



Biological Psychology

M5X00908 Brain, Behaviour, and Cognition (BBC)

Lecture 9: Biopsychology of Psychiatric Disorders

Dr Kate Williams

Psychiatric Disorders



- Disorders of psychological function that require treatment.
- Psychiatrist/clinical psychologist must decide if a person's psychological functioning is pathological
- Diagnosis guided by DSM of the APA or International Statistical classification of Diseases & Related Health Problems (ICD) of the World Health Organisation (WHO).



Psychiatric Disorders



- **Major issue = can be very difficult to diagnose.**

1. **Patients with same disorder can display different symptoms**

2. **Patients with different disorders display same symptoms**

Can result in disagreement between experts & guidelines change with new editions.

Today: discuss what we (think) we know about 4 specific psychiatric disorders, possible treatment options, & discuss clinical trials with drugs aimed to help manage these conditions.

Schizophrenia



- “Splitting of psychic functions”
 - Refers to breakdown of integration of emotion, thought, and action
- Affects ~1% of the population
- A diverse & complex disorder – multiple types exist with varied profiles
 - Can overlap with other psychiatric disorders & even change during progression.
- Symptoms can be classed as either:
 - Positive: represent an excess or distortion of normal function
 - Negative: represent a reduction or loss of normal function.

Schizophrenia



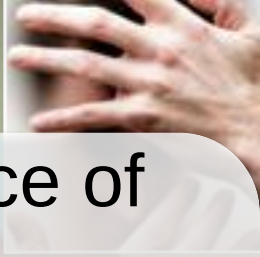
- **Positive symptoms:**
 - Delusions (of being controlled, persecution, or grandeur), hallucinations (imagine voices), inappropriate affect (display incorrect emotions for context), incoherent speech/thought, difficulty performing everyday tasks, lack of personal hygiene, remaining motionless.
- **Negative symptoms:**
 - Affective flattening (absence of emotional expression), Alogia (no speech), Avolition (absence of motivation), and anhedonia (unable to experience pleasure).
- Recurrence of any 2 for 1 month is sufficient for diagnosis.
- Delusion on its own can be enough particularly if it is very bizarre or person has an hallucination that includes voices.

Causal Factors in Schizophrenia



- **Evidence for a genetic contribution**
 - **Inherit an increased risk for the disorder but experience may also influence it developing**
- **Multiple causes**
 - **Several different chromosomes implicated**
 - **Associated with various early issues – birth complications, infections, autoimmune reactions, toxins, traumatic injury, stress**
- **Appears that interference with the normal development of susceptible individuals may lead to development of the disorder**

Discovery of the First Antipsychotic Drugs



- Understanding of schizophrenia is a consequence of drugs that are able to treat it
- **Chlorpromazine**: originally developed as antihistamine to counteract swelling from surgery
 - Surgeons noticed its calming effect, so given to calm agitated schizophrenics & to activate emotionally blunt schizophrenics
 - Does not cure schizophrenia, just reduces severity.
- **Reserpine**: also found to be effective, but no longer used due to dangerous side effects.
- Although chemical structure of both were different, their effects were similar (i.e., no effect for 2-3 weeks, also Parkinson-like motor effects were seen), suggesting they were both working through the same mechanisms.

Dopamine Theory of Schizophrenia



- **1960 – link between dopamine and Parkinson's disease established**
 - **Striatum had been depleted of dopamine, suggesting a disruption of dopaminergic transmission might produce Parkinson's disease.**
- **Due to this & the already established relationship between symptoms of Parkinson's & anti-schizophrenic effects of chlorpromazine and reserpine, it was suggested that anti-schizophrenic drug effects might be produced in the same way.**
- **Led to development of the dopamine theory of schizophrenia – too much dopamine causes schizophrenia & conversely, anti-schizophrenic drugs exert their effects by decreasing dopamine levels.**
- **Supported by facts that:**
 - **Reserpine depletes brain of dopamine and other monoamines by making vesicles leaky**
 - **Chlorpromazine antagonizes dopamine activity by binding and blocking dopamine receptors**
 - **So, both antagonize transmission of dopamine but in different ways**
 - **Amphetamine/cocaine are dopamine agonists & produce psychosis**

Dopamine Theory of Schizophrenia



- Lack of activity at postsynaptic receptors sends feedback signal to presynaptic cells that increases their release of dopamine.
 - Explains why dopaminergic activity is reduced while extracellular levels of dopamine stays the same and why levels of metabolites increased.
- This led to revision of the dopamine theory
 - Instead of high dopamine levels, the main factor is the high levels of activity at dopamine receptors.
- 1970s: degree to which various anti-schizophrenia drugs bind to dopamine receptors was assessed.
 - Radioactively labelled dopamine was added to samples of dopamine-receptor-rich neural membrane obtained from calf striatum
 - Then unbound dopamine molecules rinsed away & amount of radioactivity left was measured to obtain number of dopamine receptors.

Dopamine Theory of Schizophrenia

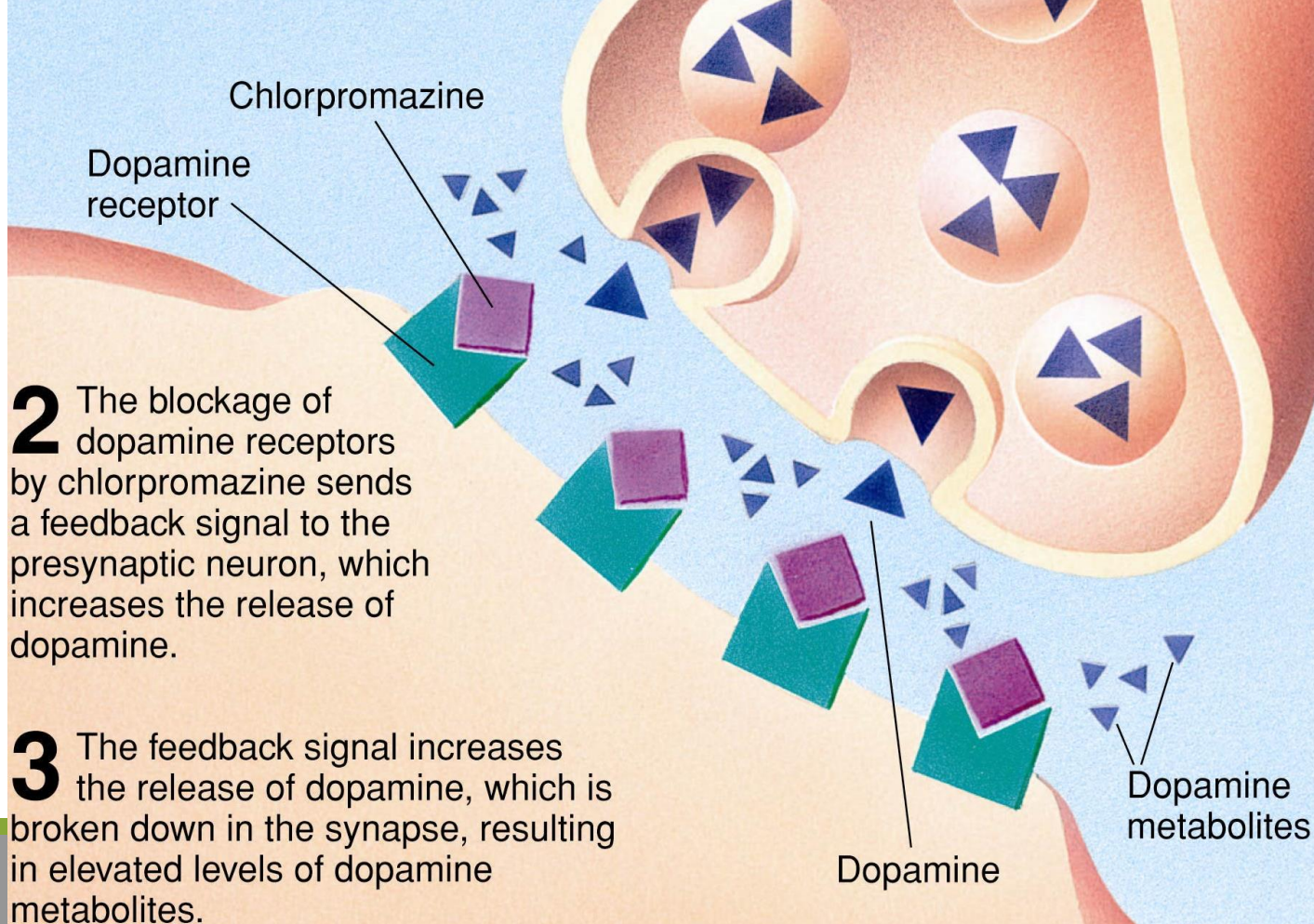


- Drugs ability to block binding of radioactive dopamine was assessed - assumed that drugs with high affinity for dopamine receptors would leave fewer sites available for the dopamine.
- Chlorpromazine & others had high affinity for dopamine receptors whereas ineffective drugs had low affinity.....
- Except for haloperidol: very potent but had low affinity.
- Solution: came from discovery that dopamine binds to more than one receptor subtype – 5 have been identified.
- Chlorpromazine & others bind effectively to D1 & D2 receptors, whereas haloperidol bind effectively to D2 but not to D1.
- This discovery of selective binding led to further revision of the dopamine theory to suggest that schizophrenia is caused by hyperactivity specifically at D2 receptors rather than at dopamine receptors in general.

Dopamine Theory of Schizophrenia



1 Chlorpromazine binds to postsynaptic dopamine receptors; it does not activate them, and it blocks the ability of dopamine to activate them.



2 The blockage of dopamine receptors by chlorpromazine sends a feedback signal to the presynaptic neuron, which increases the release of dopamine.

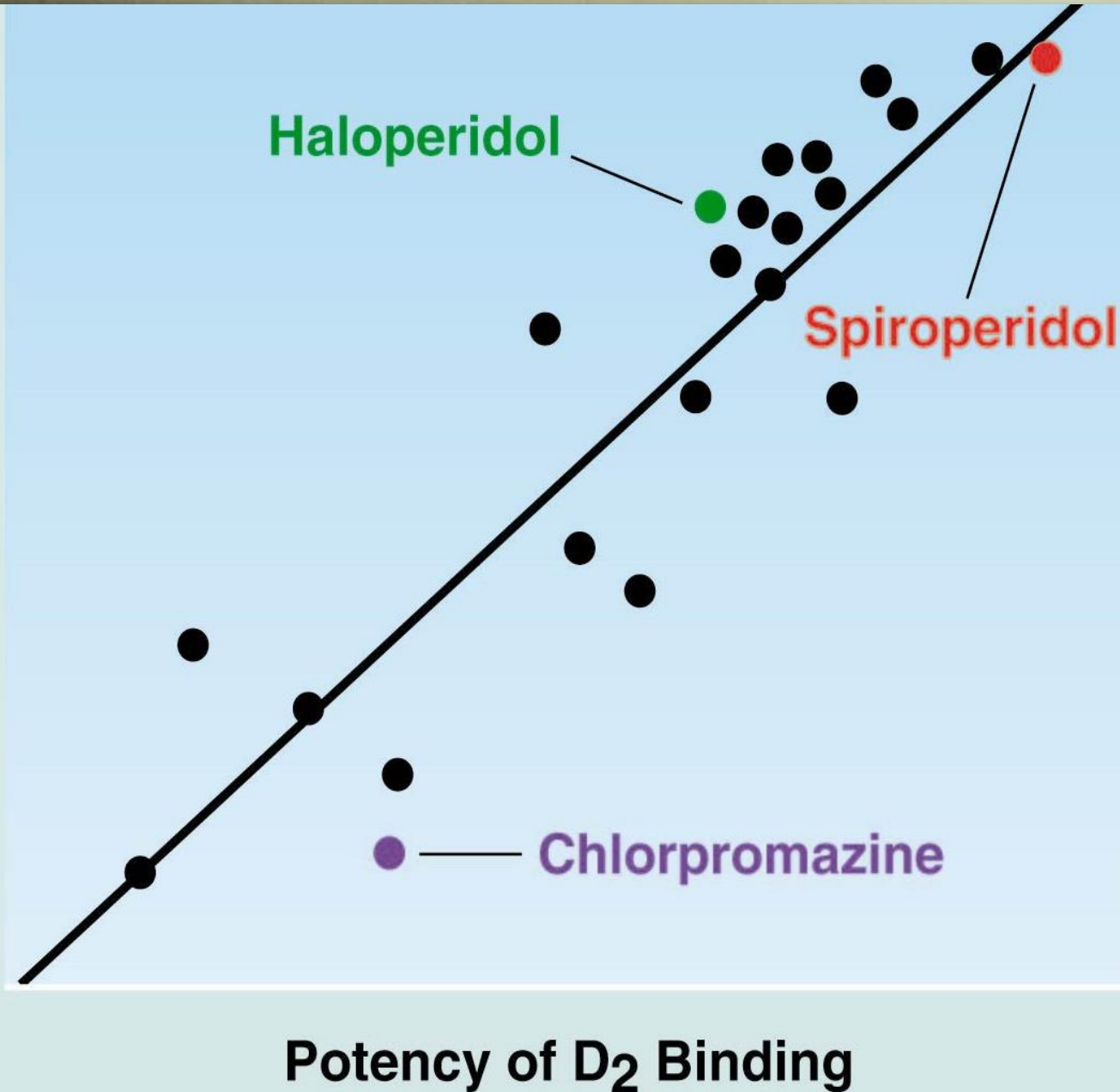
3 The feedback signal increases the release of dopamine, which is broken down in the synapse, resulting in elevated levels of dopamine metabolites.

Chlorpromazine is a receptor blocker at dopamine synapses. Chlorpromazine was the first receptor blocker to be identified, and its discovery changed psychopharmacology.

Dopamine Theory of Schizophrenia



Antischizophrenic Potency



The positive correlation between the ability of various neuroleptics to bind to D₂ receptors and their clinical potency. (Based on Snyder, 1978.)

Limitations of the Dopamine Theory



- Four key discoveries about neural basis of schizophrenia cannot be explained by D2 version of dopamine theory.
- These suggest that although over activity at D2 receptors plays a role, other factors are prevalent.
 1. Other receptors also involved: glutamate, GABA, & serotonin.
 - Evidence from studies on LSD, which produce schizophrenia-like symptoms by acting on serotonin & glutamate receptors.
 - Atypical neuroleptics, such as clozapine has an affinity for D1, D4, & serotonin receptors but not for D2 receptors.

Limitations of the Dopamine Theory



2. Neuroleptics block D2 receptors within hours but it takes weeks to alleviate symptoms.
 - Time difference suggests blockage of D2 receptors is not only aspect involved.
3. Schizophrenia is associated with widespread brain damage, & meta-analysis of studies has shown reduced volume in 50 different brain regions.
 - Postmortem studies reveal neuron loss & abnormalities of neuron structure & circuitry in many parts of the brain.
 - Two aspects about pattern of brain damage observed that causes problems for the dopamine theory:
 - A. Little evidence of damage to dopamine circuits
 - B. Theory does not explain why there is brain damage to such a diffuse area.

Limitations of the Dopamine Theory



4. Neuroleptics are only marginally effective.
 - If dopamine theory was correct & was the only factor involved then neuroleptics should be effective to treat all patients.
 - But they do not & they only help with some symptoms not others:
 - Conventional neuroleptics (D_2 blockers) are mainly effective for positive symptoms, while negative symptoms might be caused by brain damage.
- Better to think of schizophrenia as multiple disorders with multiple causes.

Affective Disorders: Depression & Mania



- **Depression:** normal reaction to loss, abnormal when it persists or has no cause.
 - Experience anhedonia: loss of capacity to experience pleasure for no apparent reason.
 - Unable to meet the essential requirements of daily life – keeping a job, having a social life, eating, keep an acceptable level of hygiene and have sleep disturbances.
- **Mania:** overconfidence, impulsivity, distractibility, and high energy – again for no apparent reason.
 - When extreme it is a clinical problem: wake up in total enthusiasm with nonstop talking that switches rapidly between topics & overconfidence can lead to disaster.

Major Categories of Affective Disorders



Affective disorders:

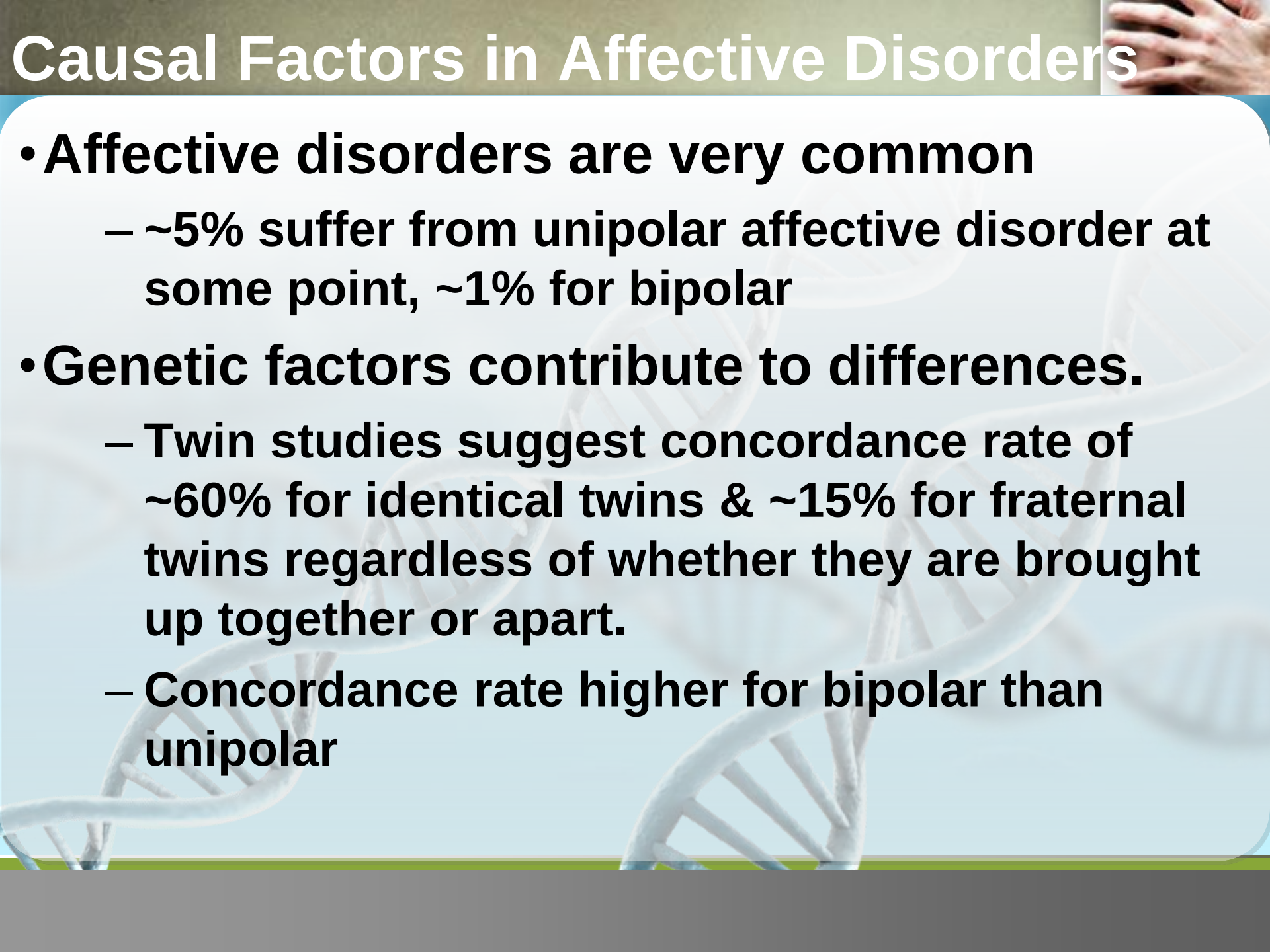
- Psychiatric disorders characterized by mood or emotion disturbances.
- Also known as mood disorders
- Includes depression and mania
- Can be seen as opposite to each other but many depressive patients can experience periods of mania.

Types of depression

- Unipolar & Bipolar
- Reactive (triggered by negative experience)
- Endogenous (from within with no apparent cause)



Causal Factors in Affective Disorders



- **Affective disorders are very common**
 - ~5% suffer from unipolar affective disorder at some point, ~1% for bipolar
- **Genetic factors contribute to differences.**
 - Twin studies suggest concordance rate of ~60% for identical twins & ~15% for fraternal twins regardless of whether they are brought up together or apart.
 - Concordance rate higher for bipolar than unipolar

Causal Factors in Affective Disorders



- Most research on causal role of experience on affective disorders has focused on stress.
 - Although evidence suggests depression is a stress-related disorder, evidence linking them is sparse.
 - Stress can trigger attacks in those already depressed but little evidence showing stress increases susceptibility.
 - Extreme stress is more likely to cause **post-traumatic stress disorder (PTSD)** than depression.
- Two affective disorders where the cause is more apparent due to timings of the attacks:

1. Seasonal Affective Disorder (SAD)

- Wintertime depression and lethargy, due to reduction of sunlight
- Evidence: incidence rates different between N. America & Florida
 - Light therapy thought to reduce symptoms

2. Postpartum depression



Discovery of Antidepressant Drugs



- Four major classes of drugs used in the treatment of affective disorders

1. Monoamine oxidase inhibitors (MAOIs): Iproniazid

- Increases levels of monoamines by preventing their breakdown by oxidase enzymes in cytoplasm of neuron
- Must avoid foods high in tyramine – “cheese effect”
- Normally these foods have little effect on blood pressure because tyramine is metabolized in the liver by MAO, but people who take MAO inhibitors & eat food containing tyramine run the risk of stroke caused by surges in blood pressure.

Discovery of Antidepressant Drugs



2. Tricyclic antidepressants – Imipramine

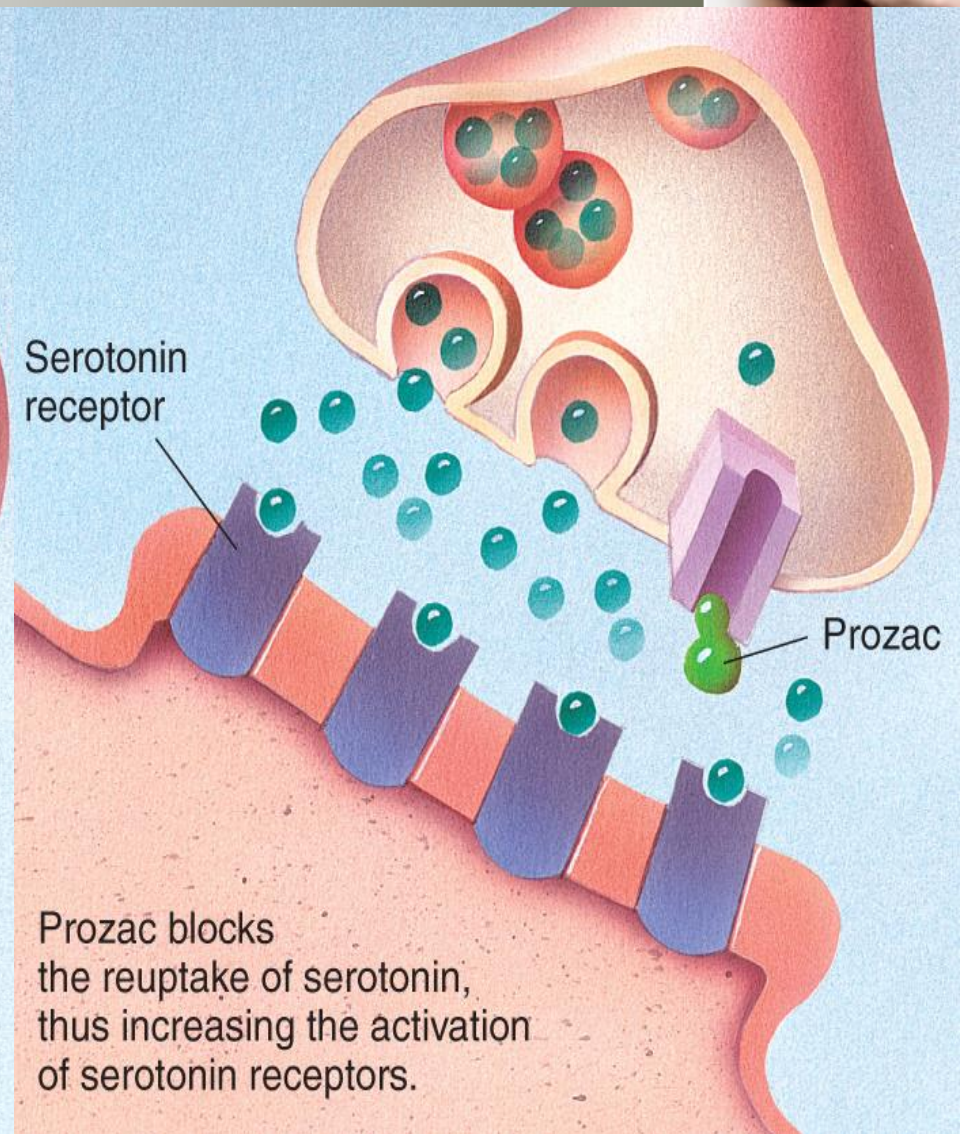
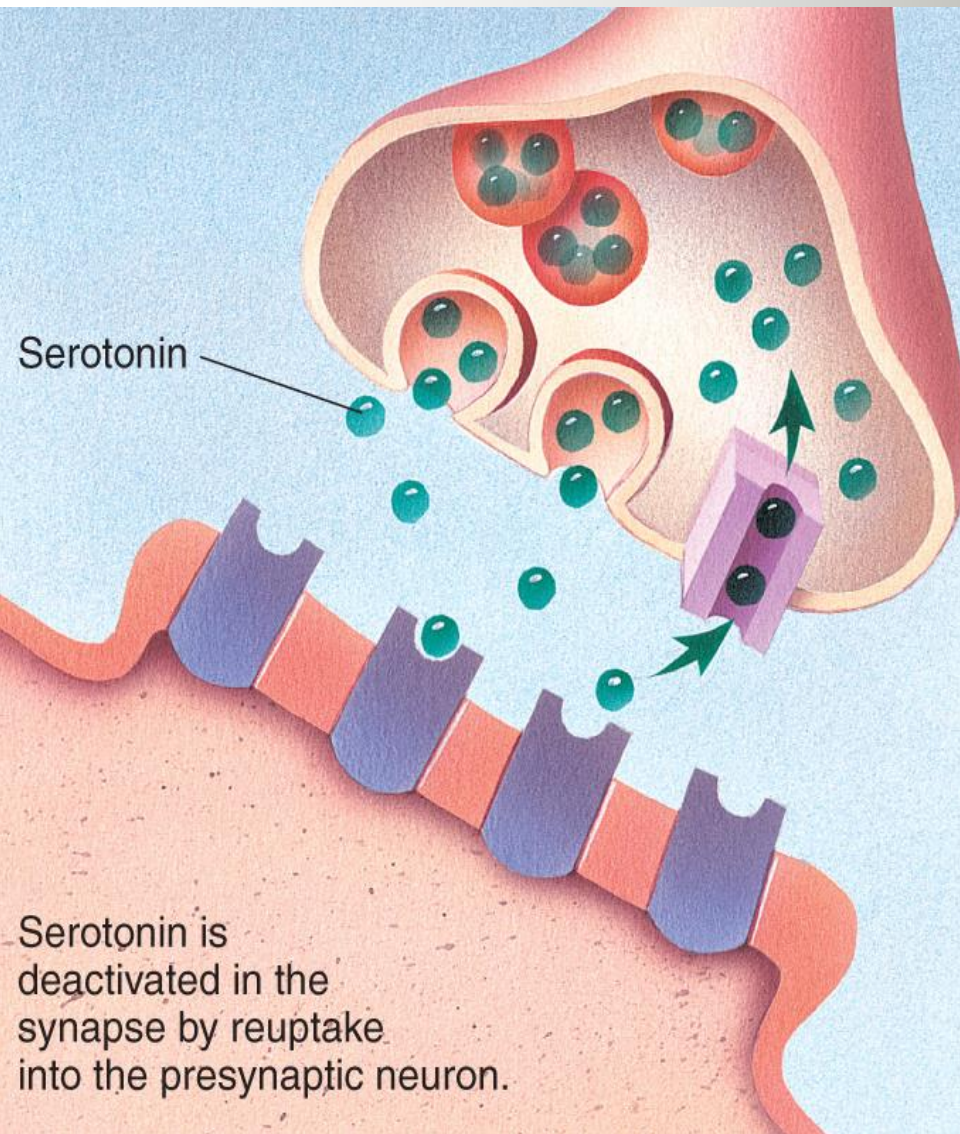
- Their chemical structure includes 3 rings of atoms
- They block reuptake of serotonin and norepinephrine
 - Thus, increasing levels of these in the brain
- They are thought to be safer than MAOIs

3. Selective serotonin-reuptake inhibitors (SSRIs)

- They are serotonin agonists that exert effects by blocking the reuptake of serotonin from synapses.
- Include Prozac, Paxil, Zoloft, and others
- No more effective than tricyclics, but side effects are few and they are effective at treating other disorders

4. Selective norepinephrine-reuptake inhibitors (SNRIs): also effective & block reuptake of norepinephrine

SSRIs



Effectiveness of Drugs in Treating Affective Disorders



- Lots of money spent on developing antidepressants, so we need to know if they work.
- Hollon et al. (2002) compared efficacy of various pharmacology treatments for depression and found they were about the same for MAOIs, tricyclics, & SNRIs: ~50% of clinically depressed patients improved but a control group showed a 25% improvement, so really only 25% of the depressed group were helped.
- Hirsch et al. (2008): meta-analysis indicated that placebo was about 82% as effective as anti-depressants in severely depressed individuals
 - Drugs even less effective for mild to moderately depressed individuals

Brain Pathology & Bipolar Affective Disorder

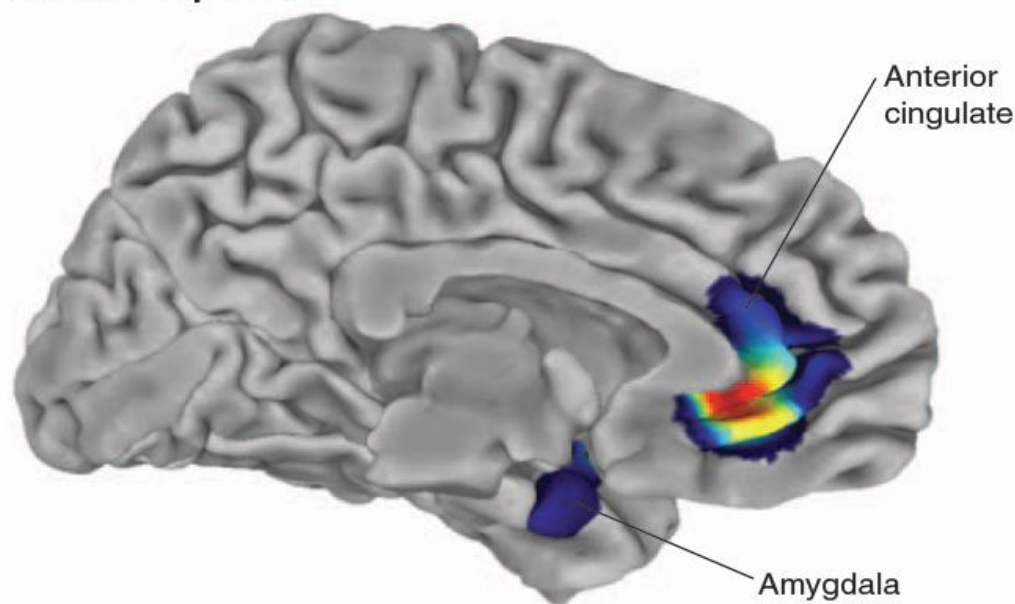


- Many MRI brain studies of bipolar patients shown reductions in overall brain size and in particular size of amygdala, cingulate cortex, and prefrontal cortex.
- But pattern of results is inconclusive because certain brain structures found to be of reduced size in one study is of normal size in other studies.
 - This suggests not all patients with bipolar by current criteria suffer from the same disorder.
- However, there are 2 structures found to be abnormal in many studies: the amygdala and the anterior cingulate cortex.
- The connections between these also seem to be disrupted in patients with affective disorders.

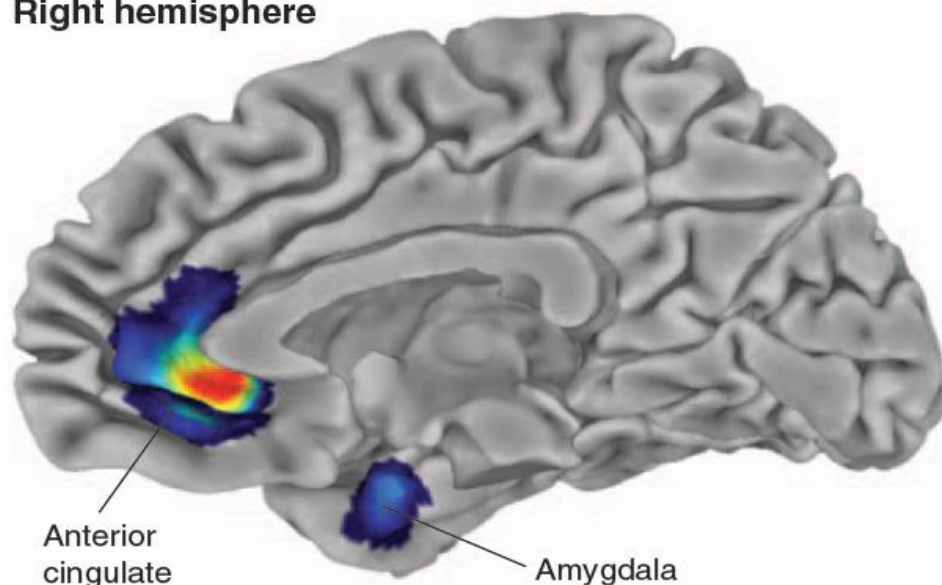
Brain Pathology & Bipolar Affective Disorder



Left hemisphere



Right hemisphere



Greatest
cell loss



Significant
cell loss

Structural MRIs of healthy volunteers with a genetic predisposition to developing depression reveals cell loss in the anterior cingulate and the amygdala.



Monoamine Theory of Depression

- Search for neural mechanisms of affective disorders has mainly focused on clinical depression.
- But mania & depression can occur in same patient, suggesting mechanisms are closely related.
- However, none of the main theories of depression deal well with its relation to mania.
- One prominent theory is the monoamine theory:
 - Suggests depression is associated with underactivity at serotonergic and noradrenergic synapses.
- Based on the fact that monoamine oxidase inhibitors, tricyclics, SSRIs, and SNRIs are agonists of serotonin, norepinephrine, or both.

Monoamine Theory of Depression



- Support provided by autopsy: serotonin and norepinephrine receptors more numerous in brains of deceased clinically depressed individuals who had not had pharmacological treatment whilst alive, which implicates a deficit in monoamine release.
- When not enough amount of a neurotransmitter is released at a synapse, there are usually compensatory increases in the number of receptors for that neurotransmitter – called Up-regulation.
- However, overall support for the monoamine theory of depression is weak and not all patients respond to monoamine agonists.

Diathesis-Stress Model of Depression



- Suggests some people inherit a diathesis (genetic susceptibility) incapable of initiating the disorder by itself.
- If susceptible people are exposed to stress early in life their systems become permanently sensitized and end up over reacting to mild stressors for the rest of their lives.
- Diathesis + stress = depression
- Support is indirect: depressed people...
 - Tend to release more stress hormones



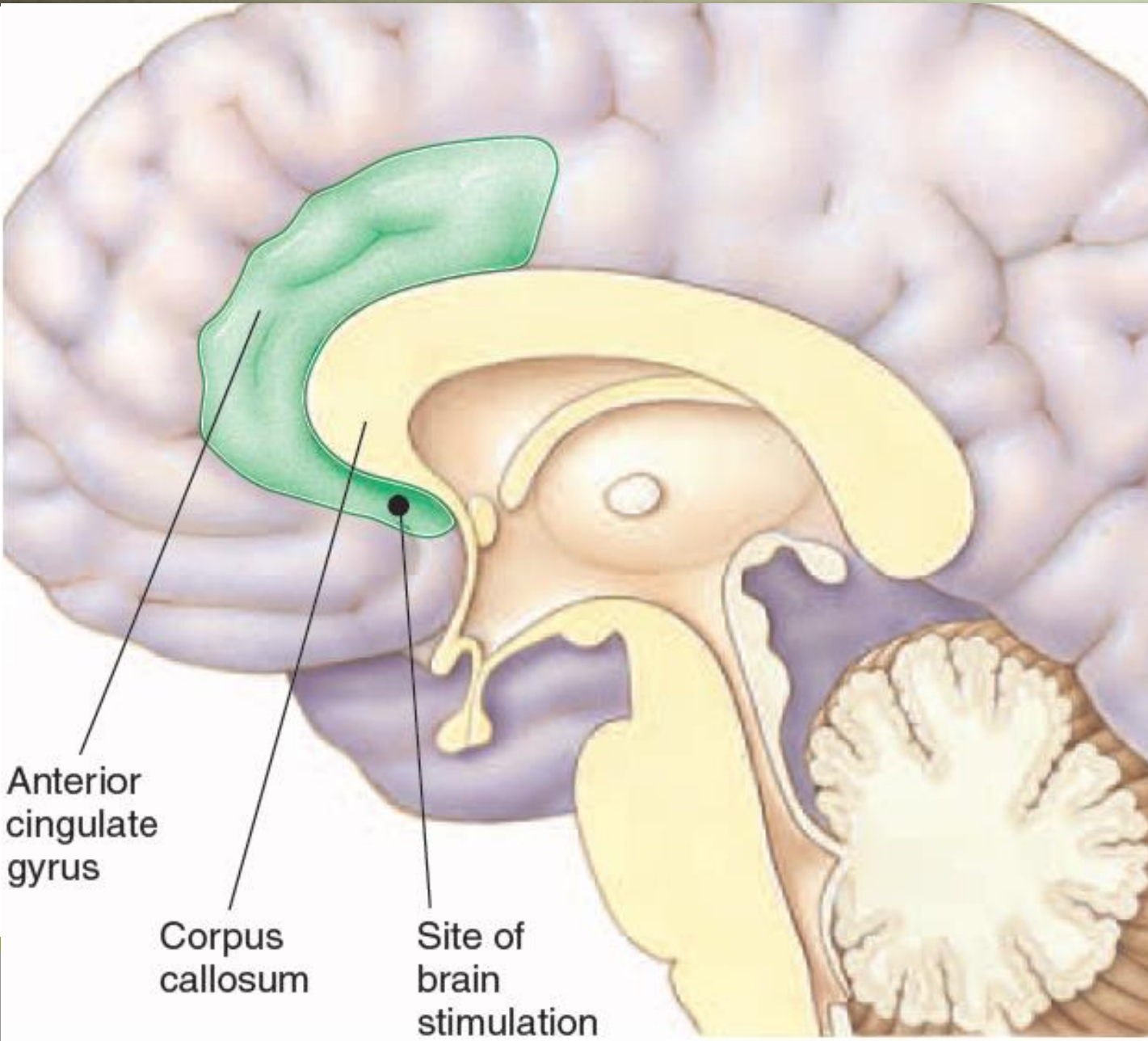
Diathesis-Stress Model of Depression



- Also, fail the dexamethasone suppression test:
 - Assesses adrenal gland function by measuring how cortisol levels change in response to injection of dexamethasone....
 - which is an exogenous steroid that provides negative feedback to the pituitary gland to suppress the secretion of adrenocorticotrophic hormone.
- Weakness of theory:
 - Evidence of early stress based on recollections of distant past - likely faded or perhaps even distorted
 - May not be any way of confirming the events recalled.
 - Sometimes there is no evidence of excessive early stress in the lives of a number of depressed patients.



Treatment of Depression with Brain Stimulation



Lozano & colleagues (2008) found that chronic electrical stimulation near the anterior cingulate gyrus helped relieve depression in treatment-resistant patients

Other Treatments for Affective Disorders



Sleep deprivation

- More than 50% of depressed patients improve after one night of sleep deprivation
- Depression returns with normal sleep pattern
- Not explained by any current theory

Exercise

- Helps reduce depression
- Increases adult hippocampal neurogenesis
- Findings suggests that depression may be caused by reduced adult hippocampal neurogenesis

Anxiety Disorders



- **Anxiety** – chronic fear in the absence of threat
- **Anxiety disorder** – when anxiety interferes with normal functioning
 - Associated with feeling fear & worry
 - Accompanied by physiological symptoms – rapid heartbeat (tachycardia), hypertension, sleep disturbances, breathing difficulties, nausea, etc.
- The most prevalent psychiatric disorders



Five Classes of Anxiety Disorders



- **Generalized anxiety disorders** – stress and anxiety in the absence of a causal stimulus
- **Phobic anxiety disorders** – similar to generalized, but triggered by a particular stimulus (e.g., birds)
- **Panic disorders** – attacks of extreme fear and stress; may occur with other disorders or alone
- **Obsessive-compulsive disorders (OCDs)** – obsessive, recurring, uncontrollable thoughts alleviated by compulsive actions
- **Posttraumatic stress disorder** – pattern of psychological distress following extreme stress

Etiology of Anxiety Disorders



- **Given that anxiety disorders are often triggered by an identifiable stressful event or is focused on a particular object or situation, the role of experience in shaping the disorder seems clear.**
- **But there is also a significant genetic component with heritability estimates ranging from 30-40% and concordance rates are substantially higher for identical twins than for fraternal twins.**
- **However, timing & focus of anxiety disorders often reflects the particular experiences of the patient and no specific gene or genes have yet to be linked to anxiety disorders.**

Pharmacological Treatment of Anxiety Disorders



- **Benzodiazepines** (e.g., Librium, Valium)
 - Most widely prescribed & also used as hypnotics, anticonvulsants, muscle relaxants
 - They are GABA_A agonists – bind to receptor & facilitate effects of GABA; but highly addictive.
 - Also, many side effects: sedation, nausea, etc.
- **Serotonin agonists** (e.g., buspirone, SSRI)
 - Has selective agonist effect on the 5HT receptor.
 - Re-duce anxiety without sedation, but side effects include headaches, dizziness, nausea.
- **Antidepressants** – effective due to comorbidity of anxiety and depression.

Animal Models of Anxiety



- Animal models have helped with understanding of anxiety disorders & development of anti-anxiety drugs
- Weakness: they involve animal defensive behaviors – implicit assumption being that defense is motivated by fear and that fear and anxiety are similar states.
- **Elevated-plus-maze test:** rats placed in a 4 arm plus sign 50cm off the floor, where 2 of the arms have sides and 2 do not – the measure of anxiety is the proportion of time the rats spend in the enclosed arms rather than going in to the exposed arms.



Animal Models of Anxiety

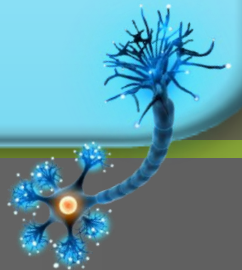


- **Defensive-burying test:** rats receive unpleasant stimulus expelled from dowel in test chamber – measure of anxiety is amount of bedding they throw over source of unpleasant stimuli.
- **Risk assessment test:** after single exposure to a cat, rats run away to their burrows and freeze & then engage in risk assessment behaviors before behavior returns to normal – measure of anxiety is amount of time rat spends frozen and risk assessing.
- All have been validated by demonstrations that benzodiazapines reduce the indices of anxiety used in the tests whereas non-anti-anxiety drugs do not.
- But many cases of anxiety do not respond to benzodiazapines.

Neural Basis of Anxiety Disorders



- Current theories rely on analysis of the effects of drugs.
- The fact that many anxiolytic drugs are agonists at either GABA or serotonin receptors has focused attention on the role of deficits in both GABA and serotonin transmission in anxiety disorders.
 - There is also substantial overlap between the brain structures involved in affective and anxiety disorders
 - e.g., amygdala and anterior cingulate cortex have been implicated in affective disorders & in anxiety disorders.
 - Although both these structures have been implicated the patterns of evidence has differed.....



Neural Basis of Anxiety Disorders



- Affective disorders = shrinkage to these structures.
- Anxiety disorders = no overall damage.
- Most evidence linking amygdala & anterior cingulate cortex to anxiety disorders has come from functional brain imaging studies
 - Abnormal activity in these areas has been recorded during the performance of various emotional tasks
 - For example, there is increased activity in the amygdalae of patients with spider phobias when they viewed photographs of spiders.



Tourette Syndrome



- Disorder of tics (involuntary repetitive movements) or vocalizations
- Begins in childhood (more frequent in males)
- Major genetic component
- Many also have signs of ADHD and/or OCD
- No animal models, no genes identified, imaging difficult due to tics
- Patients tend to have smaller caudate nuclei, but also appears to be widespread brain damage in other areas & MRI on children has shown a thinning of the sensorimotor cortex.



Tourette Syndrome: Treatment



- First get those involved in patients life to understand & help deal with emotional issues.
- Treatment of tics usually done with neuroleptics
 - D2 receptor blockers used in treating schizophrenia.
- Reduce tics by ~70% but benefits are moderate & side effects: e.g., weight gain, fatigue and dry mouth.
- But success of D2 receptor blockers in blocking tics is consistent with current hypothesis that disorder is related to abnormality of the basal-ganglia-thalamus-cortex feedback circuit.
- Efficacy of drugs implicates striatum, which is target of many dopaminergic projections to basal ganglia.

Clinical Trials: Development of New Psychotherapeutic Drugs



- **How are drugs developed in order to treat the various psychiatric disorders discussed?**
- **Through Translational research**
 - **Research designed to translate basic scientific discoveries into effective clinical treatments**
- **Initially development of psychotherapeutic drugs was hit and miss with new drugs being tested on patient populations with little justification and then quickly marketed to the public before it was discovered that they were ineffective for their purpose.**

Clinical Trials: Development of New Psychotherapeutic Drugs



- **Nowadays testing of experimental drugs on humans are regulated by agencies.**
- **Process of gaining permission from the government to market a new psychotherapeutic drug involves:**
 - **Synthesis of the drug.**
 - **Developing procedures for synthesizing it economically**
 - **Collecting evidence from non-human subjects to show that it will likely be safe for humans & has potential benefit.**
- **The initial steps take a long time - at least 5 years – and only then if evidence is good enough will permission be granted to proceed to clinical trials.**

Clinical Trials: Development of New Psychotherapeutic Drugs



TIME

First Phase: BASIC RESEARCH

At least
5 years

Discovery of the drug, development of efficient methods of synthesis, and testing with animal models

About
1 year

Application to begin clinical trials and the review of basic research by government agency

Second Phase: HUMAN CLINICAL TRIALS

COST

About
1.5 years

Phase I
Screening for safety and finding the maximum safe dose

About
2 years

Phase II
Establishing most effective doses and schedules of treatment

About
3.5 years

Phase III
Clear demonstrations that the drug is therapeutic

About
1.5 years

Application to begin marketing and reviews of results of clinical trials by government agency



Third Phase: SELLING TO THE PUBLIC

Ongoing

Recovering development costs and continuing to monitor the safety of the drug



Clinical Trials: Development of New Psychotherapeutic Drugs



- Giving humans a drug for the first time is risky because there is no way of knowing how they will respond.
- Phase 1 Ps are usually healthy paid volunteers.
- Phase 2 Ps are patients suffering from the target disorder with placebo-control double-blind designed
- Phase 3 involves study on a large scale based on phase 2.
- **Controversial aspects of clinical trials**
 - Requirement for double-blind design and placebo controls: potentially effective drug withheld from desperate patients randomly assigned to control group
 - The need for active placebos: have side effects but no therapeutic value in order to stop patients from guessing whether they have had the drug or the placebo
 - Length of time required – people who are desperate for treatment have to wait long time but safety needs to be paramount.

Clinical Trials: Development of New Psychotherapeutic Drugs



Financial issues

- Conflict of interest: drug companies test their own drugs; may forbid scientists from publishing negative findings
- Drugs for rare diseases are unprofitable so drug companies tend not to focus on developing them.
- Translational bottleneck: due to high costs of clinical trials, few scientific findings translate to new drugs

“Clinical trials can be trustworthy, fast, or cheap; but in any one trial, only two of the three are possible.” (Zivin, 2000)