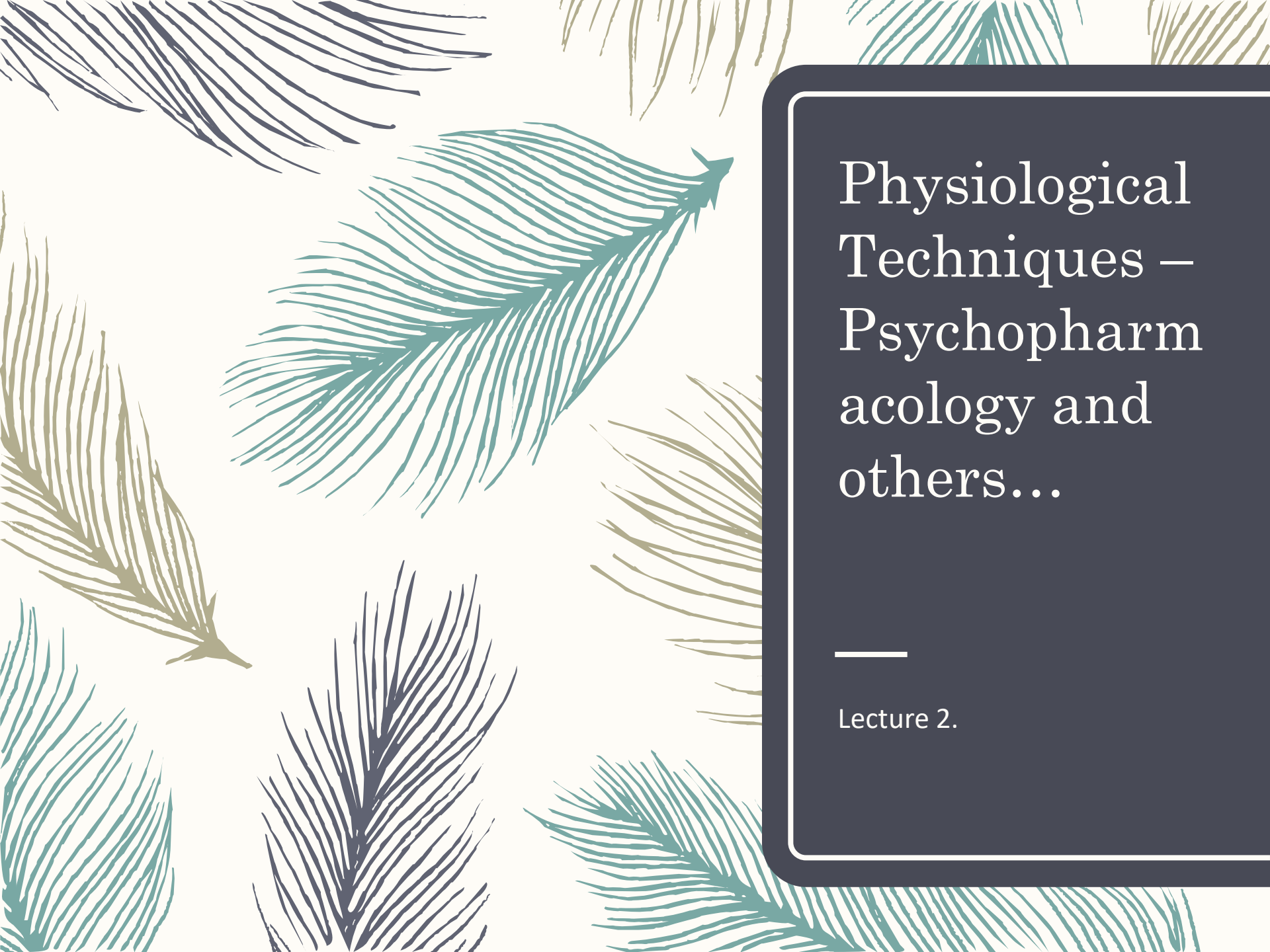




Physiological Techniques – Psychopharm acology and others...

Lecture 2.

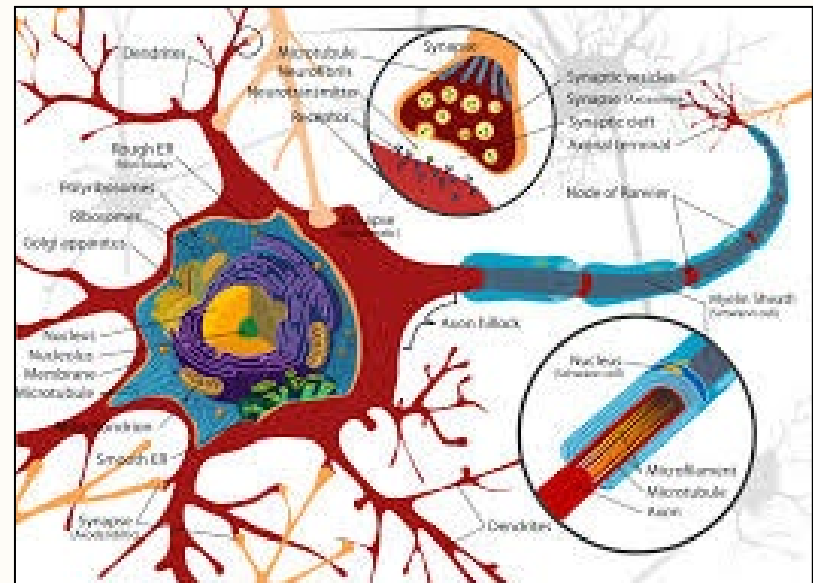
The Biological Paradigm

- The search for biological abnormalities which cause abnormal behaviour. E.g. The discovery of general paresis and syphilis (Ehrlich 1910).
- But, 1800's: no non-invasive way to observe the structures of the brain.
- Was impossible to look at structure-function relationship in the living.



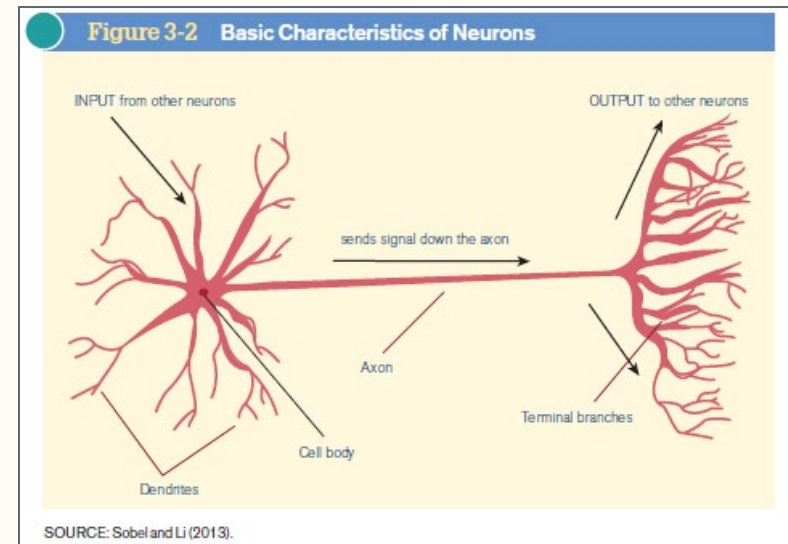
Biological Factors

- Brain anatomy and physiology
- Hormones and neurotransmitters
- Genetics and inheritance
- Brain injury or insult
- Illness or infection



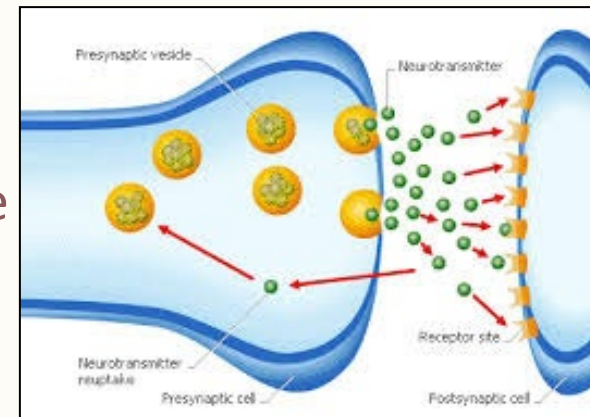
Basics of neuronal communication

- Neurons connected by branching dendrites.
 - *Synapses*
 - *Chemical or electrical*
 - *Neurotransmitters*
- Action potentials (from near cell body) at a critical value of electrical activity
 - *Excitatory or inhibitory*



Basics of neuronal communication: Neurotransmitters

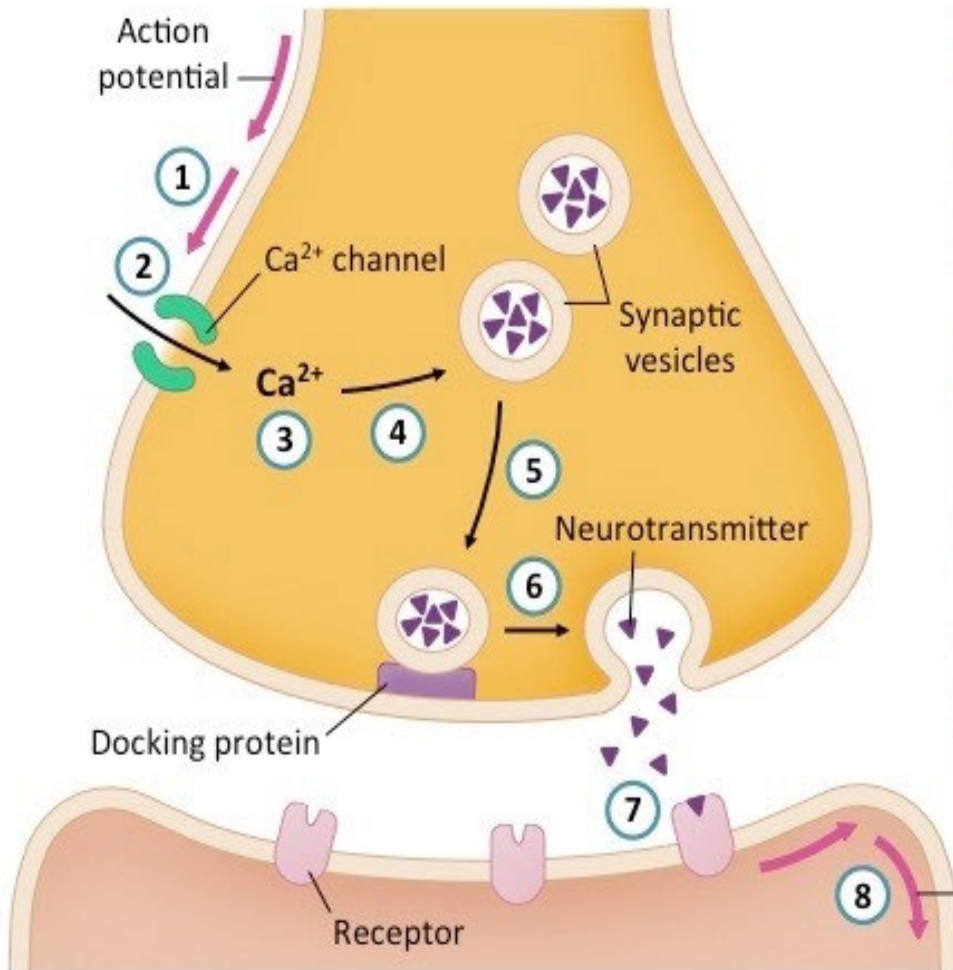
- Two **structural** categories: Small molecule and large molecule.
 - Small molecule: Single amino acid
 - Large molecule (neuropeptides): 3-36 amino acids
- Three **functional** categories:
 - Mediate communication: Glutamate and GABA
 - Pain system: Opioid peptides
 - Large system communication: serotonin, dopamine, adrenaline and noradrenaline



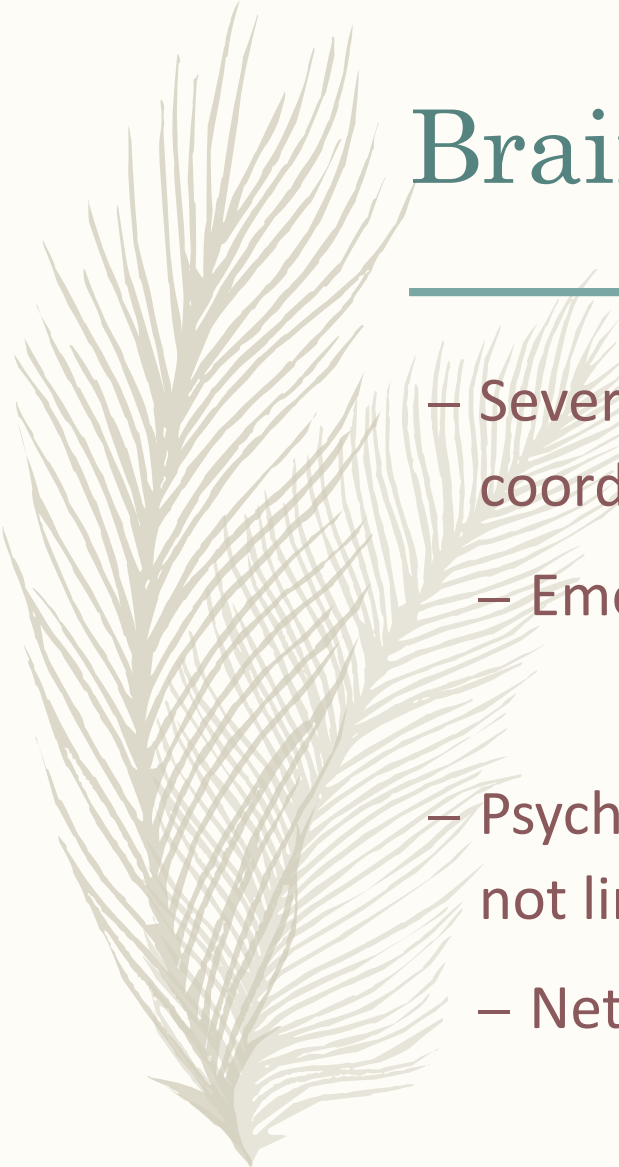
Basics of neuronal communication

- Passing information from one neuron to another involves a number of steps.
- Neurotransmitters need to be created and stored.
- Action potentials travel down the axon to the terminal.
- Neurotransmitter is released into synapse.
- Neurotransmitters then bind with specific proteins in the post-synaptic neuron.
- This binding increases (excitatory) or decreases (inhibitory) the likelihood of an action potential.
- Synapse returns to neutral and neurotransmitter is removed.

Synaptic transmission



- 1 Action potential arrives at axon terminal
- 2 Voltage-gated Ca^{2+} channels open
- 3 Ca^{2+} enters the presynaptic neuron
- 4 Ca^{2+} signals to neurotransmitter vesicles
- 5 Vesicles move to the membrane and dock
- 6 Neurotransmitters released via exocytosis
- 7 Neurotransmitters bind to receptors
- 8 Signal initiated in postsynaptic cell

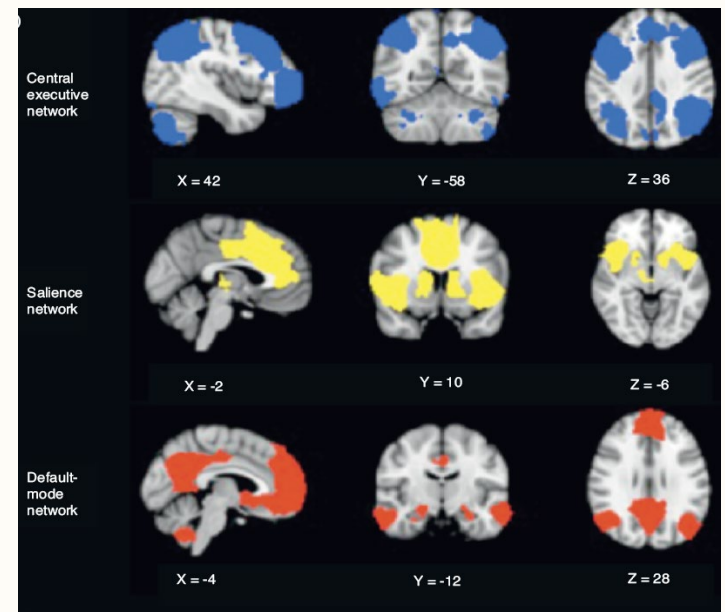


Brain networks

- Several areas of the brain work together to coordinate complex functions.
- Emotions, cognition, and motor processes.
- Psychopathology is similarly complex and often not limited to a single area.
- Network wide processing disturbance.

Brain networks

- Intrinsic (default) network
- Active networks
 - Central executive network
 - *Higher order cognitive and attentional tasks*
 - Salience network
 - *Monitoring external events and internal states*



Major brain structures and their behaviours

Hindbrain- medulla, pons, cerebellum

- Few abnormal behaviours arise from here, this area is for basic bodily functions.

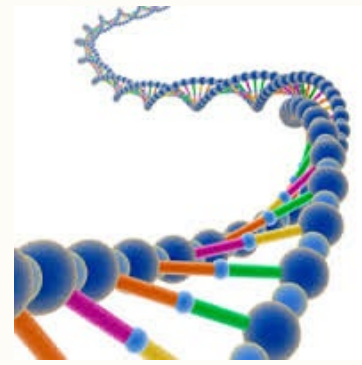
Midbrain- RAS, pons and medulla

- Activities such as fighting, sex, sleeping and waking. Disorders of sleep, sexual behaviour and aggression.

Forebrain- limbic system (thalamus/hypothalamus). Cerebral hemispheres

- Basic biological urges, eating, drinking, sex, and ANS functioning. Endocrine system.

Genetics: Inheritance



- Genotype- actual genetic structure
- Phenotype- the expression of a genotype
- Polygenic disorders- multiple genetic influences
- Genetic influence on brain development?
 - Maternal vs paternal influence
- Maternal inheritance: Mitochondrial inheritance

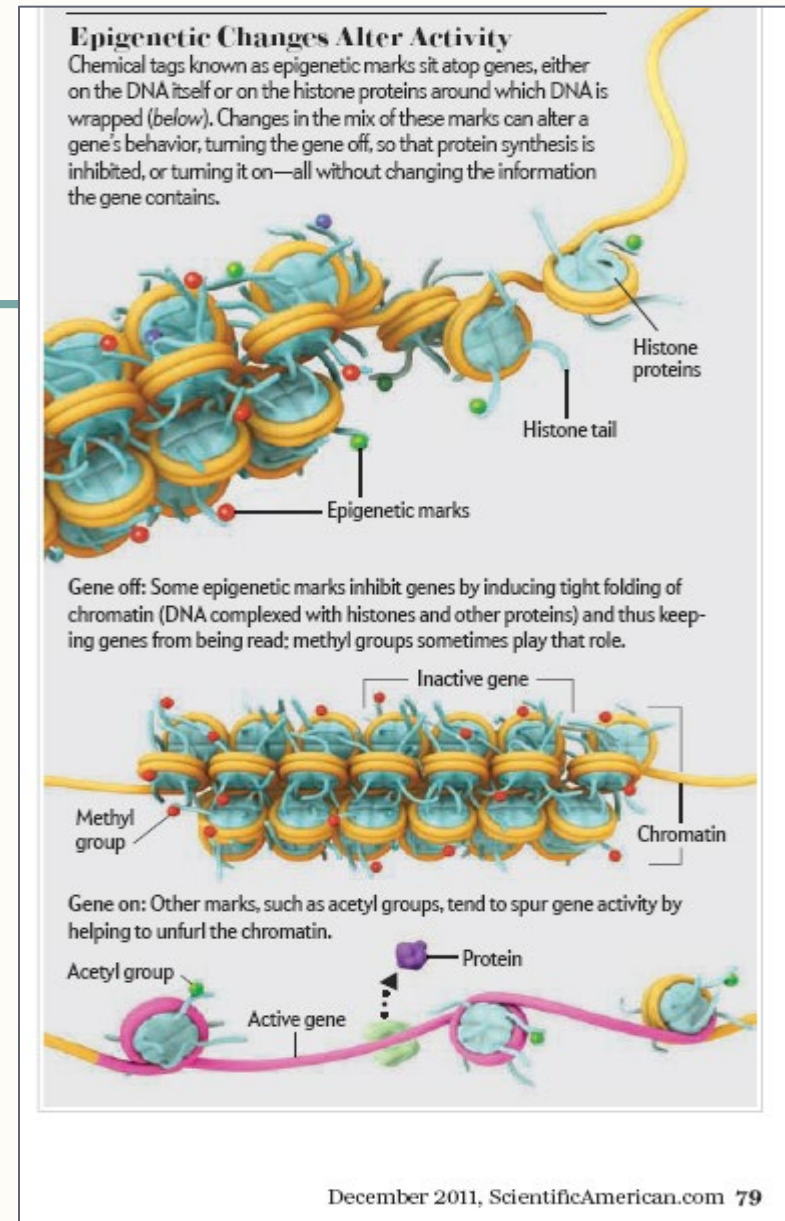
Studying genetic factors

- Twin studies, monozygotic, dizygotic
- Family history studies
- Adoption studies
- What about gene environment interactions (Plomin, 2008)



Epigenetics

- Genes can be modified by experience/environment.
- Epigenetic markers “tags” promote (writers) genetic activity or inhibit (erasers) genetic activity.



Epigenetics: Example

- Weaver et al. (2004) the impact of passive vs. active nurturing rat mothers.
- Mothers grooming style influenced development of offspring.



Mother taking care of her pups

Photo by Seweryn Olkowicz, Wikipedia

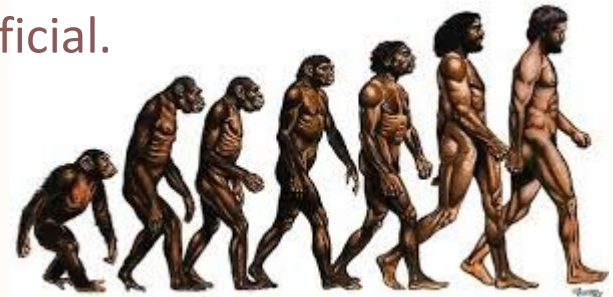


Evolutionary perspective

- Both physical and cultural environment influence genetic change.
- Also possible that metacognitive factors influence gene expression.
- Complex set of physical cultural and emotional factors influence the development of psychopathology.

Evolutionary perspective

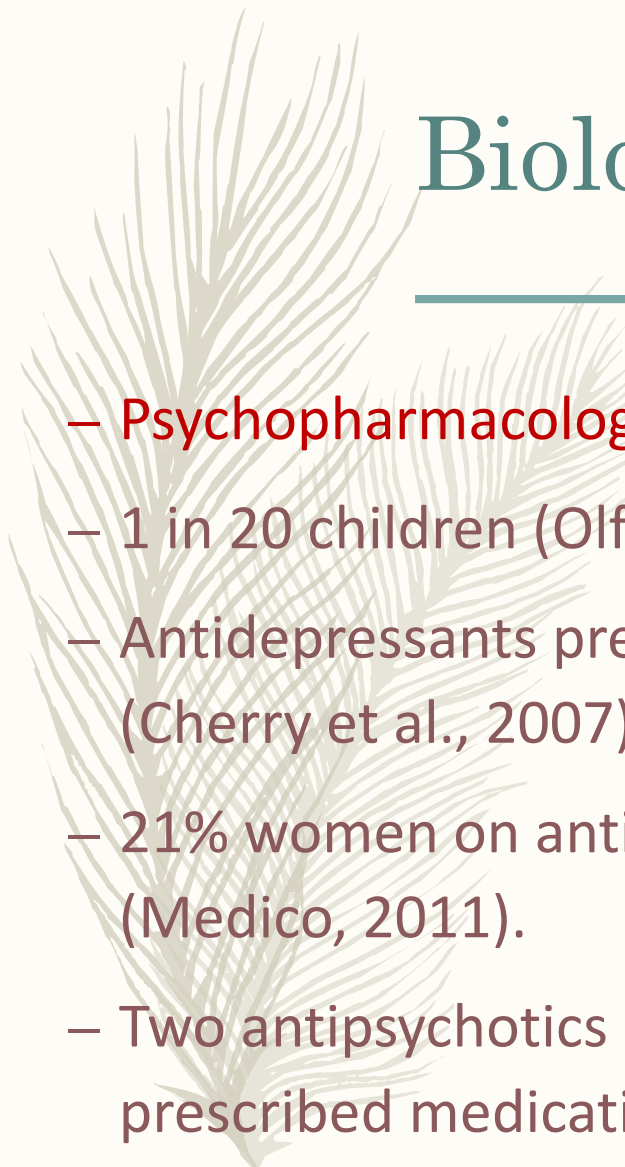
- Genetic aspects of psychopathology evolved and were maintained in the human population.
- Maladaptive traits may have once benefited the species.
- Example 1: Schizophrenia is maladaptive yet it is maintained in the human population at ~1%
- Example 2: Personality disorders: Psychopaths are excellent at manipulating people.
- In some circumstances psychopathy may be beneficial.



Universal psychopathology?

- If psychopathology is part of the human experience then we should expect to see similar rates of pathology across culture.
- Different cultures refer to and categorize pathology differently (Murphy, 1976).
- However, the disordered behavior is universal.





Biological Treatments

- **Psychopharmacology**- psychotropic medications.
- 1 in 20 children (Olfson & Marcus 2009)
- Antidepressants prescribed more than any other medication! (Cherry et al., 2007).
- 21% women on antidepressants and half that figure in men (Medico, 2011).
- Two antipsychotics medications were the 5th & 6th most prescribed medications in 2011 in the US.



Psychopharmacology

- Psychopharmacology for schizophrenia/psychosis
- Major depression
- Bipolar disorder
- Anxiety disorders – social anxiety disorder (SAD), panic disorder, general anxiety disorder
- OCD



Antipsychotic drugs and schizophrenia

- A multi-faceted approach of both acute and chronic episodes must be planned for.
- Anti-psychotic drugs are the first port of call, and can be classed as first or second generation.
- Double blind, placebo controlled studies have demonstrated their efficacy (Haddad et al. 2009). 50% of medicated patients see improvement within 4-6 weeks, whereas placebo controls often deteriorate.
- Conley & Kelly (2001) 25% see no improvement, with 30-40% being partial responders.



Schizophrenia and drugs

- ANTIPSYCHOTIC DRUGS (neuroleptics) dampen down 'psychotic' symptoms such as delusions and hallucinations. Chlorpromazine and clozapine block the neurotransmitter dopamine by binding to dopamine receptors. First generation typical drugs such as chlorpromazine have many side effects.
- Newer antipsychotic drugs such as clozapine were originally believed to have lower side effects. (Second generation atypical drugs). However more recently, research suggests that they have their own serious side effects on the immune system, cause weight gain and extrapyramidal symptoms (Young et al., 2010).



Schizophrenia and drugs

- The use of antipsychotic medication has improved the life of many, as pre- 1980`s the majority of sufferers spent extended periods of time in institutions.
- The use of neuroleptics has helped with both the positive and negative symptoms of schizophrenia, but approximately one third of sufferers will not respond to drug therapy.
- The negative side effects do have an effect on non-compliance, relapse rates, and treatment attrition.
- There is also the ethical question of administering medication without the patients consent.

Early research in Depression

Biochemical factors:

NTs: serotonin and norepinephrine

- In the 1950s, medications for high blood pressure were found to cause depression
- Some lowered serotonin, others lowered norepinephrine
- The discovery of truly effective antidepressant medications, which relieved depression by increasing either serotonin or norepinephrine, confirmed the NT role.



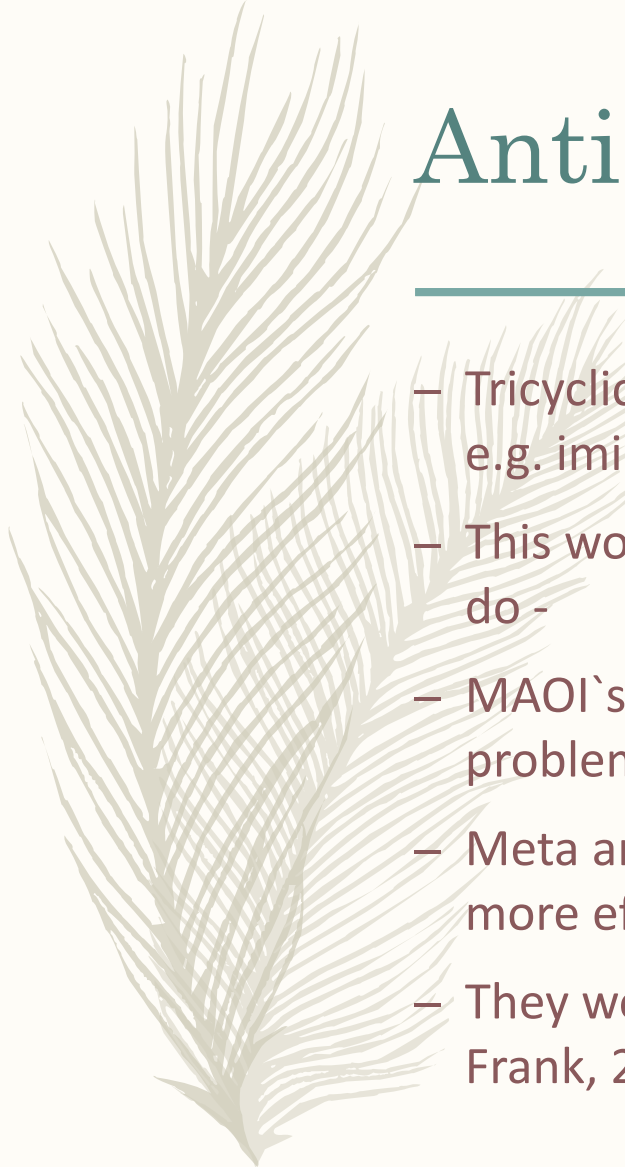
More likely to be a complicated interaction at work, and other NTs may be involved

Depression likely involves not just serotonin and norepinephrine...



Anti-depressant medication

- For major depressive disorder SSRI's are the most commonly prescribed e.g. Prozac.
- These delay the reuptake of the neurotransmitter serotonin, thus raising levels in the brain. With more natural levels of serotonin in the brain, mood is elevated from the depressed state to a more normal state of mind.
- There are a number of side effects with these drugs, although less than some of the older ones.
- Cannot ignore the risk of suicide although this is balanced against its effectiveness.
- Also good for dysthymic disorder.

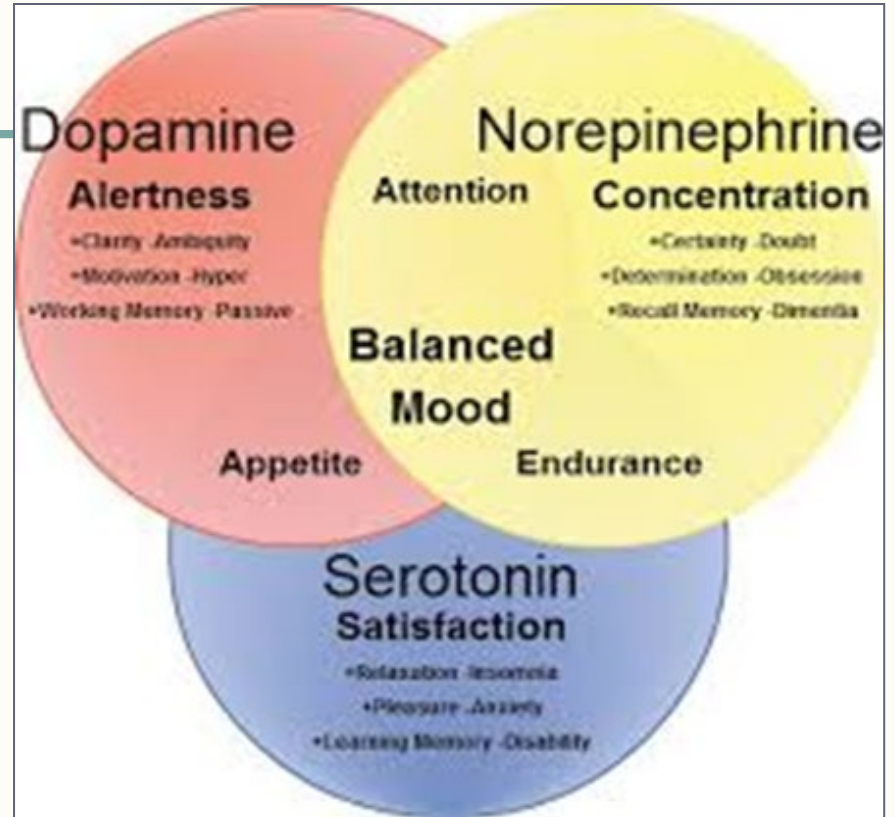


Anti-depressant medication

- Tricyclic drugs (because of the 3 ring chemical structure)- e.g. imipramine.
- This works by increasing serotonin and norepinephrine as do -
- MAOI`s – the older drugs with many side effects and problem interactions with foods e.g. tranylcypromine.
- Meta analyses have shown that both tricyclics and SSRI`s are more effective than controls in 55-60% of patients.
- They work more effectively if given alongside CBT (Kupfer & Frank, 2001).

Current research

Currently, it is thought that serotonin, norepinephrine, dopamine and neuropeptides interact together (Stockmeier 2003).





Medication for Bipolar disorder

- Lithium carbonate is prescribed for individuals with bipolar disorder
- Around 80% of patients gain relief from symptoms
- However, debate around the underlying mechanisms
- Originally believed to stabilise potassium and sodium ions or by binding to receptors to stabilise transmission
- More recently, believed to moderate transmission by affecting the expression of the genes responsible for synaptic transmission

What Are the Symptoms of Mania ?

People with a bipolar disorder experience both the lows of depression and the highs of mania

Unlike those experiencing depression, people in a state of mania typically experience dramatic and inappropriate rises in mood

Five main areas of functioning may be affected:

Emotional symptoms

- Active, powerful emotions in search of outlet

Motivational symptoms

- Need for constant excitement, involvement, companionship

Behavioral symptoms

- Very active – move quickly; talk loudly or rapidly
- Flamboyance is not uncommon

Cognitive symptoms

- Show poor judgment or planning
 - May have trouble remaining coherent or in touch with reality

Physical symptoms

- High energy level – often in the presence of little or no rest

What Causes Bipolar Disorders?

Neurotransmitters

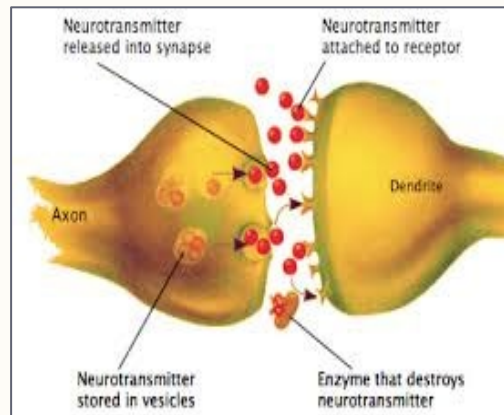
- After finding a relationship between low norepinephrine and unipolar depression, early researchers expected to find a link between high norepinephrine levels and mania
- This theory is supported by some research studies; bipolar disorders may be related to over-activity of norepinephrine

Southwick et al. (2005)

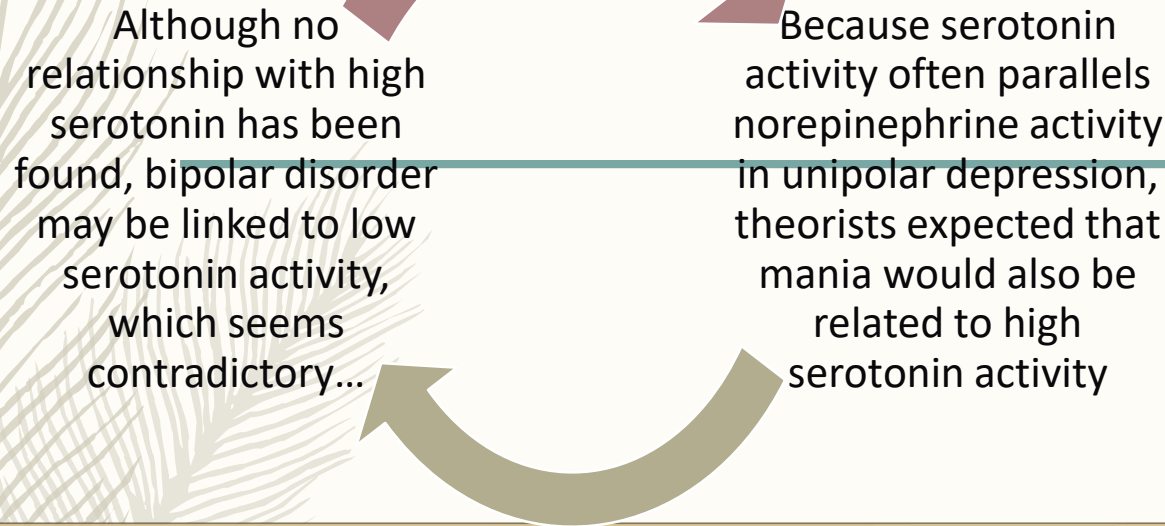
- These insights have come from research into NT activity, ion activity, brain structure, and genetic factors

More recently, biological research has produced some promising clues

Throughout the first half of the 20th century, the search for the cause of bipolar disorders made little progress



What Causes Bipolar Disorders?



Although no relationship with high serotonin has been found, bipolar disorder may be linked to low serotonin activity, which seems contradictory...

Because serotonin activity often parallels norepinephrine activity in unipolar depression, theorists expected that mania would also be related to high serotonin activity

This apparent contradiction is addressed by the “permissive theory” about mood disorders:

- Low serotonin may “open the door” to a mood disorder and permit norepinephrine activity to define the particular form the disorder will take:
 - Low serotonin + Low norepinephrine = Depression
 - Low serotonin + High norepinephrine = Mania

Goodwin and Jamison(2007)

Treating Bipolar

Lithium

Mood-Stabilizing
Drug

Has anti-manic and antidepressant effects—they exert mood-stabilizing effects in either direction.

Lithium has been more widely studied as a treatment of manic episodes than of depressive episodes

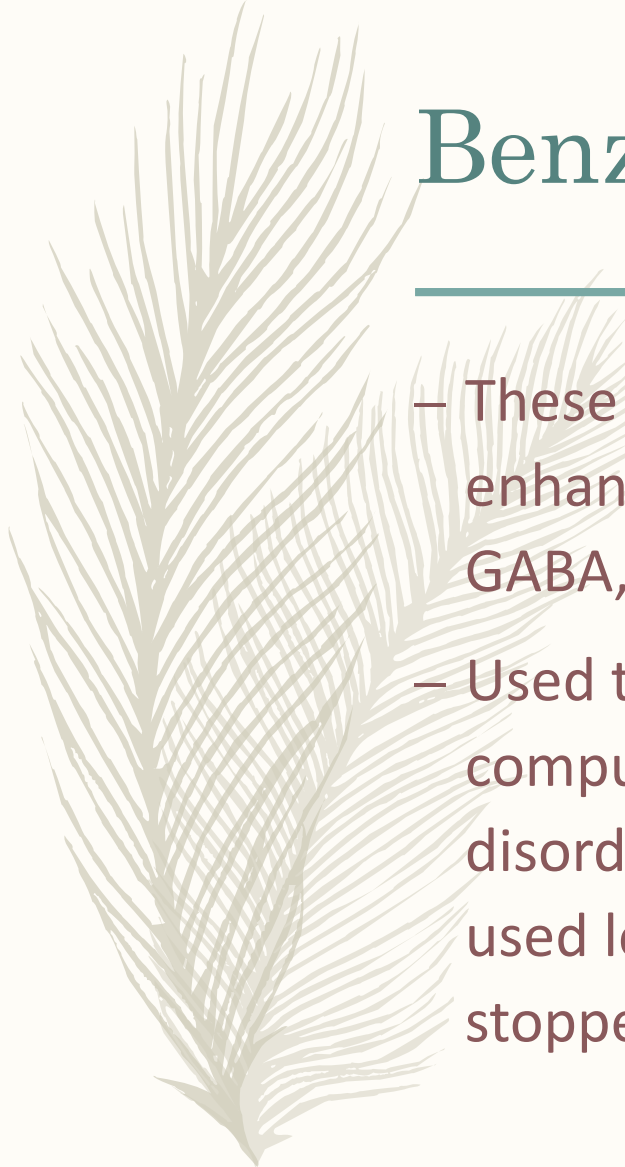
In the treatment of bipolar depression- about three-quarters show at least partial improvement (Keck & McElroy, 2007).

However, treatment with antidepressants is associated with significant risk of precipitating manic episodes or rapid cycling, although the risk of this happening is reduced if the person also takes lithium (e.g., Keck & McElroy, 2007; Thase & Denko, 2008).

Lithium - unpleasant side effects -lethargy, cognitive slowing, weight gain, decreased motor coordination, and gastrointestinal difficulties.



Long-term use of lithium is occasionally associated with kidney malfunction and sometimes permanent kidney damage (Goodwin & Jamison, 2007; Tredget et al., 2010).



Benzodiazepines

- These slow down the activity of the CNS, by enhancing the activity of the neurotransmitter – GABA, the body's natural form of anxiety relief.
- Used to treat panic disorder (PD); Obsessive-compulsive disorder; Post-traumatic stress disorder (PTSD) Phobias. Possible dependence if used long-term and withdrawal reactions if stopped suddenly.



Specific drugs for specific disorders

- Social anxiety disorder is treated with MAOI`s and SSRI`s in addition to benzodiazepines, but best outcome is when CBT, exposure therapy or social skills training is implemented.
- Panic disorder is treated with tricyclics, benzodiazepines, CBT and exposure therapy.
- General anxiety disorder responds best to medication in first instance (SSRI`s SNRI`s then followed by longer term CBT).
- Typically no drug treatment for phobias.



Medication for treating OCD

- SSRI's because they are cheap and readily available, however relapse is common on discontinuation.
- No consensus regarding the role of serotonin in OCD. May be because of ameliorative effect on brain function.
- Tricyclics work on compulsions only if depression is present.
- Comparative studies show that they are less effective than psychological therapies such as exposure therapy.



Anti-manic drugs

- LITHIUM CARBONATE or CARBAMAZEPINE if no response to Lithium.
- The first choice for mania with a lower relapse rate (Bauer & Mitchner, 2004)
- But 40% do not improve
- A problem with compliance
- A problem with switching between polars.



Psychomotor stimulants

- AMPHETAMINES such as-
- RITALIN
- DEXEDRINE
- Immediate improvements are seen, 75% of children have increased alertness and arousal to allow for focus.
- Double blind studies show efficacy (Barkley 2006).
- Whilst they help behaviour, what about learning and attention?

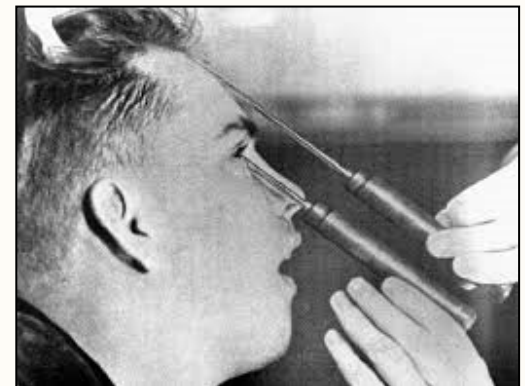
Electroconvulsive Therapy

- 6-12 sessions over two weeks, 100vltS either bilaterally or unilaterally.
- Unilateral ECT less retrograde amnesia, but less effective.
- Only given with caution, under anaesthetic and only for severe depression.

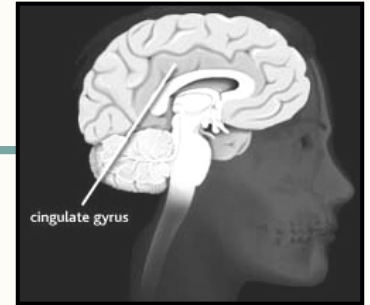


Psychosurgery

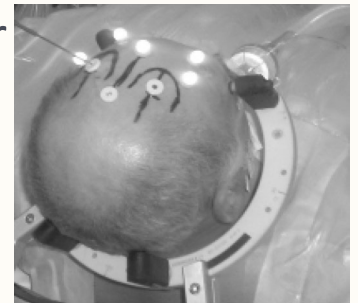
- Early Psychosurgery- Egas Moniz (1935) Destroyed nerve fibres in the frontal lobes which were involved in impulse control and mood regulation. Nobel Prize (1949) for the **prefrontal leucotomy**.
- Walter Freeman popularised the **transorbital lobotomy** during the 1940s and 1950s.



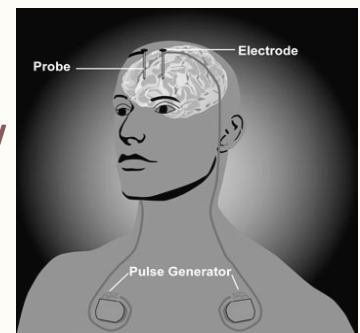
Stereotactic Psychosurgery



- More precise way of surgically treating mental disorders such as OCD, bipolar disorder, depression and eating disorders, and even for reducing chronic pain in cancer patients.



- Bilateral cingulotomy
- Capsulotomy
- Deep Brain Stimulation: e.g. Vagal nerve stimulation
- TMS- Transcranial magnetic stimulation works in first few centimeters to depolarise neurons





Final thoughts on biological therapies (Psychopharmacology)...

- Some disorders show `spontaneous remission` (Eysenck 1992)
- But... Lambert & Bergin (1994) most people have some form of `unstructured therapy`.
- 50% of clinicians prescribe placebo`s and they appear to work. Expensive ones work better than discounted ones!
- Neuroscience has shown that they reduce the brains response to pain (experience and expectancy)