



Drugs and Behaviour

Dr Stuart Jones.



Aims of the Lecture.

- To Recap on Neurons and Neurotransmitter.
- To explore 5 groups of synaptic transmitters.
- To define the term Ligand.
- To explore the role of Endogenous Ligands.
- Exploring Neuroscientific research in relation to endogenous ligands.



Aims of the Lecture.

- To discuss and define the term “Drug”
- To discuss how are drugs effective (e.g. how drugs work).
- To explore the relationship between Drugs and Behaviour in a variety of classification of drugs.
- To examine Neuroscientific studies exploring the role of how drugs might influence behaviour.



- People have tasted, sipped, chewed, swallowed all kinds of substances.
 - Animal, Vegetable and Mineral.
- Learning from these experiences.
- Not just the need of nourishment.
 - Relieve pain, control anxiety, pursue pleasure.
 - Almost every species does this (Siegel, 1989).



- Neurochemistry – Branch of Neuroscience concerned with the chemical composition and processes of the nervous system.
- Neuropharmacology – Also known as Psychopharmacology – Scientific field concerned with the discovery and study of compounds that selectively affect the functioning of the nervous system.

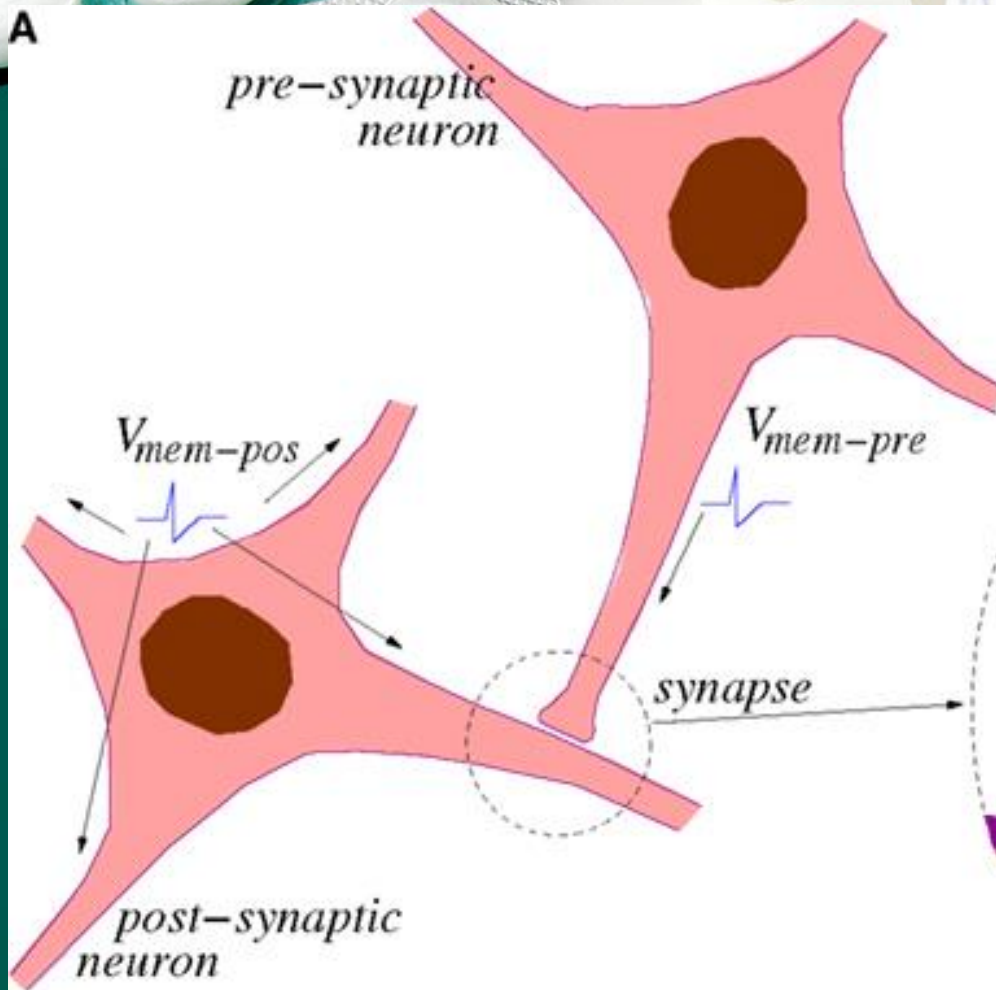


Recap.

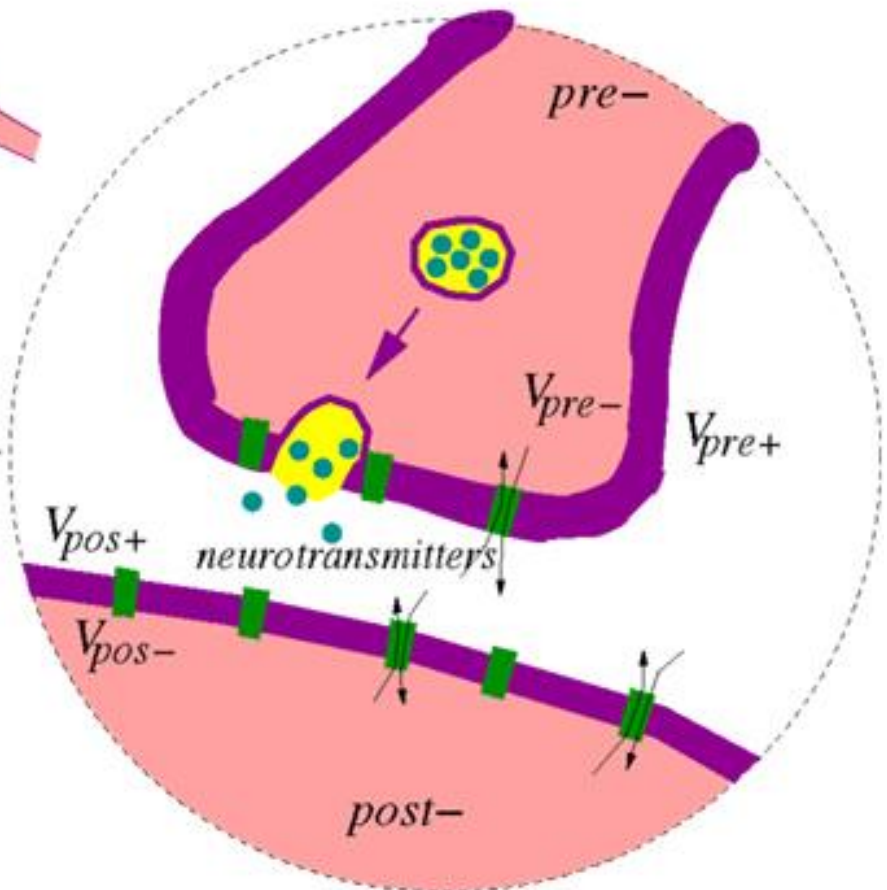
- Neurons release a chemical known as a Neurotransmitter – communicates with target cells (usually neurons).
- Criteria for substance acting as a neurotransmitter.
 - Exists in the presynaptic axon terminals.
 - Presynaptic cell contains appropriate enzymes.
 - Substance released in significant quantities when action potentials reach the terminals.
 - Specific receptors recognise the substance.
 - Application of the substance produces changes in the postsynaptic potentials.
 - Blocking release of the substance prevents presynaptic nerve impulses from altering the activity of the post synaptic cell.



A



B





Recap on Neurotransmitters.

- Introduction to NT's.
- <http://www.youtube.com/watch?v=haNoq8UbSyc>
-
- Introduction to Neurones – Inhibitory / Excitatory potential.
- <http://www.youtube.com/watch?v=LT3VKAr4r00>



Excitatory Response

- Stimulation of an excitatory presynaptic neuron will produce an all or nothing ACTION POTENTIAL that spreads to the Axon Terminal.
- Excitatory Postsynaptic Potential (EPSP).
 - A potential that is caused by excitatory presynaptic impulses – more likely for the post synaptic neuron will fire an action potential.
- Combined effect of many excitatory synapses is required to elicit an action potential in a postsynaptic neuron.



Inhibitory Response

- Looks exactly like an excitatory pre synaptic neuron.
- Post synaptic quite different.
- Inhibitory Postsynaptic Potential (IPSP)
 - Less probability that the post synaptic neuron will fire an action potential



IPSP

- Result from the opening of chloride ions (Cl^-) to enter the cell.
- Chloride ions are negatively charged and high levels of chloride ions will make the post synaptic cell negative.
- Important to note that Excitatory and Inhibitory neurons get their name from their actions on postsynaptic neurons – NOT on their effects on behaviour.
 - Although both play a vital role in the neural processing of information and behaviour.



Excitatory or Inhibitory?

- What determines whether a synapse excites or inhibits the postsynaptic cell?
- The Neurotransmitter.
 - Some will generate EPSP others generate IPSP.
- The BALANCE between the number of excitatory or inhibitory signals the postsynaptic neuron receives will determine the likelihood of an action potential.



Synaptic Transmitters.

- Amines.
 - e.g. Acetylcholine.
 - Monoamines – Norepinephrine/Noradrenaline, Epinephrine/Adrenaline, Dopamine, Serotonin, melatonin.
- Amino Acids.
 - Gamma-aminobutyric acid, Glutamate, Glycine, Histamine.
- Neuropeptides.
 - - Opioid peptides – Enkephalins: Met-enkephalin, Leu-enkephalin,
 - - Endorphins: B-endorphin.
 - - Dynorphins: Dynorphin A.



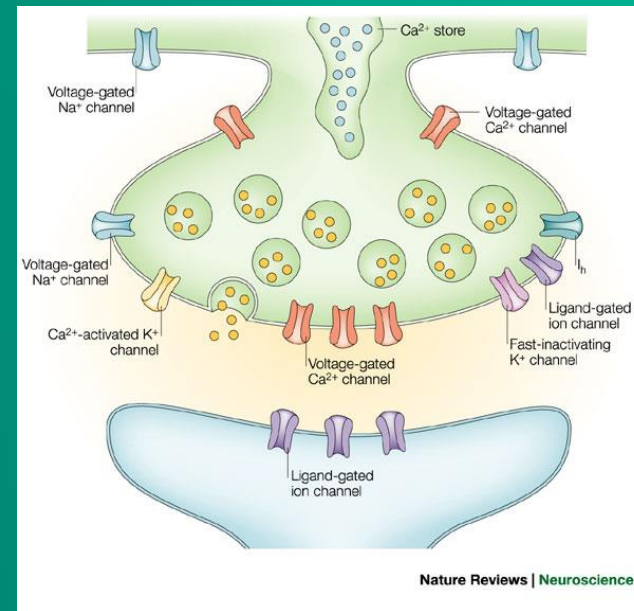
Synaptic Transmitters.

- Peptides.
 - Oxytocin, Substance P, Cholecystokinin, Vasopressin, Neuropeptide Y, Hypothalamic releasing hormones.
- Gases.
 - Nitric Oxide, Carbon Monoxide.



- Neurotransmitters affect their targets by interacting with receptors.
- Binds to the receptor changing its shape to open an ion channel (fast ionotropic receptor).
- Or
- Alters chemical reaction with the target cell (slow metabotropic receptors).

- <http://www.youtube.com/watch?v=Du-BwT0UI2M>





- Receptor subtype – Any type of receptor having functional characteristics that distinguish it from other types of receptors from the same neurotransmitter.
- **Drug development capitalises on the existence of receptor subtypes.**
 - Drugs can selectively affect a receptor subtypes
 - producing specific effects associates with that receptor.



Ligand.

- Ligand = Substance that binds to a receptor.
- Effects of a Ligand.
- 1) When bound to a receptor, a ligand classified as an agonist initiates the normal effects of the receptor.
- 2) Antagonist – ligand which binds to a receptor and does not activate it – blocks other ligands.
- 3) Inverse Agonist – Initiates an effect that is reverse of the normal function of the receptor.

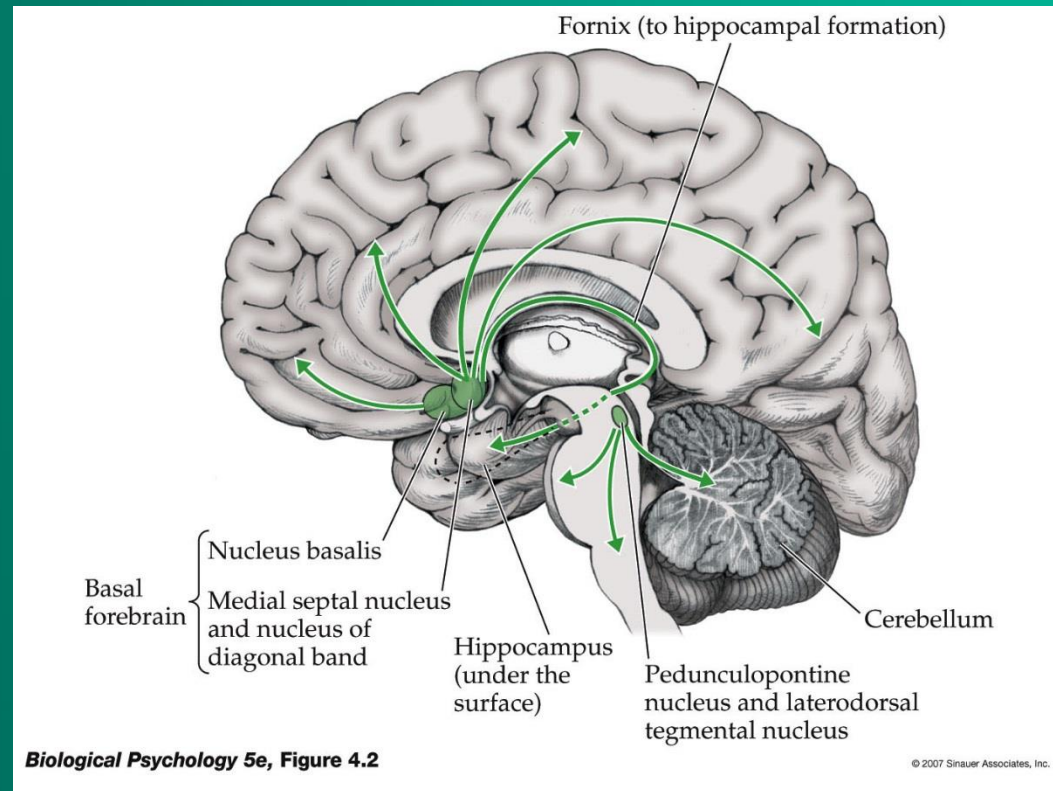


Endogenous Ligands.

- Acetylcholine (ACh).
- First chemical identified as a Neurotransmitter.
 - Stimulates Muscle Contraction.
- Basal forebrain includes major groups of cholinergic (ACH-containing) cells.
- Losses – evident in Alzheimer's disease.
 - Cholinergic hypothesis

Cholinergic Pathways in the Brain.

<http://www.youtube.com/watch?v=0-KmO0Lg7Kw>





Acetylcholine and Memory...

- Francis et al 1999 Review highlighted the cholinergic hypothesis in relation to Alzheimer's disease (AD).
- Studies revealed deficits in the enzyme responsible to ACh synthesis.
- Cholinergic hypothesis – degeneration of cholinergic neurons in the basal forebrain and subsequent loss of cholinergic neurotransmission in cerebral cortex contributes significantly to the deterioration of cognitive functioning seen in AD patients.



Neuroscientific studies on Ach and Memory

- Goekoop et al 2005.
- 28 patients with mild cognitive impairment (MCI) – Memory losses.
 - Often a precursor to Alzheimer's disease.
- Required to do a series of memory tasks at 3 stages.
 - Working Memory tasks and facial encoding and retrieval tasks.
- Under fMRI conditions.



Goekoop et al 2005....

- Stage 1 – Baseline.
- Stage 2 – One week later, after a single dose of Galantamine.
- Stage 3 – A further week later after multiple doses of Galantamine.
- Galantamine = Drug used in MCI patients to improve memory – which prevents the REUPTAKE of ACh.



Goekoop et al 2005

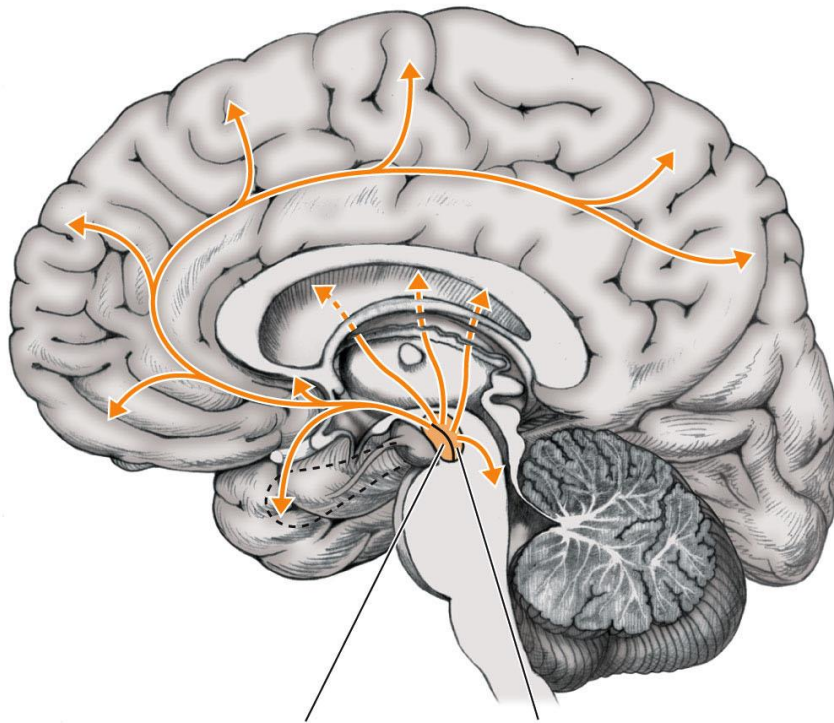
- Findings.....
- Significant improvements in memory scores between stage 1 and stage 3.
- Significant alterations in FMRI, more activation in Cholergerenic pathways.
- Critique of this study?



Monoamines.

- Catecholamines
 - E.G. Dopamine
- Indoleamines.
 - E.g. Melatonin and Serotonin.
- Catecholamines.
 - Dopamine
 - Mesostriatal Pathway and Mesolimbocortical Pathway.
 - Mesostriatal Pathway – Motor Control.
 - Mesolimbocortical pathway – Reward and Reinforcement (Nader et al, 1997); Verbal Learning (Fried et al, 2001); Schizophrenia.

Dopaminergic Pathways in the Brain.



Mesolimbocortical pathway:
ventral tegmental area to nucleus
accumbens, cortex, and hippocampus

Mesostriatal pathway:
substantia nigra to striatum
(caudate and putamen)

Biological Psychology 5e, Figure 4.3

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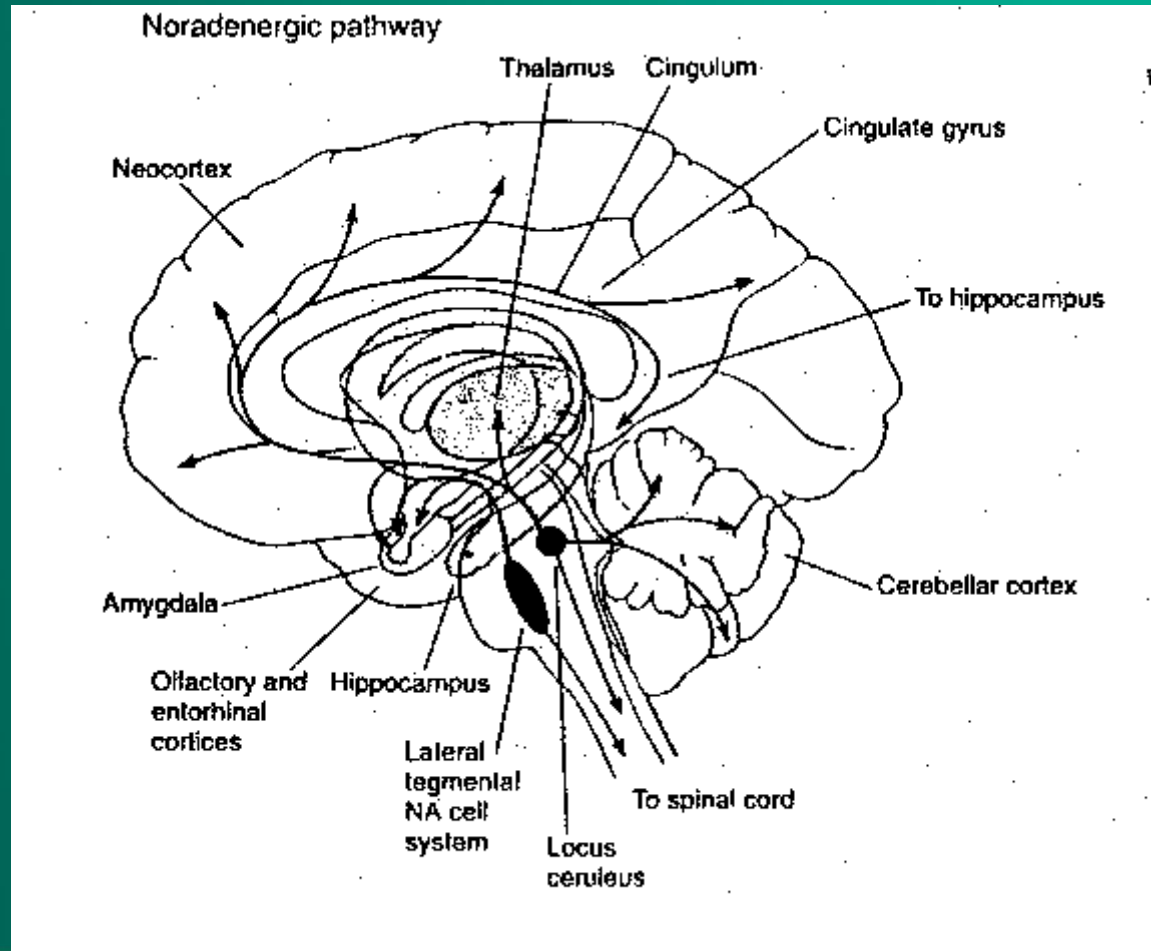
Dopamine and Reward related memory.

- Wittman et al 2005.
- FMRI study.
 - Compared encoding and retrieval of reward related (financial) stimuli compared to non-reward related stimuli.
- Greater activation during encoding stage in reward related areas for reward stimuli.
- In follow up, greater success and greater activation in hippocampus (long term memory) for reward related stimuli compared to non-reward related stimuli.



- Norepinephrine/Noradrenaline.
 - Organised into 3 clusters in the Brain Stem.
 - Locus Coeruleus in the Pons.
 - Lateral Tegmental System (midbrain).
 - Dorsal Medullary Group.
- Many behavioural and Physiological Processes.
 - Mood, Overall Arousal and Sexual Behaviour.

Noradrenic Pathways in the Brain.





Differences between Adrenaline and Noradrenaline.

- **Chemically** distinct - adrenaline is produced by the body via a modification of noradrenaline.
- Secondly, they are used in **slightly different places**. Noradrenaline = postganglionic neurones of the sympathetic nervous system. Adrenaline = adrenal medulla.
- Role of Adrenaline as a NT less known.
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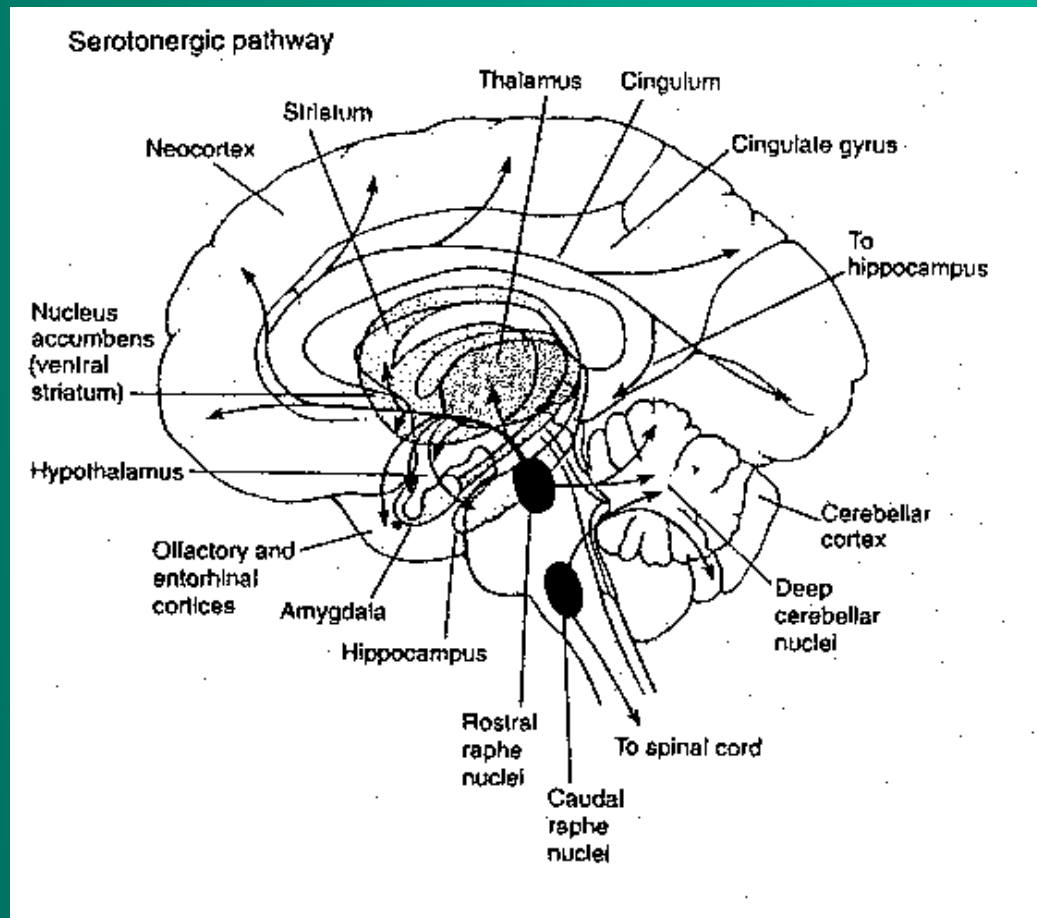
- Serotonin (5HT).
- 5HT Cell bodies concentrated in the Raphe Nuclei.
- Only 200,000 human neurons are Serotonergic – but influence is widespread.
- Sleep States, Mood, Sexual Behaviour, Anxiety.



Serotonin.

- Serotonin and Depression a Debate.
- <http://www.youtube.com/watch?v=sWE3UGl7Kfk>
-
- Serotonin Deficiency Neuroscience.
-
- https://www.youtube.com/watch?v=bX0_AB9Sqt8

Serotonergic Pathways in the Brain.





Morris Miller et al 2013.

- FMRI study to examine the effect of SSRI's on emotional word processing on patients with Major Depressive Disorder.
 - SSRI = Selective Serotonin Re-uptake inhibitors.
 - Escitalopram
- 17 un-medicated MDD patients were presented 60 words (20 positive, 20 negative, 20 neutral) and were asked to identify 10 words that....
 - Represented them when down / depressed
 - Represented them when happy
 - 10 personally relevant neutral words when neither happy or down.
 - Under FMRI conditions.



- Required to repeat the task following 8 weeks of standardised Escitalopram treatment.
- Findings –
- Lower midbrain, dorsolateral prefrontal cortex, para cingulate, anterior cingulate, thalamus and caudate nuclei correlated significantly with greater improvement following escitalopram treatment.
- More positive responses in 2nd condition – quicker time to answer the 10 positive emotions.



Amino Acids.

- Glutamate and Aspartate = Excitatory Neurotransmitters.
- Glutamatergic Transmission involved in learning and memory.
- Glutamate associated with Excitotoxicity – Exacerbates the effects of stroke.
 - <http://www.youtube.com/watch?v=tvnjeMiHSL8>



- Gamma-aminobutyric acid (GABA) and Glycine = Inhibitory transmitters.

GABA receptors are in classes:

- GABA_A - ionotropic, producing fast, inhibitory effects
- GABA_B - metabotropic, slow inhibitory effects through *neurogliaform* interneurons
- GABA_C - ionotropic with a chloride channel

GABA agonists, like Valium, are potent tranquilizers.



Peptides.

- Peptides have a prominent role as neurotransmitters.
- 1) Opioid Peptide – Mimic opiate drugs such as Morphine – include dynorphin.
- 2) Those found in Spinal Cord = e.g. Substance P.



Gases.

- Neurons use gas molecules that dissolve in water to communicate information.
- Nitric Oxide (NO).
- Produced in other areas of the Neurons – e.g. Dendrites.
- Doesn't interact with membrane bound receptors – diffuses into target cell.
- Retrograde Transmitter – diffuses post synaptic neuron back to the presynaptic neuron.



Drugs, The brain and Behaviour.

Stuart Jones.



- The use of the term drug used in different ways in Everyday English.
- A medicine to treat diseases
- A psychoactive agent.
- Some evolved from plants.
- Others a human made.



Definition of a Drug

- an exogenous chemical not necessary for normal cellular function that significantly alters the function of certain cells when taken in fairly low doses and has clear effects on experience, mood, emotion, activity and/or health.
 - Breedlove et al, 2010.



How are drugs effective.

- Some drugs interact with lipid molecules that make up the membrane.
- Others can directly alter the activity of particular enzymes.
- Ligands – that interact with specific receptors.



- A drug can be targeted to interact with one or a few receptor subtypes.
- E.g. Serotonin vs Anti Depressants.
- Serotonin – All serotonin receptors.
- Anti depressants – specific 5-HT receptors.
 - E.g. 5-HT₃
 - Produces a powerful and specific effect.



Lock and Key.

- Drug molecules do not seek out particular receptor molecules
- Spread widely throughout the body and when they come in contact with SPECIFIC receptor molecules – the two bind together.
- Lock and Key
 - Once key binds to the lock it alters activity
 - Activation or blocking it.
 - When it breaks away – receptor resumes its unbound shape.



Drug-Receptor Interactions.

- The tuning of drug molecules to receptors is not absolutely specific.
- Bind strongly to one kind of receptor, more weakly to other types etc.
- E.g. Side effects of Prescribed drugs.



Drug – Receptor Interactions.

- Binding Affinity.
 - The Degree of chemical attraction between a ligand and a receptor.
 - High Affinity = Binding even at low doses – will stay bound for a long time.
- Efficacy (or intrinsic activity).
 - The extent to which a drug activates a response when it binds to a receptor.
 - Agonists = high efficacy, Antagonists = low efficacy.



Dose – Response Relationship.

- Important aspect for the safe administration of drugs.
- Administering larger doses – increases the proportion of receptors that are bound and affected by the drug.
- Dose-Response Curve (DRC).



Repeated Treatment.

- Our bodies are very adaptable – and its evident when viewing research on drug tolerance.
- Metabolic Tolerance (e.g. Liver).
- Functioning Tolerance – Decreased responding to a drug after repeated exposure.
- Cross Tolerance – Tolerance for administered drug causes to develop tolerance for another drug.



Drugs and Behaviour.

- Antipsychotic drugs
 - Neuroleptics – Schizophrenia.
 - Act as selective antagonists of Dopamine D₂ receptors.
 - Atypical neuroleptics.
 - (e.g. Clozapine) – Not involved with Dopamine.
 - Blockade of certain Serotonin.





Drugs and Behaviour.

- Antidepressants.
- 5.8% of Men and 9.5% of women will experience an episode of depression (WHO, 2001).
 - Monoamine oxidase inhibitors (MAOI)– blocks breakdown of monoamine NT's at synapses - resulting in accumulation of monoamine transmitters in synapses.
 - Tricyclics – named after 3 ringed molecular structure.
 - Increasing synaptic content of Nor-epinephrine and Serotonin.
 - SSRI – Selective Serotonin Re-uptake inhibitors.
 - Blocks the re-uptake of serotonin.



Antidepressants



Tricyclic ↑

SSRI →



MOAI



SSRI

Anxiolytics.

- Also known as Tranquilizers.
- Depressants – Reduce Neural Activity.
- Benzodiazepine agonist.
 - Valium – GABA_A receptors – enhance the activity of GABA (Walters et al, 2000).
- Buspirone (Buspar).
 - Serotonin (5HT_{1A}) Agonist.
 - Also Dopamine D₂ Agonist (low affinity).





Alcohol.

- Mixed findings with regards to the effect of alcohol on health.
 - Davies et al (2002); Leroi et al, 2002; Mukamal et al, 2003.
- Excessive – linked to more than 60 disease processes.



Alcohol.

- Biphasic psychoactive effect.
 - Stimulant Phase followed by a Prolonged Depressant Phase.
- GABA_A plays an important part in mediating the role between Alcohol and the Brain.
 - Increases post-synaptic inhibition
 - Allow more Cl⁻ ions to enter Neurons.
 - Social disinhibition.
 - Impairment of Motor Co-ordination.
 - Hancher et al (2005).



Alcohol.

- Low doses of Alcohol stimulate Dopamine Pathways = increasing Dopamine – feelings of euphoria.
- Chronic abuse – damages Nerves Cells.
 - Superior Frontal Cortex, Cerebellum, Hippocampus.



Drinking during Pregnancy.

- Main cause of foetal alcohol syndrome.
 - Facial abnormalities
 - Mental impairment.
 - Stunted growth.
- Low level of drinking linked to.
 - Below average birth weight.
 - Spontaneous abortion.
- What (if any) constitutes a safe level of drinking.
 - Are risks restricted to certain period of foetal development
 - Current medical opinion – not to drink at all.

Brain Recovery.

- Kril et al (1997) – Chronic Alcohol Abuse and damage to the frontal lobe.
- These effects can be reversible with abstinence.
 - Dlugos and Pentney, (1997)
 - Study on Rats.
- MRI in humans – Pfeferbaum et al, 1995



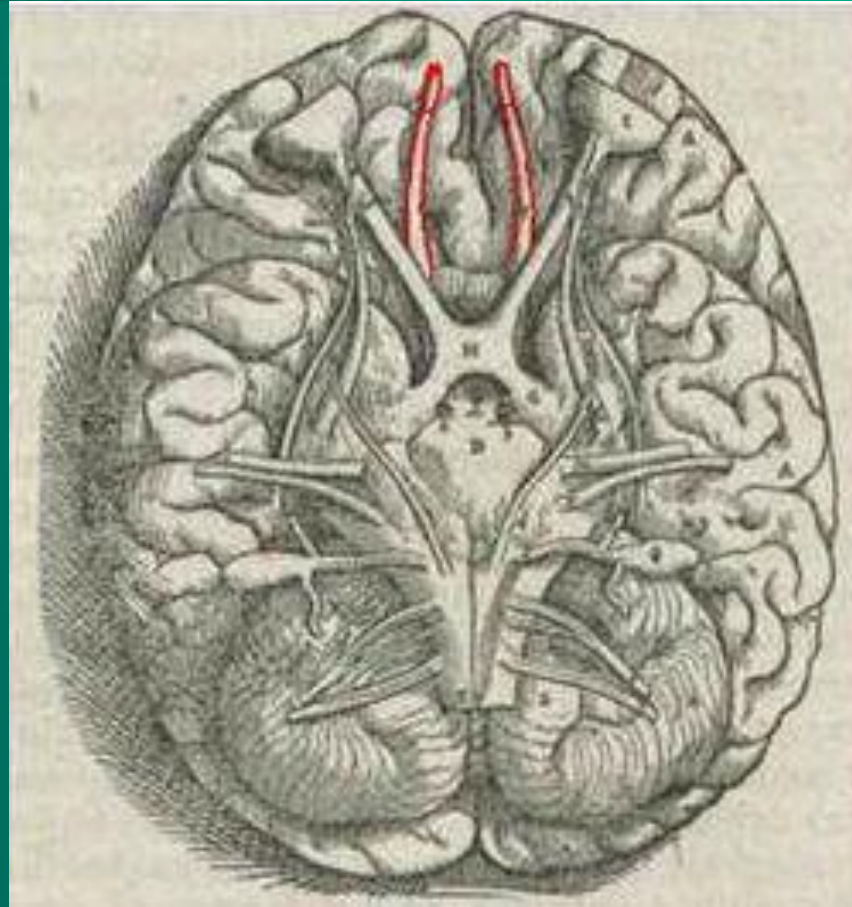


Binge Drinking.

- In addition to other health matters – Binge Drinking may cause damage to the Brain.
- Obernier et al (2002) – Study of Rats.
 - 4 Days – Neural Degeneration in Several Areas.
 - Olfactory Bulbs and Limbic Structures.
 - Neurogenesis – formation of new Neurons in Hippocampus (Nixon and Crewes, 2002).



Olfactory Bulb





Alcohol and Driving.....

- Meda et al (2009).
- 37 participants performed a driving simulator under three randomised (to reduce practice effects) blind conditions.
 - High blood alcohol conditions.
 - Low blood alcohol conditions.
 - Placebo.
- Findings.....
- FMRI – Dose related decrements in a number of regions.
 - Superior, middle and orbito frontal gyri, anterior cingulate, primary/supplementary motor areas, basal ganglia, and cerebellum
 - Performance decrements in high blood alcohol condition.
 - Particularly opposite white line crossing (going into the other lane!).



Opiates.

- Opium – extracted from poppy seedpods.
- Morphine – Analgesic (Painkiller).
 - Very addictive – Heroin is an artificial modified form of Morphine
- Bind to Opioid Receptors – found in limbic and hypothalamic areas of the Brain.





Opiates.

- Endogenous opioids.
 - Body's own Pain Killer / Sleep inducer.
- Enkephalins
- Endorphins.
- Dynorphins.



Cannabinoids.

- Marijuana – obtained from the Cannabis Sativa Plant.
 - Most widely used of all illicit drugs.
- Subjective experience
 - Relaxation, Mood Alteration, Stimulation, Hallucination and Paranoia.
- Sustained Use.
 - Addiction (Maldonado and Rodriguez De Fonseca, 2002).
 - Respiratory Diseases.
 - Psychiatric Disturbances (Henquet et al, 2005).





Cannabinoids.

- Brain contains orphan cannabinoid receptors.
 - Anandamide is the endogenous NT that binds to cannabinoid receptors.
 - Concentrated in the Substantia Nigra, Hippocampus and Cerebellar Cortex and Cerebral Cortex (Devane et al, 1988).
 - Relieving pain, lowering blood pressure, helping in glaucoma.



Neuroscience and Marijuana – Smith et al, 2010

- Ten marijuana users 14 non-using controls performed a visuospatial 2-back task.
- Performance in visuospatial 2-back task was similar in both groups.
- However,
 - fMRI revealed greater activation in the inferior and middle frontal gyri in the Marijuana group.
 - Associated with visuospatial memory.
 - Also right superior temporal gyrus.
 - Not associated with visuospatial memory.
 - Conclusion – “Marijuana use leads to altered neural functioning during visuospatial working memory.... This alteration appears to be compensated for by the recruitment of blood flow in additional brain regions”.
 - Critique – Cause and effect, was the increase in blood flow in additional regions as a consequence of the task? Could it be replicated in real life.



- Stimulants....
- Increase the activity of the nervous system by activating excitatory influences.
- Some increase excitatory synaptic potentials, other block inhibitory processes.
- Examples of Stimulants include: Nicotine, Caffeine, Amphetamine, Cocaine.





Nicotine.

- Nicotine from Cigarettes enters the blood and brain far more rapidly than Chewing Tobacco or smoking a pipe or cigars.
- Largely unhealthy neural consequences.
 - Although can enhance aspects of cognitive performance
 - Gazzaniga et al 2009.
- Activates Nicotonic receptors (Ach receptors).
 - Ventral tegmental area.
 - Dopamine (Kenny et al, 2006).



Cocaine

- Coca Shrub (South America).
 - Chewed, Brewed as a Tea.
 - Increase Endurance, alleviate hunger, increase well-being.
- Artificially purified extract (Cocaine) – is powerfully addictive harmed millions of lives.



- Cocaine blocks monoamine transporters – especially dopamine
 - Prevents reuptake
 - Attracts more dopamine
- Neurotoxic effects – Overdose can produce Strokes.... Haemorrhage in the Brain.
- High sensitisation – Easy to have chronic use and could cause psychosis.
- Very uncomfortable withdrawal symptoms.
- <http://www.youtube.com/watch?v=4OS2C4NemJI&feature=related>



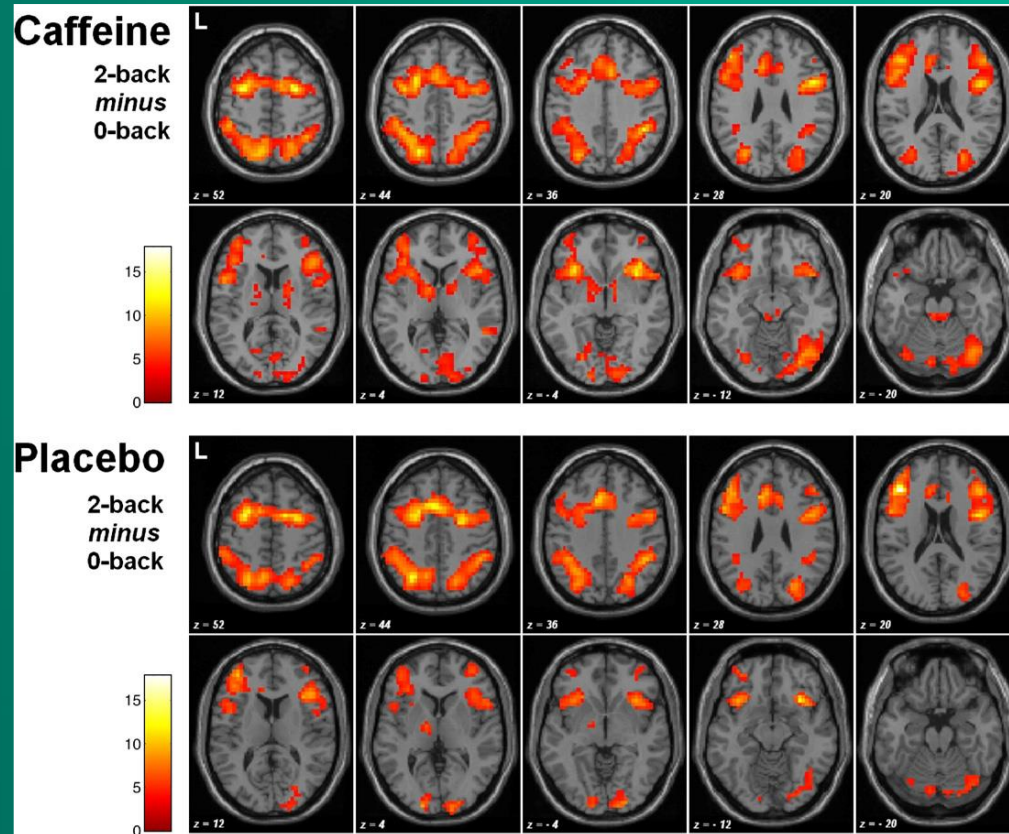
Caffeine – Koppelstaetter et al 2008

- Does Caffeine modulate the working memory performance?
- 15 Participants (moderate caffeine users) performed 2 working memory tasks under fMRI conditions 24 – 48 hours apart.
 - Given 100 mg of Caffeine 20 minutes prior to the testing.
- Another 15 participants (moderate caffeine users) required to perform the same task, under same conditions – but were given a placebo.
 - A blind study, so neither group knew which condition they were in.



Findings....

Important to
note... No
significant
difference in
actual
performance
between two
groups.





Amphetamine

- Synthetic psychostimulant – structure closely resembles that of Catecholamine transmitters (Noradrenaline, adrenaline and *dopamine*).
- Enhance the activity – Variety of Behavioural Effects.
 - Heightened Alertness, Euphoria, Sustained effort without rest, confidence, motivation (but not ability).



Amphetamine.

- Highly Tolerant – so people have to take larger doses to get the effect.
 - Sleeplessness, weight loss, Paranoia, agitation.
 - High Blood pressure, dizziness, sweating etc.



Hallucinogenic and Dissociative Drugs.

- Term is a misnomer – hallucination takes place in the absence of sensory stimulation (e.g. hearing voices that are not there).
- Drugs in this category – alter or distort existing perceptions.



LSD.

- Molecular structure resembles Serotonin.
 - 5HT_{2A} receptor agonists.
- Soon found to active serotonin receptors in the visual cortex.
- Flashbacks?



Ecstasy

- MDMA (3,4-Methylenedioxymethamphetamine)
- Increase in the release of Serotonin, Stimulation of $5HT_{2A}$ receptors, changes in dopamine, and certain hormones (e.g. Prolactin).
 - Positive Emotions, Empathy, Euphoria, Sense of Well being, Colourful visual phenomena.



Ecstasy

- Monks et al (2004) – Chronic Use – effects on serotonin-producing neurons – reduction in serotonin capabilities.
- Psychiatric and Cognitive effects (Wareing et al, 2000; Sumnall and Cole, 2005).



Some useful web links.

- <http://www.nida.nih.gov/ResearchReports/Cocaine/Cocaine.html>
- <http://www.niaaa.nih.gov/Pages/default.aspx>
- <http://www.nida.nih.gov/ResearchReports/Steroids/AnabolicSteroids.html>
- <http://www.drugabuse.gov/infofacts/ecstasy.html>
- <http://www.nida.nih.gov/ResearchReports/Heroin/Heroin.html>



Useful Web links

- <http://www.nida.nih.gov/ResearchReports/Inhalants/Inhalants.html>
- <http://www.drugabuse.gov/infofacts/marijuana.html>
- <http://www.nida.nih.gov/ResearchReports/methamph/methamph.html>
- <http://www.nida.nih.gov/researchreports/nicotine/nicotine.html>
- <http://www.breggin.com/>



Useful Web links

- <http://www.spineuniverse.com/conditions/back-pain/low-back-pain/anti-depressant-medication-used-treat-low-back-pai>
- <http://www.anesthesiapatientsafety.com/patients/about/default.asp>
- <http://www.rci.rutgers.edu/~lwh/drugs/>