

Separation Anxiety

- Usually occurs in children
- Recurrent, excessive distress about anticipation or being away from home
- Constant, excessive worry about losing a parent or loved one
- Repeated nightmares about separation

Anxiety Disorders

- “Fear Network”

- Amygdala, Anterior Cingulate Cortex (ACC), & Insula

- Amygdala

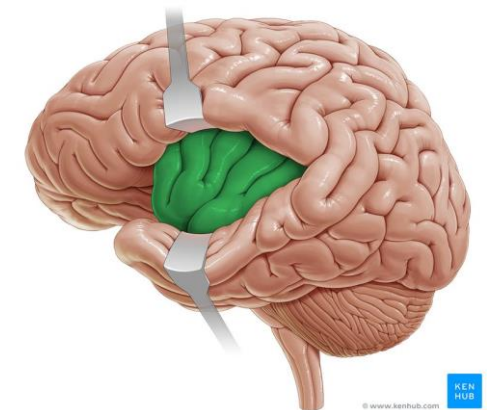
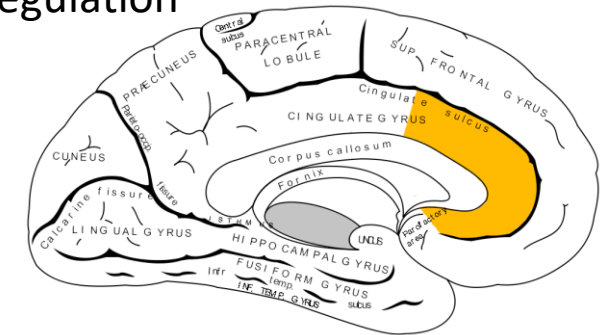
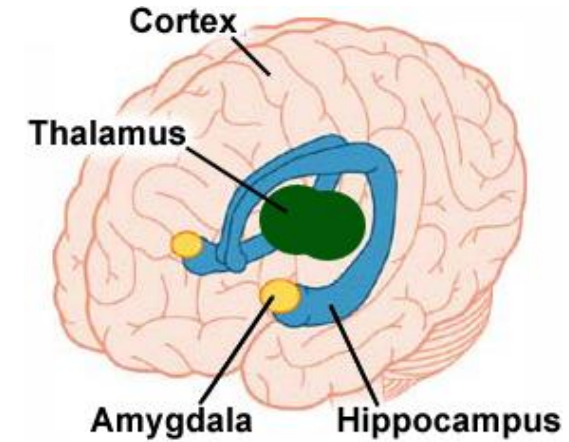
- Emotions – Fear
- Determines salience of emotional & social stimuli/ Stimulus Valuation
- Hyperactivation (right) -> inappropriate perception of threat & Emotion dysregulation

- ACC

- Conflict monitoring & Fear learning
- Detection & appraisal of social situations
- Emotional awareness
- Pain perception

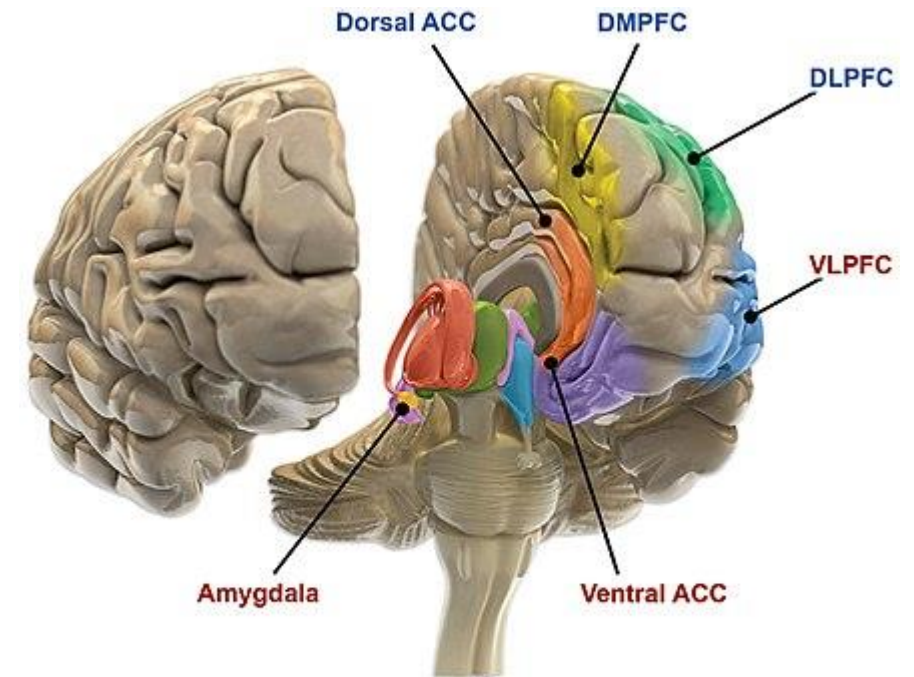
- Insula

- Self-awareness, interpersonal experience, Sense of agency
- Social experience -> norm violations, emotional processing, empathy, social decision making
- Dysfunctional anticipatory processing
- Hyperactivation (right)



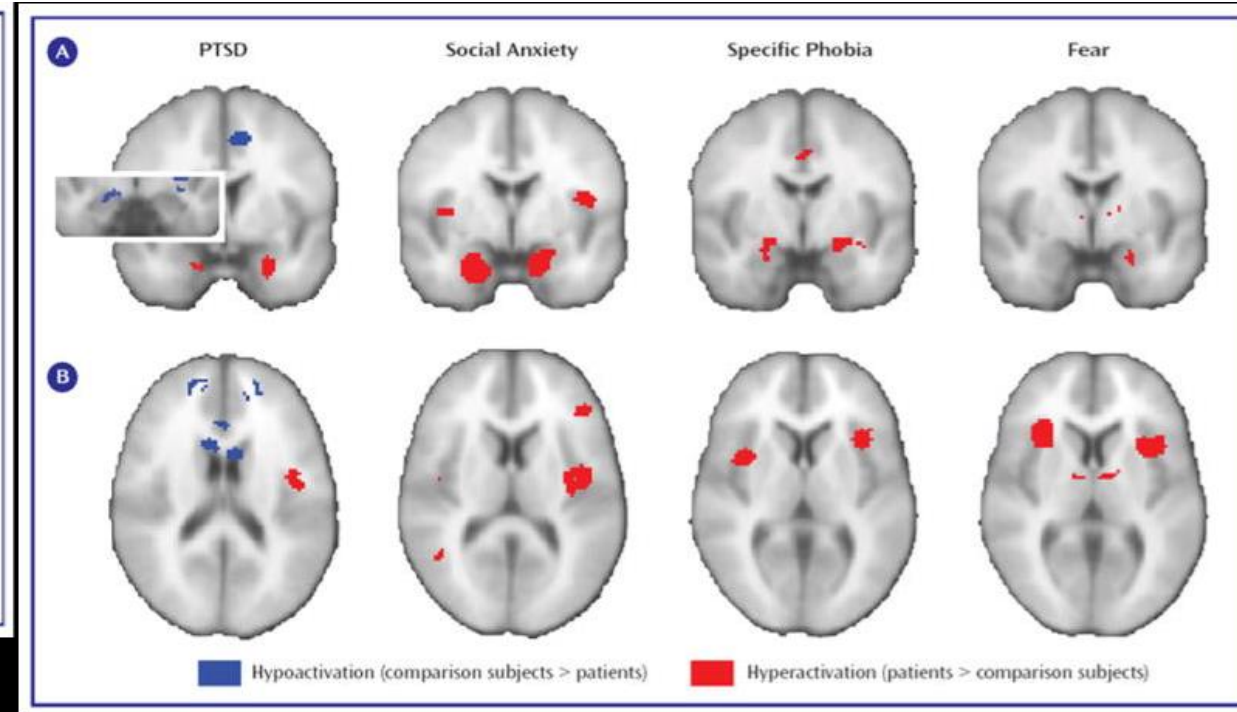
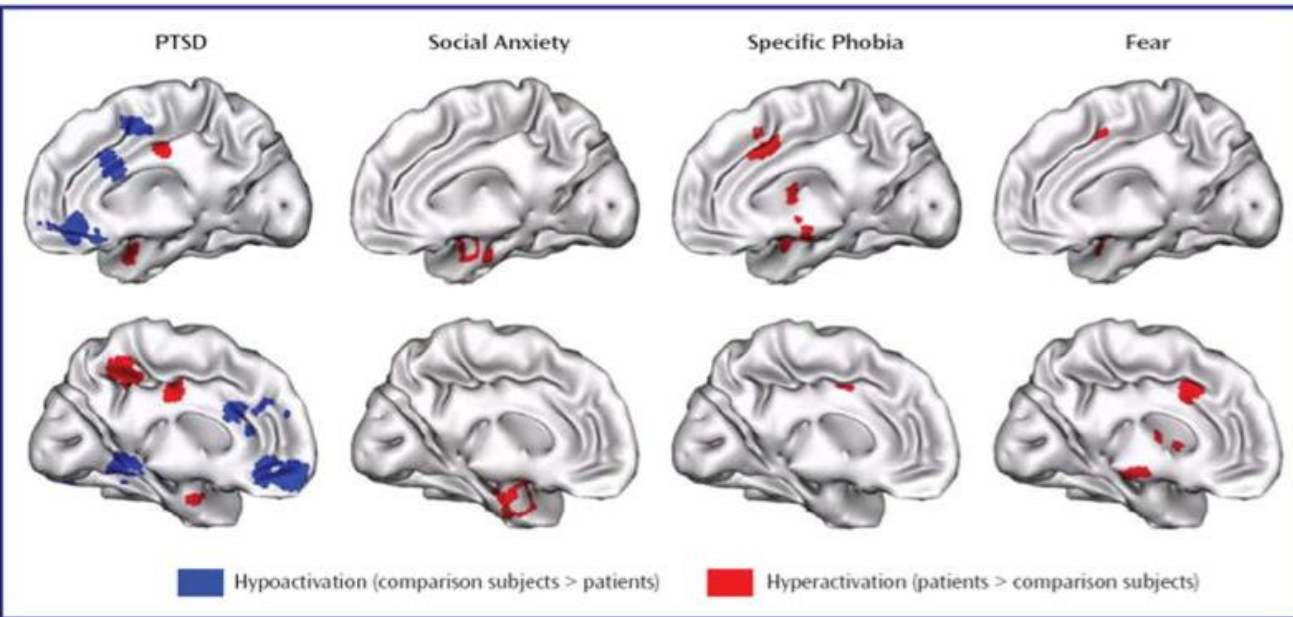
Anxiety Disorders

- Dorsal Prefrontal Cortex
 - (Right)
 - Associated with increased attentional bias toward threat /vigilance toward threatening stimuli
 - Decreased ability to disengage (Increased perseveration)
- Ventral Lateral Prefrontal Cortex
 - Activation inverse relationship to social avoidance behavior
 - VMPFC (underactive)
 - dampen signal from amygdala
- Greater Insula activation (specifically right) associated with reduced activity of superior & medial frontal gyrus



DLPFC: Dorsolateral prefrontal cortex
VLPFC: Ventrolateral prefrontal cortex
DMPFC: Dorsomedial prefrontal cortex
ACC: Anterior cingulate cortex

- Most anxiety disorders associated with overactivity of right limbic regions
- PTSD, in particular, associated with under-active frontal regions



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FIGURE 3. Significant Clusters of Hyperactivation or Hypoactivation in Medial Prefrontal Regions for Patients With PTSD, Social Anxiety Disorder, and Specific Phobia, and in Healthy Subjects Undergoing Fear Conditioning

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FIGURE 2. Clusters in Which Significant Hyperactivation or Hypoactivation Were Found in Patients With PTSD, Social Anxiety Disorder, and Specific Phobia Relative to Comparison Subjects and in Healthy Subjects Undergoing Fear Conditioning^a ^a Results are shown for

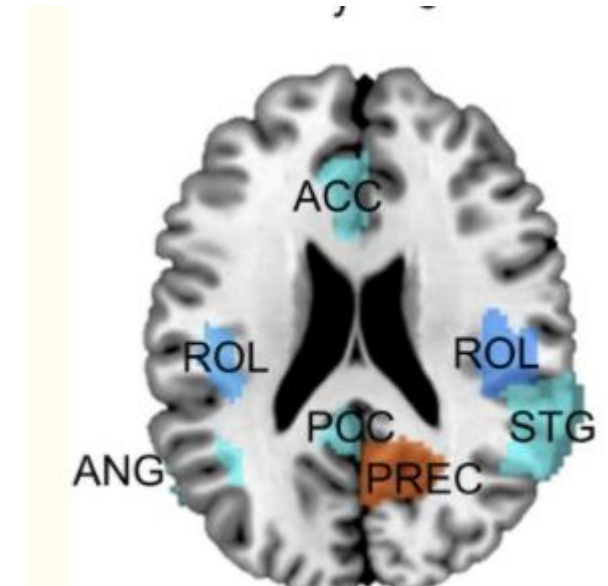
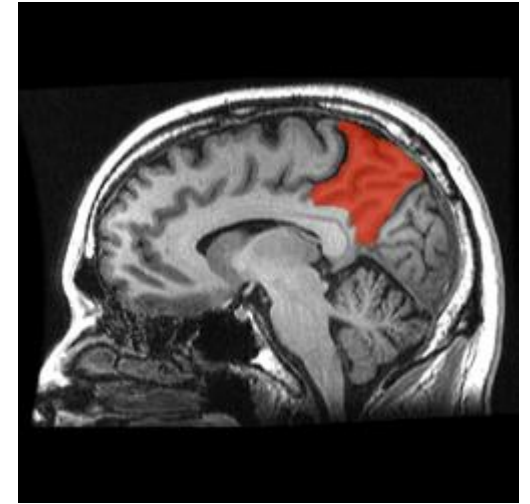
Anxiety Disorders: PTSD

- Orbitofrontal Cortex
 - Codes information, controls impulses, regulates mood
 - Underactive
- VMPFC
 - Reward processing visceral response to emotions
 - Dysregulated, underactive
- Anterior ACC
 - Dysregulated, underactive
- Amygdala
 - Hyperactive
- Hippocampus
 - Studies disagree – Under or over activity likely depends on type of trauma and type of memory test employed
- Insula
 - Increased right insula

Anxiety Disorders: PTSD

- Precuneus

- Mental imagery concerning the self – episodic memory, self-consciousness, self-awareness, rate own personality traits relative to those judged by others
- Works with left prefrontal in recall of episodic memories
 - Source memory
 - Contextual information to aid hippocampus in memory
- Integration of information (gestalt) relating to perception of the environment
- Implicated in migraine
- Right precuneus overactive in PTSD



Developmental Trauma

- Sexual Abuse

- Reduced volume in hippocampus, parahippocampal gyrus, caudate nucleus, corpus callosum, and frontal cortical grey matter
- Hyperactivity of right amygdala
- Reduced volume in genital representation in somatosensory cortex
 - Adaptive response to reduce sensory input

- Physical Abuse

- Reduced volume in right mPFC, right dorsal ACC, left dlPFC

- Emotional Abuse

- Hyperactivity of amygdala (verbal abuse)
- Poor connectivity between right amygdala, ACC, vmPFC

- Emotional Maltreatment

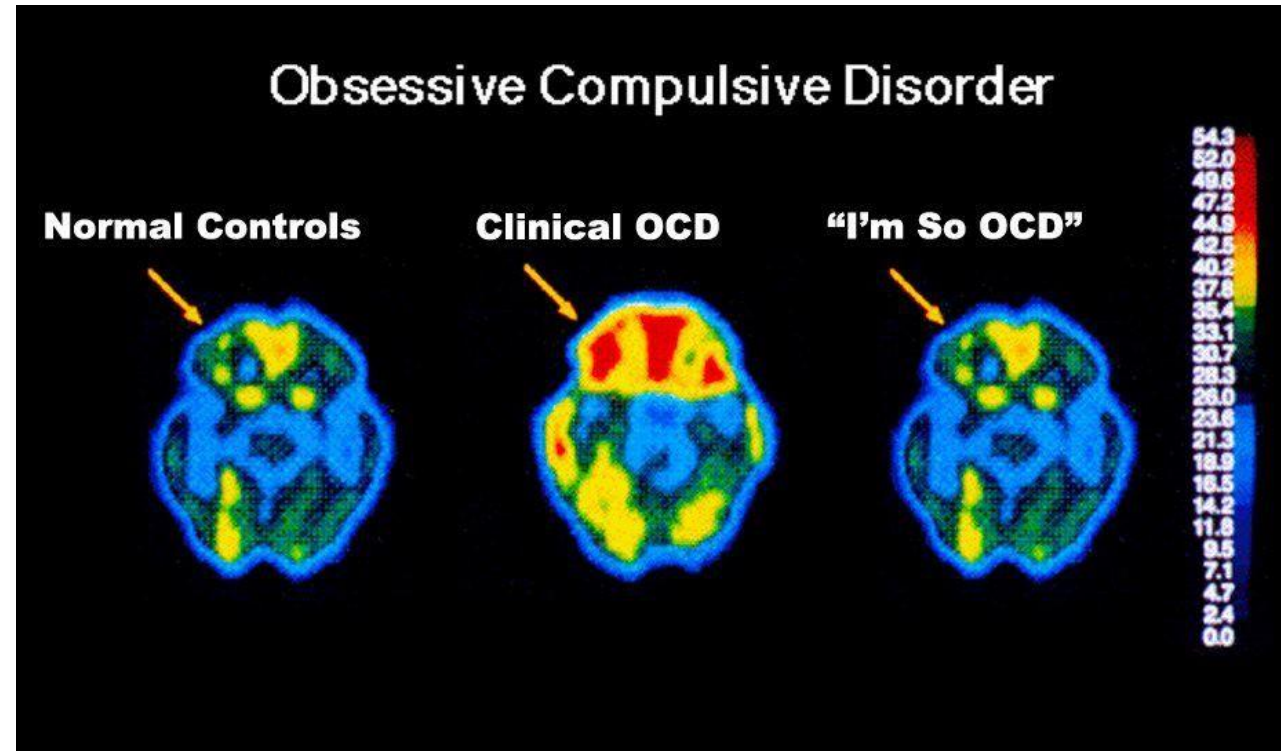
- Reduced functional connectivity between right amygdala and bilateral inferior parietal cortex, precuneus, orbitofrontal cortex, hippocampus, putamen. As well as between right dACC & precuneus.
- Reduced volume in dmPFC
- Hypoactivity in mPFC

Developmental Trauma

- General Neglect
 - Reduced limbic connectivity -> prefrontal cortex (dlPFC, vlPFC, dmPFC)
- Physical Neglect
 - Dysfunctional connectivity between amygdala and left anterior middle temporal gyrus
 - Reduced corpus callosum volume
- Emotional Neglect
 - Witnessing domestic violence -> lower cortical thickness in occipital regions
- Reduced insular network connectivity
 - Adaptive response reduce experience of adverse bodily sensations (e.g., hunger, pain) or emotions (e.g., feelings of low self-worth, loneliness, rejection) that accompany neglect

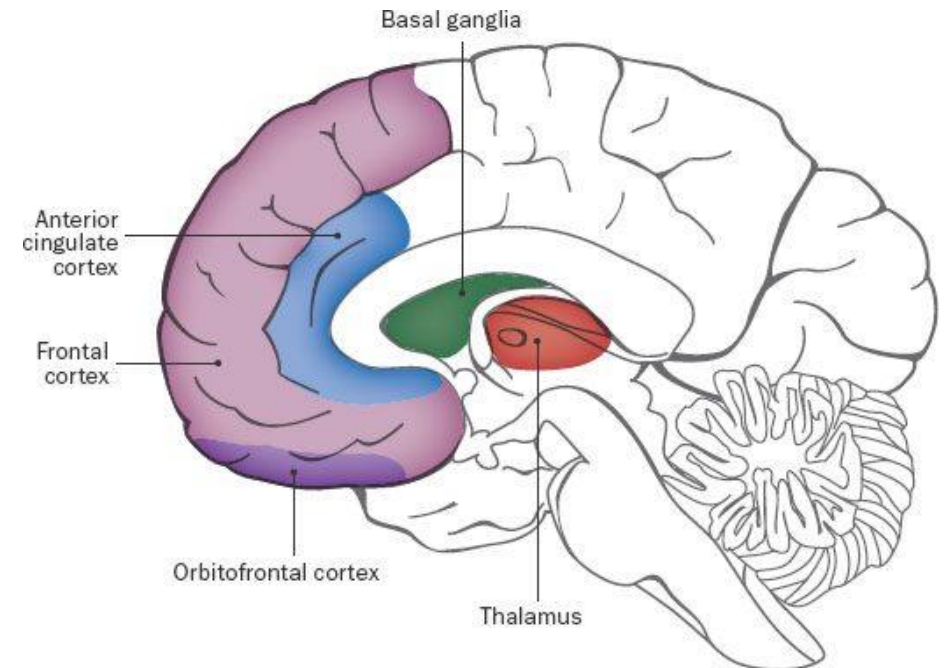
Anxiety Disorders: OCD

- Likely as much of an impulse control (executive function) problem as it is an anxiety disorder
- Dysfunctions & associated brain regions of OCD
 - Error detection → ACC
 - Threshold for activation of motor/behavioral patterns → Basal Ganglia
 - Memories of behavioral sequences → PFC/Hippocampus
 - Inhibitory control
 - Globus pallidus (decreased white matter)
 - Angular gyrus (decreased grey matter)
 - Compulsive checking behavior → Superior Temporal Gyrus



Anxiety Disorders: OCD

- **Orbital cortex**
 - Reward processing
 - Evaluates whether a task was performed correctly or incorrectly.
 - Overactive -> pts to believe they did something wrong and that the task needs to be performed again
 - Reduced grey matter (inhibition & attentional control)
- **Cingulate Gyrus**
 - Motivation & behavioral responses
 - Receives input from limbic system (Reward/Learning)
 - Orbitocortex, “you did something wrong,” cingulate gyrus-> feel discomfort or anxiety until you fix it
 - Overactive
- **Caudate Nucleus**
 - Procedural learning, associative learning, inhibitory control of actions
 - Helps set shifting, exert control to override compulsions or intrusive thoughts
 - Underactive



Treatments

- Psychotherapy
- Medications
 - MAOIs -> noradrenalin
 - Benzodiazepines → enhance GABA limbic system, specially in amygdala (emotional behavior)
- NFB
 - Right side
 - Ruminations (Fz)

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