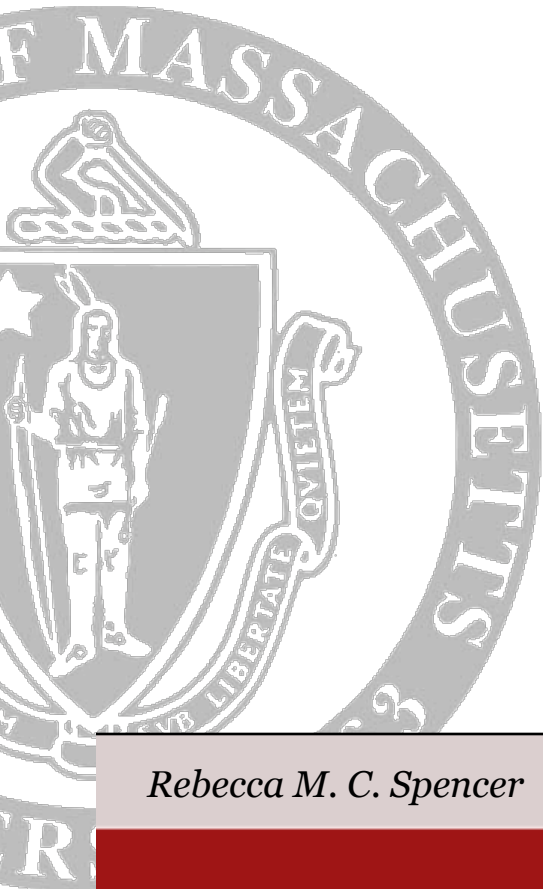


Neurobiology of brain dysfunction

Mood & anxiety disorders



Anxiety & Mood Disorders:

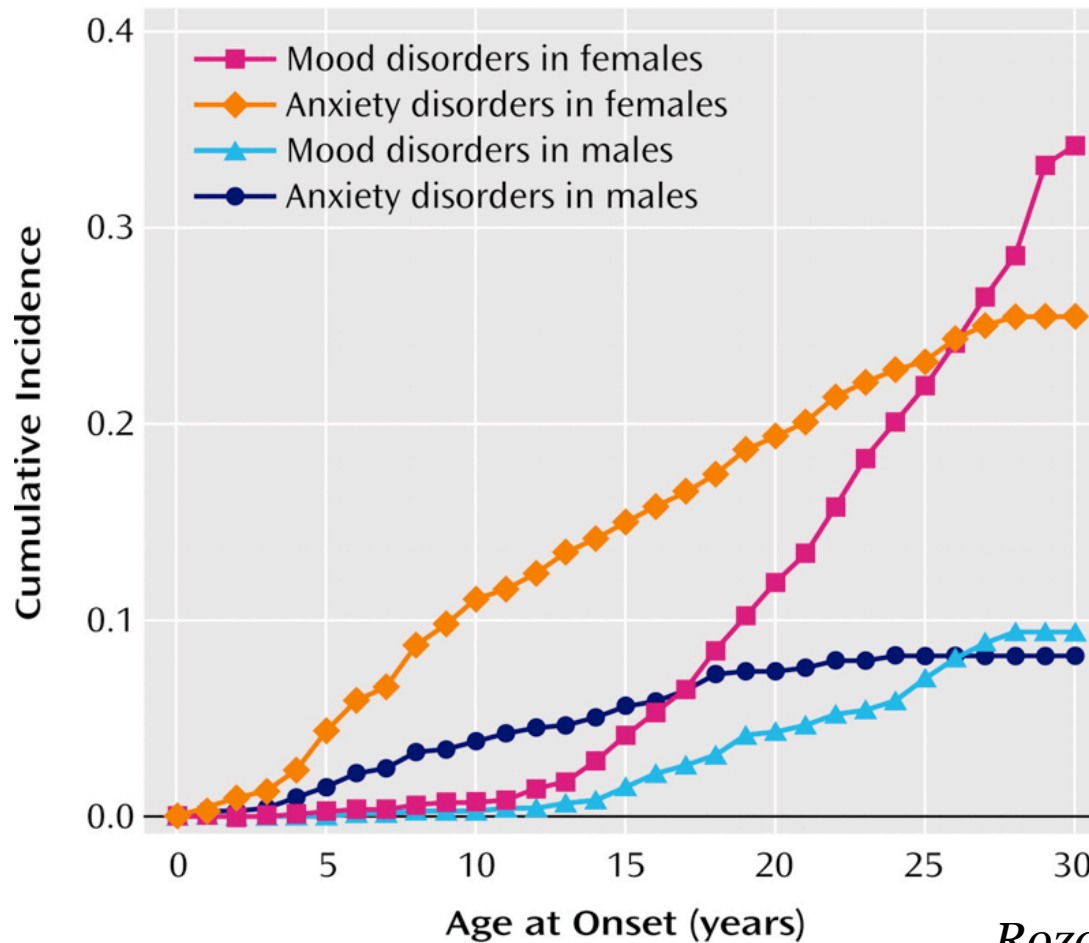
Mood disorders:

- **Depressive**
- **Bipolar**

Anxiety disorders:

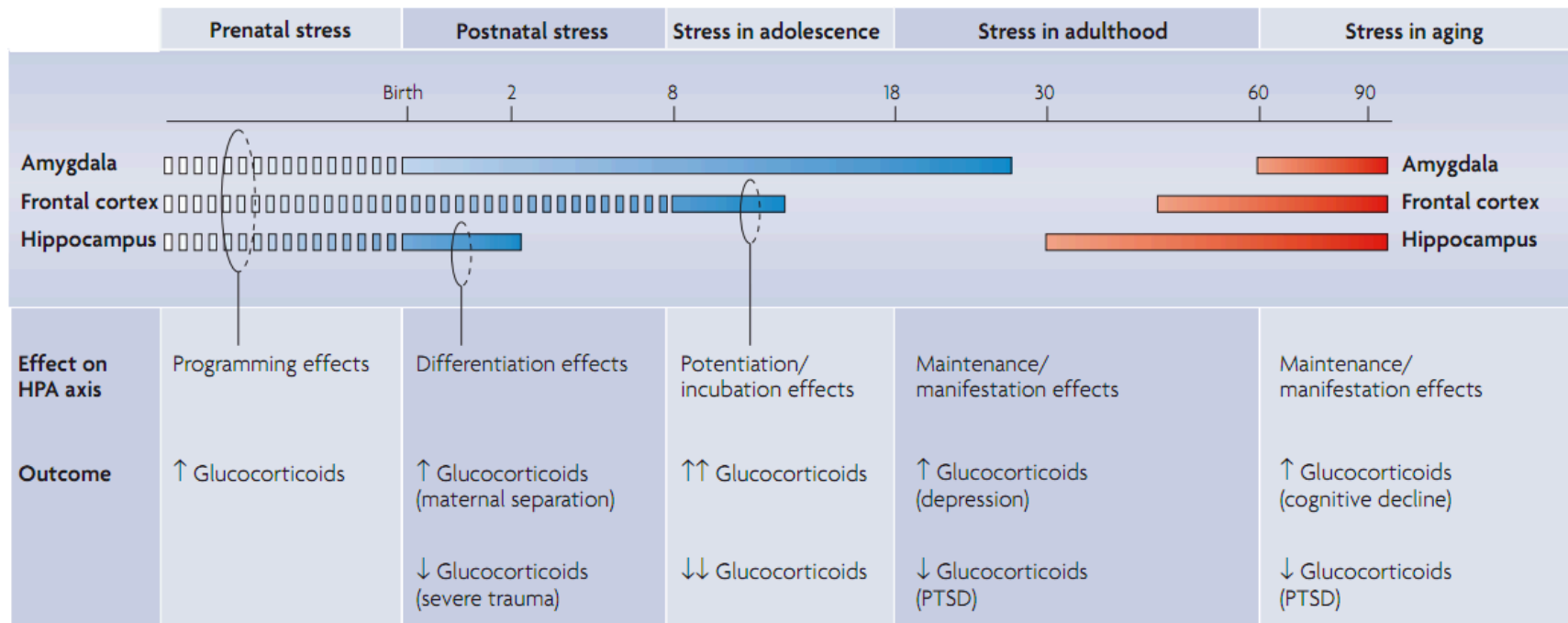
- Generalized
- Panic disorder
- **Phobias**
- **OCD**
- PTSD

Anxiety & Mood Disorders - incidence



Roza et al., Am J. Psych, 2003

Stress and Anxiety



Lupien, Nature Rev, 2009

Major Depressive Disorder - Diagnosis

5 or more of the following symptoms present for >2 weeks:

- Depressed mood
 - Anhedonia, diminished interest
 - Weight change
 - Disrupted sleep
 - Psychomotor agitation or retardation
 - Loss of energy
 - Inappropriate guilt
 - Recurrent thoughts of death and/or suicide
- Not due to mixed state (bipolar disorder)
 - Causes distress and impairment
 - Not due to substance abuse, medication or medical illness
 - Not due to bereavement unless >2 months

Major Depressive Disorder - genetics

- Life-time prevalence: ~10%. 2-fold more prevalent in women.
- Concordance rate in identical twins: ~40%.
- Risk is increased by 3-fold in first degree relatives of affected probands.
- Complex genetics: multiple partially overlapping sets of susceptibility genes that interact with environment predispose individuals to similar syndromes that are indistinguishable on clinical grounds.
- Candidate genes: s5HTT, BDNF Val166Met , TPH2
- Genome-wide association studies (GWAS). 5 studies are negative; meta-analysis of 13,600 identified 6 SNPs at 3p21.1 ($P=3.63 \times 10^{-8}$)

Major Depressive Disorder - imaging

- Structural: Reduced hippocampal volume, especially with chronic or recurrent MDD; reduced volume of the anterior cingulate cortex (ACC)
- Functional imaging: increased activation of the amygdala with challenges, increased activity (BOLD) of ACC; reduced functional connectivity between prefrontal cortex and limbic system
- Positron Emission Tomography: reduced 5-HT_{1A} receptor binding; reduced (variable) 5-HTT binding.

Major Depressive Disorder - treatment

- Norepinephrine uptake inhibitors: desipramine, protryptiline, Maprotiline
- Serotonin uptake inhibitors: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
- Combined uptake inhibitors: amitryptaline, doxepin, imipramine, trimipramine, duloxetine
- Dopamine uptake inhibitor: bupropion
- Monoamine oxidase inhibitors:
 - MAO-A: clorgiline, moclobemide (Europe)
 - MAO-B: selegiline patch
 - Nonselective: isocarboxazid, phenelzine, tranylcypromine

Major Depressive Disorder - treatment

- Tricyclic antidepressants: cardiac arrhythmias (death), dry mouth, constipation, hypotension, impotence
- SSRIs and SNRIs: anorgasmia, weight gain, akathisia, suicidality, emotional detachment
- Bupropion: weight loss, fewer sexual side-effects
- MAOIs: tyramine effect (hypertension), weight gain, serotonin with SSRIs

Major Depressive Disorder - treatment

Neurogenesis and the therapeutic effects of antidepressants

- Depression is associated with atrophy of the dentate gyrus of the hippocampus
- Animal models of depression (chronic stress, social defeat) results in reduced neurogenesis and decreased BDNF in the hippocampus.
- BDNF is reduced in hippocampus in suicide
- Antidepressants regardless of mechanism and electroconvulsive treatment restore neurogenesis
- Blockade of neurogenesis prevents recovery in animal models

Major Depressive Disorder

Inflammation and depression: a distinct subtype?

- Peripheral inflammatory markers (C-reactive protein, IL-6, α -TNF) are elevated in late life depression.
- Late life depression is predictive of Alzheimer's Disease.
- Depression with myocardial infarction associated with inflammatory markers and increased risk of death.
- Obesity is associated with elevated inflammatory markers, diabetes and depression.
- Depression with diabetes is associated with increased risk for peripheral vascular disease and blindness.
- Depression after stroke is associated with poor outcome and premature death.
- Antidepressant treatment enhances survival after a stroke.

Bipolar disorder - diagnosis

Symptoms of mania or a manic episode include:	Symptoms of depression or a depressive episode include:
<p>Mood Changes</p> <ul style="list-style-type: none"> - A long period of feeling "high," or an overly happy or outgoing mood - Extremely irritable mood, agitation, feeling "jumpy" or "wired." <p>Behavioral Changes</p> <ul style="list-style-type: none"> - Talking very fast, jumping from one idea to another, having racing thoughts - Being easily distracted - Increasing goal-directed activities, such as taking on new projects - Being restless - Sleeping little - Having an unrealistic belief in one's abilities - Behaving impulsively and taking part in a lot of pleasurable, high-risk behaviors, such as spending sprees, impulsive sex, and impulsive business investments. 	<p>Mood Changes</p> <ul style="list-style-type: none"> - A long period of feeling worried or empty - Loss of interest in activities once enjoyed, including sex. <p>Behavioral Changes</p> <ul style="list-style-type: none"> - Feeling tired or "slowed down" - Having problems concentrating, remembering, and making decisions - Being restless or irritable - Changing eating, sleeping, or other habits - Thinking of death or suicide, or attempting suicide.

In addition to mania and depression, bipolar disorder can cause a range of moods, as shown on the scale.



Bipolar Disorder - Diagnosis

DSM IV-TR for Bipolar I

- Occurrence of an episode of mania, mixed state or major depression
- At least one prior episode of mania or mixed state
- Clinically significant impairment
- Not the result of schizoaffective disorder or schizophrenia
- Not due to drugs or medical condition
- Specifiers: longitudinal course, seasonal pattern, rapid cycling

DSM IV for Bipolar II

- Presence or history of 1 or more episodes of Major Depression
- Presence or history of one or more hypomanic episodes
- No Manic or mixed state episodes
- Not schizoaffective or schizophrenia
- Clinically significant impairment

Bipolar Disorder - Genetics

- Life-time prevalence: 1-3% (including Bipolar II)
- Concordance rate in identical twins: ~80%
- Risk in first degree relatives of probands: 10-20%
- A disorder of complex genetics with multiple interacting risk alleles of modest leading to phenotype
- GWAS has identified 3 potential risk genes:
 - DGKH-diacylglycerol kinase- ϵ .
 - CACNA1C
 - ANK3-ankyrin3,

Bipolar Disorder - structural

- Compared to controls, bipolars underactivate the inferior frontal cortex (IFG) and putamen and overactive the hippocampus, amygdala and basal ganglia.
- IFG abnormalities occur during emotional and cognitive tasks.
- Limbic abnormalities occurred with emotional tasks.
- Amygdala overactive even in normal state

OCD - diagnosis

One or Both:

- **Obsession:**
 - recurrent thoughts
 - (not due to excessive worry)
 - person ignores/supresses
 - person recognizes the thoughts/impulses were self-generated
- **Compulsive:**
 - Repetitive behaviors or mental acts (counting, repeating words)
 - Goal of behaviors is to reduce distress

Obsessive compulsive disorder (OCD)

- Person must recognize that behaviors are unreasonable
 - Must be time-consuming or otherwise interfere
 - Not due to drugs or medical condition
-
- Childhood onset OCD is greater in males
 - Adult onset (typically in 20's) is greater in females

Obsessive compulsive disorder - neurobiology

- hSERT (serotonin transporter gene) mutations in OCD
 - Serotonin – regulates mood (happiness) and alertness
- Genetic factors account for 40-60% of OCD symptoms in children with OCD
 - i.e., a heritable factor for neurotic anxiety
- OFC is overactive (decision-making, reward)-hyperactive dopaminergic activity
- And serotonin function is reduced in basal ganglia

Phobias

- Overactive amygdala-hippocampal response