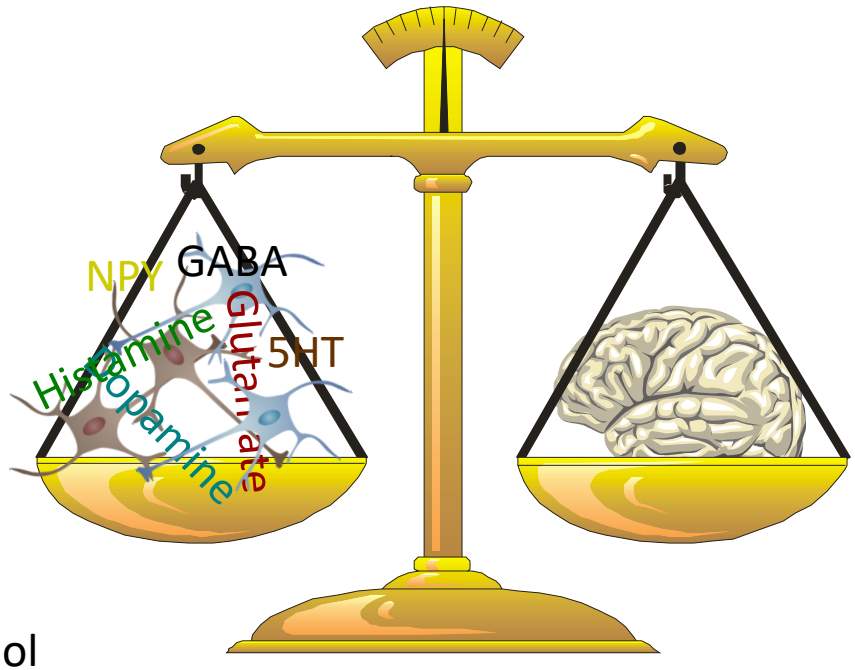
Neuroscience and Mental Health

Processing thought processing



Dawn Collins
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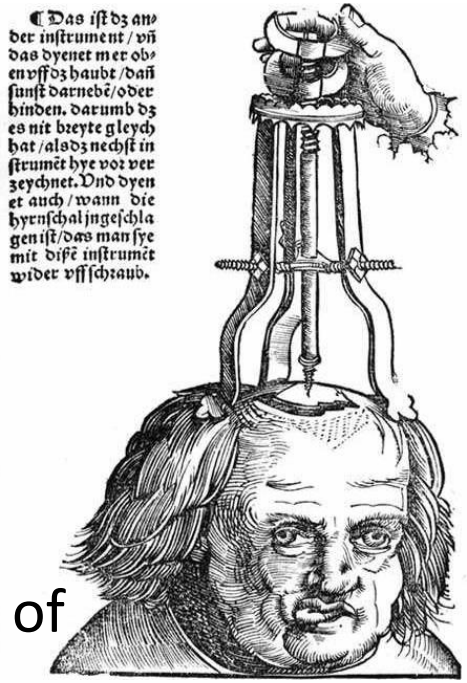
Dysfunction of the nervous system

- Occurs for a number of reasons:
  - Damage by trauma or disease*
  - Neurons lose ability to produce transmitters
  - Neurons over- or under-produce transmitters
  - Neurons fail to recognise transmitters
  - Effector organs fails to respond



- Can manifest as:
  - **Loss**: of sensation or function
  - **Gain**: appearance of new feature
  - **Change**: alteration in behaviour/personality of perception

*If the cell body is intact, regeneration of neurons may occur.

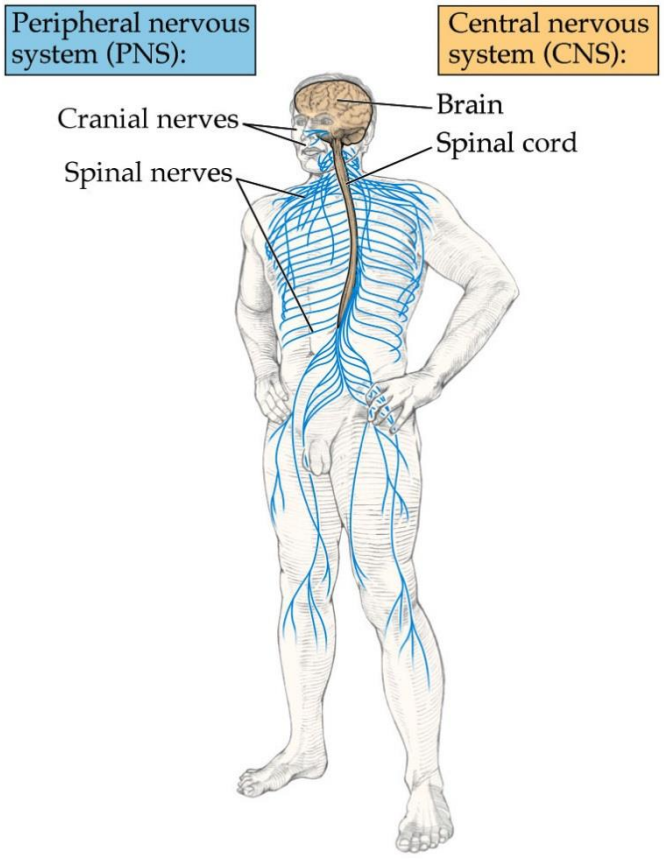
The Central Nervous System

Brain

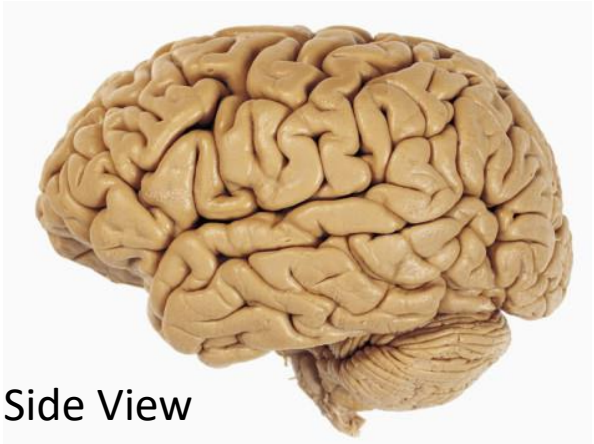
Cerebrum
- Cerebral hemispheres
- Basal ganglia, Cerebellum
- Thalamus, Hypothalamic regions

Brainstem
- Midbrain
- Pons
- Medulla

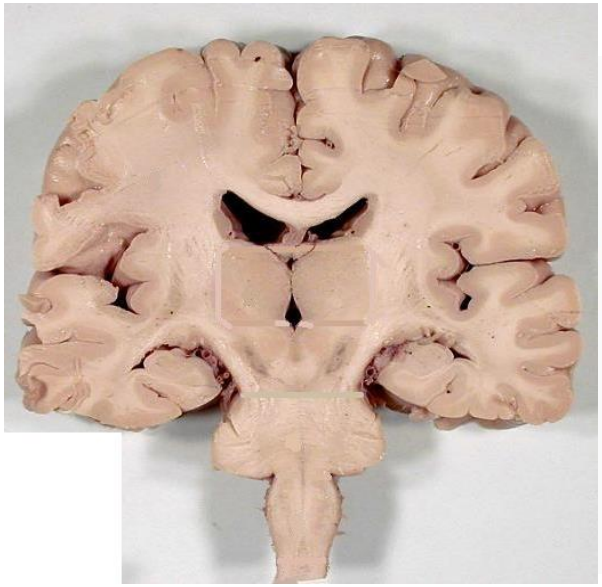
Spinal Cord



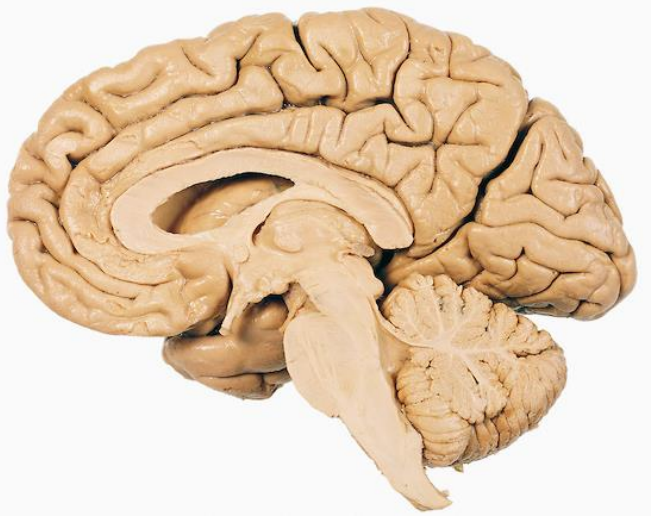
The Brain



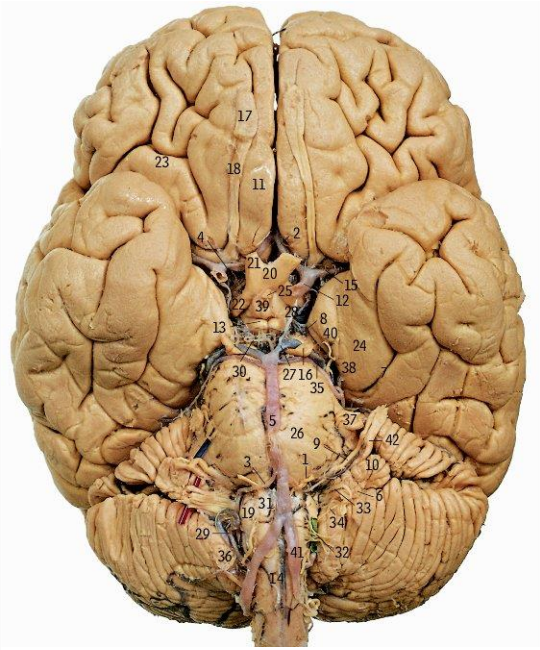
Side View



Coronal section



Sagittal section

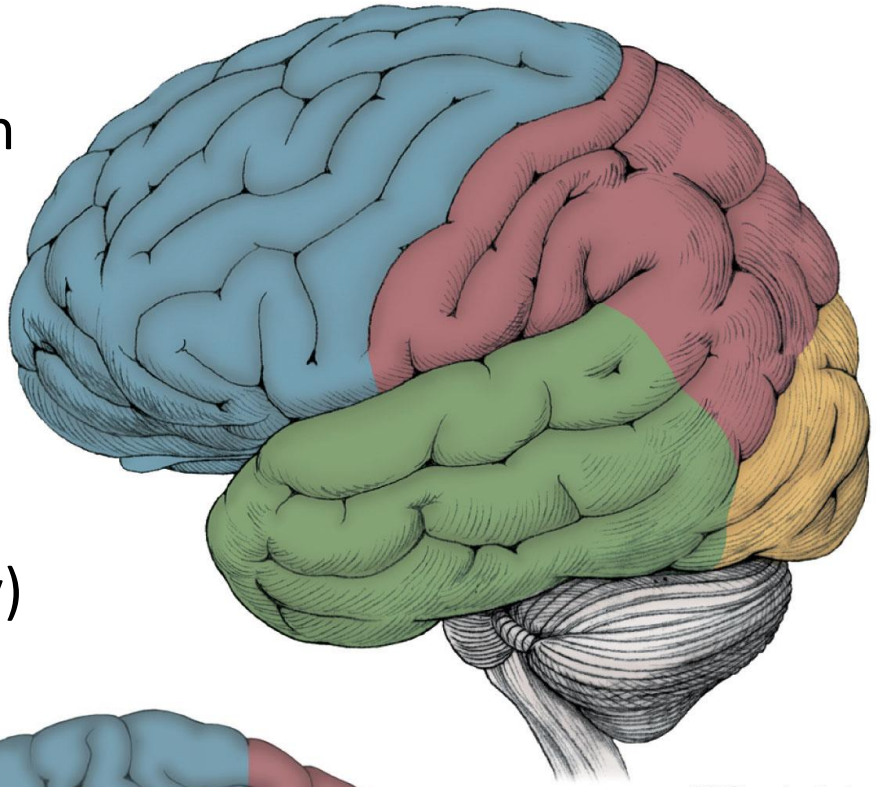


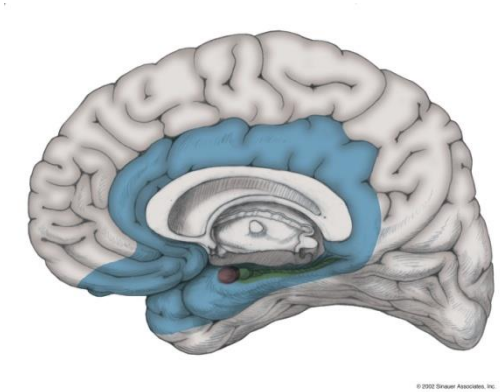
View of base of brain

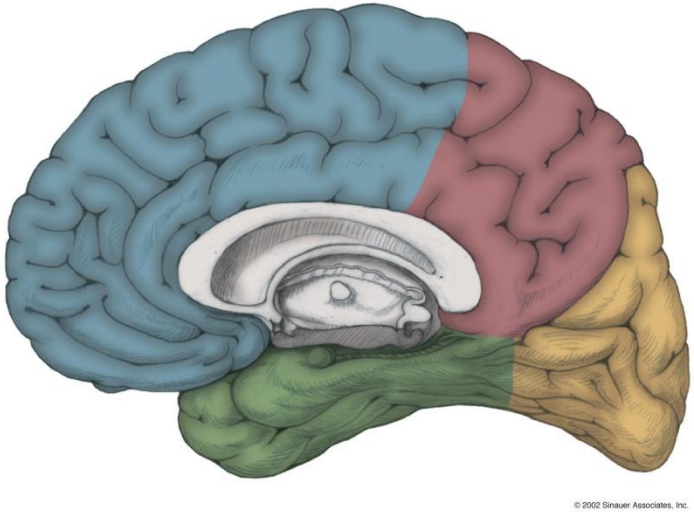
The Cerebral Lobes

- Frontal – Motor, higher cognition
- Parietal – Sensory
- Occipital – Vision
- Temporal – Language
- Insula – Emotional control

(Limbic system – Learning/Memory)



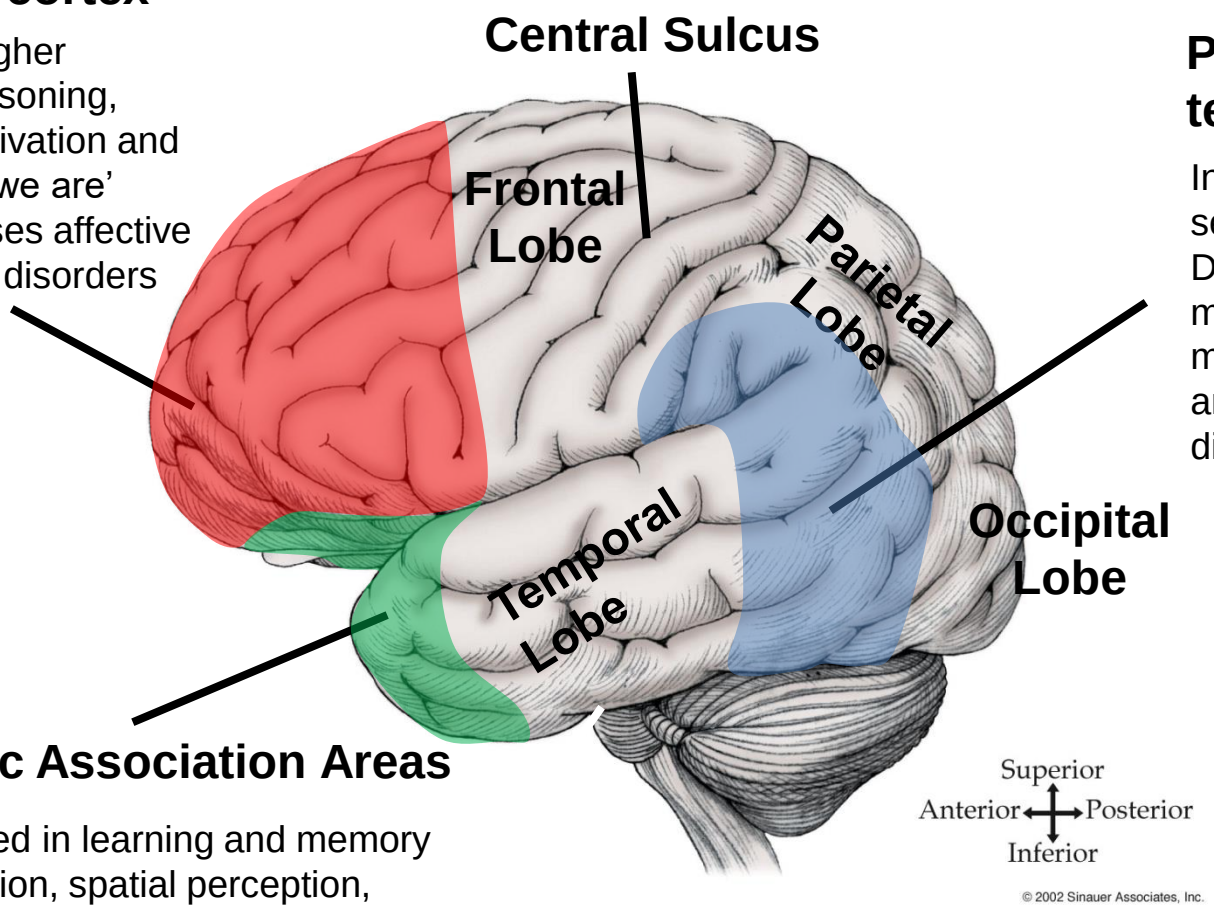




The Cortical Association Areas

Prefrontal cortex

Involved in higher cognition, reasoning, rationale, motivation and moods; 'who we are'
Damage causes affective and cognitive disorders



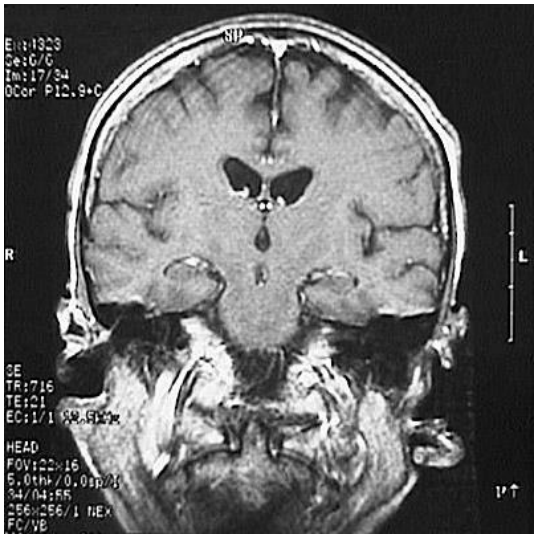
Parieto-occipito-temporal cortex

Interacts with primary sensory and motor areas
Damage causes the majority of sensory, motor, proprioceptive and dissociation disorders

Limbic Association Areas

Involved in learning and memory formation, spatial perception, motivation and emotional processing
Damage causes affective and cognitive disorders

3D Images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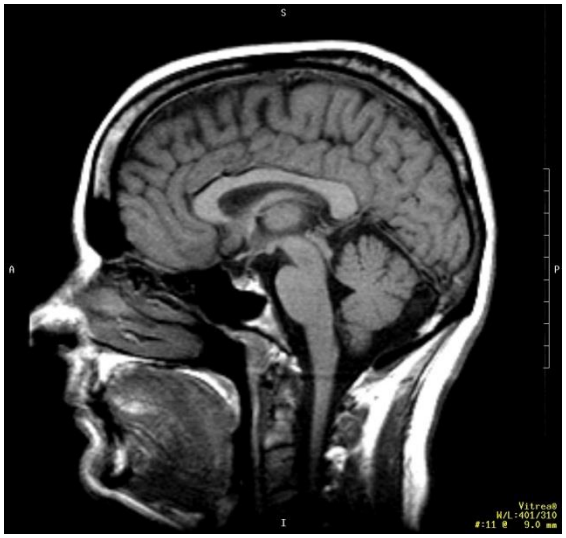
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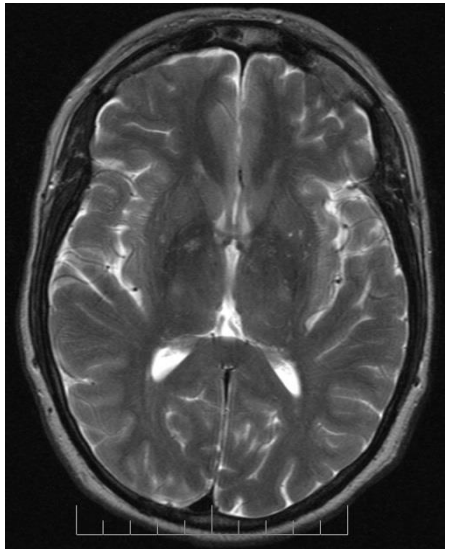
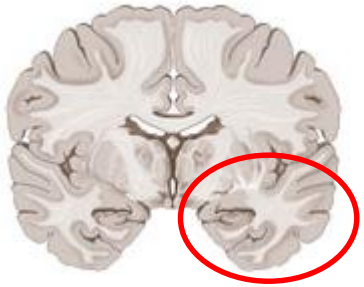
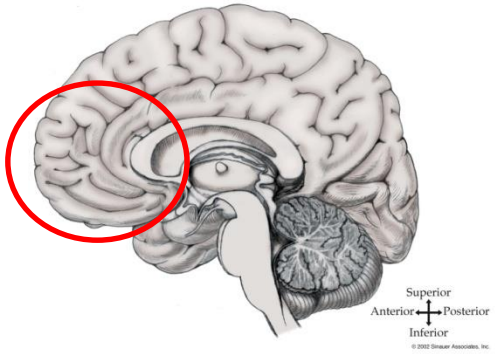
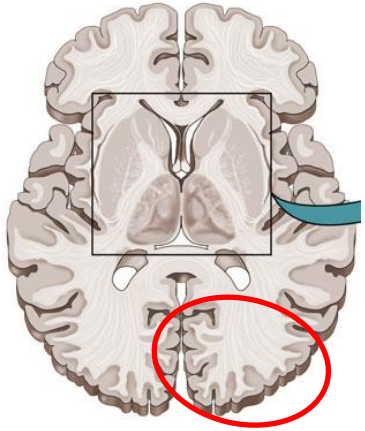




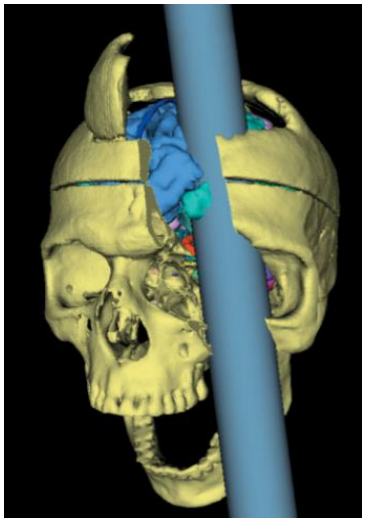

Superior
Anterior
Posterior
Inferior



Prefrontal cortex and ‘higher cognition’

Pre-frontal cortex refers to any region of the frontal lobe preceding the motor areas

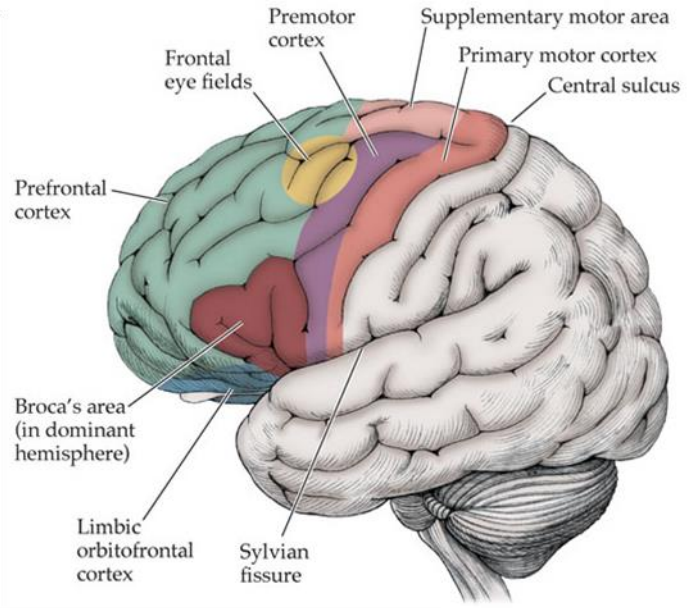
- Main roles: integration and decision making
- Responsible for personality
- Famous case: Phineas Gage

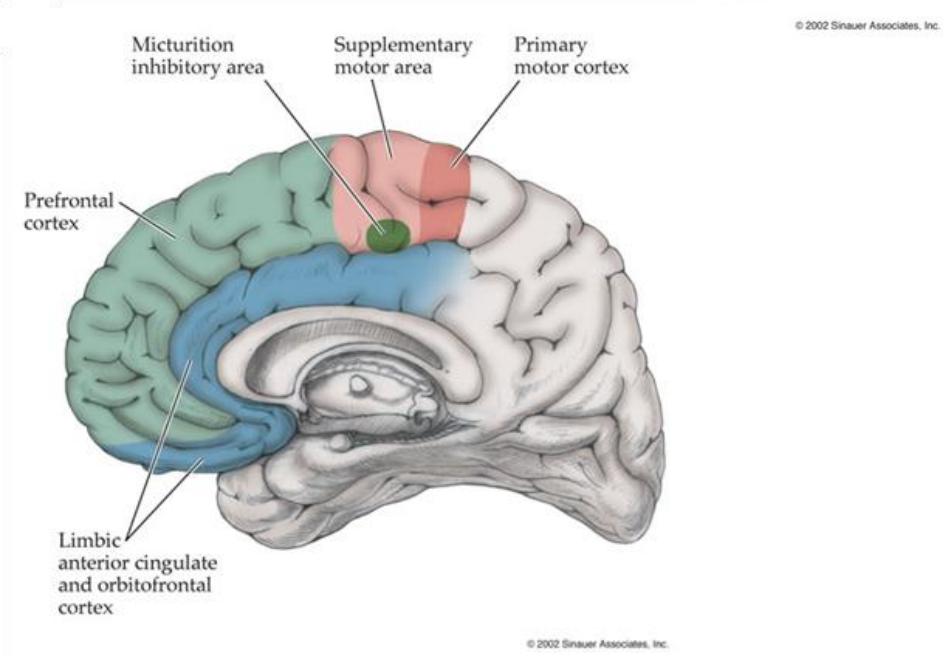


Ratiu & Talos NEJM http://www.nejm.org/doi/full/10.1056/NEJMicm031024

Prefrontal Cortex

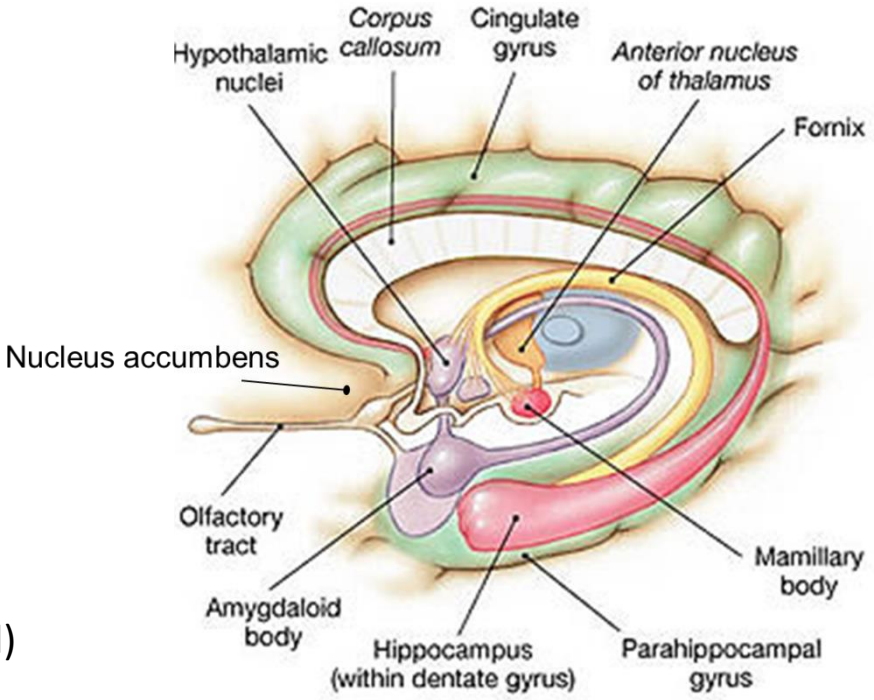
- 'Higher control,' involved in:
  - Restraint behaviours
    - Concentration
    - Judgement
    - Foresight
    - Focus
  - Initiating behaviours
    - Motivation/Drive
    - Spontaneity
    - Personality
    - Curiosity
  - Ordering behaviour
    - Planning/Sequencing
    - Working memory
    - Abstract thought
    - Perspective





Limbic system

- Group of deep cortical and subcortical structure, includes:
  - Hippocampus
  - Amygdala
  - Nucleus accumbens
  - Cingulate gyrus
  - Mammilary body
  - Thalamic and hypothalamic nuclei
  - Entorhinal and perirhinal cortices

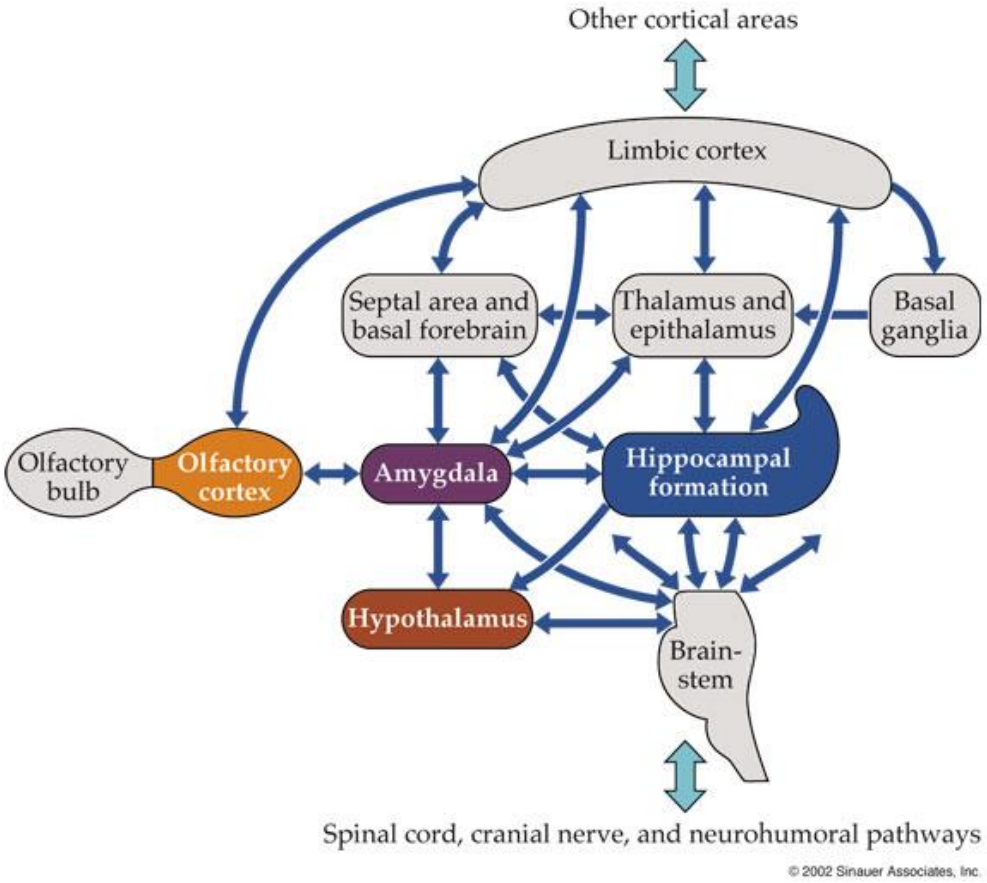


- Involved in:
  - Memory
  - Learning
  - Perception (sensory, emotional and spatial)
  - Motivation

- Links to Insula, the hidden lobe, moderates emotional responses and links limbic to homeostatic regions, also contains taste centre

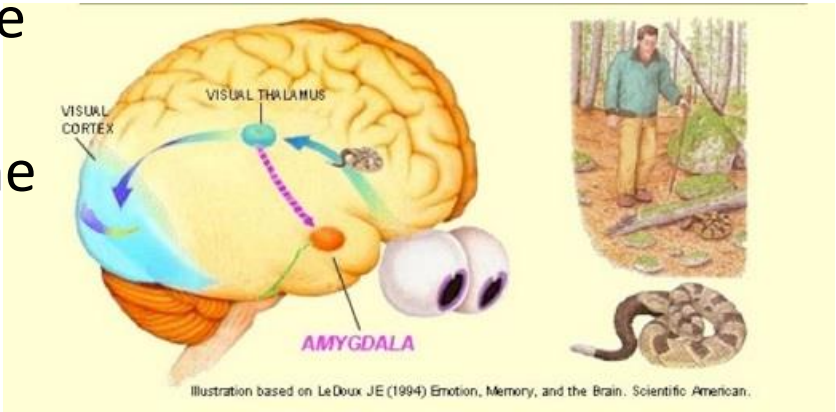
Circuitry within the limbic system

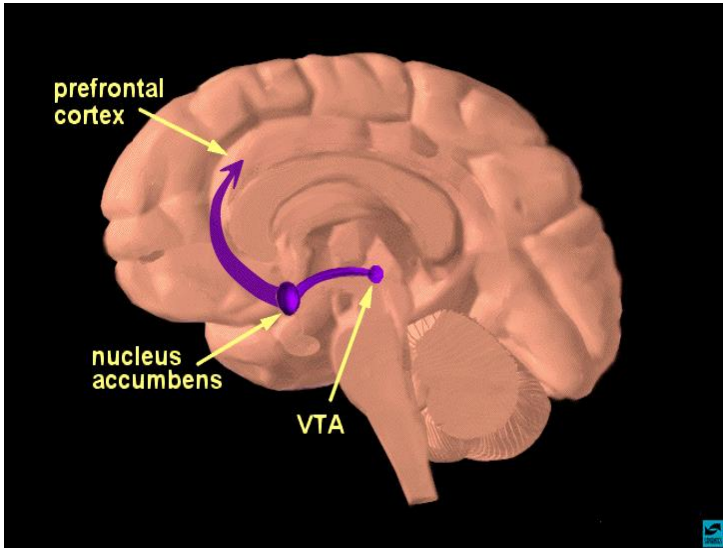
- Interplay within limbic system, and cortex aids integration relevant to:
  - Arousal
  - Learning
  - Memory
  - Emotions
  - Higher cognition



Reward and Fear

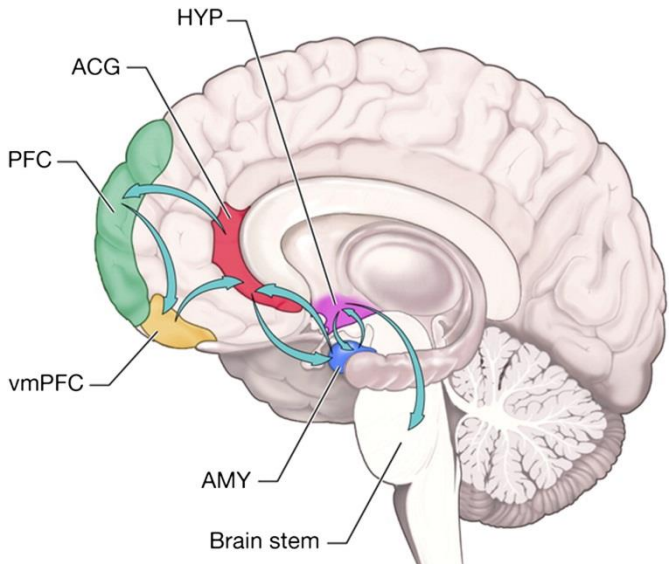
- Regions of the limbic system are implicated in positive and negative emotions
- Nucleus accumbens is linked to the reward pathways
- Amygdala linked to negative emotions
- The uncinate fasciculus links amygdala to PFC
- The insula sets the threshold of response
- Hippocampus put everything into context and remembers it



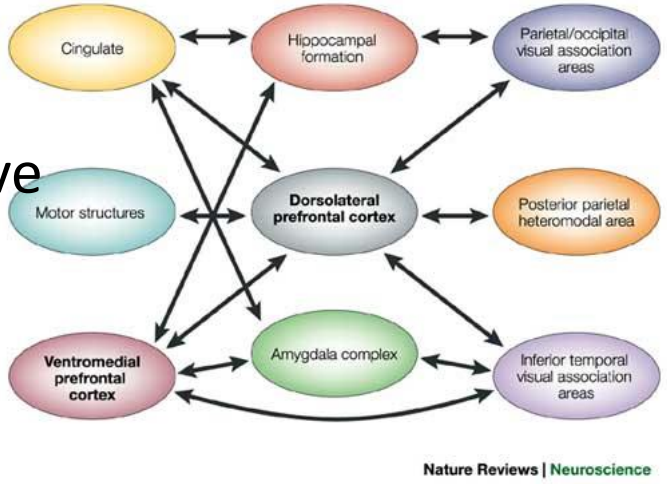


Regional Interactions

- Large tracts between and within frontal lobes and limbic system allow for intricate ‘high level’ processing
- Also link sensory, motor and basic biophysical information
- Insula sets emotional thresholds
- Changes in tract activity detected in psychotic episodes and major depressive disorders and bipolar disorders



Social-emotional processing.
Tost & Lindenberg, PNAS, 2010, 107, 17071-2.

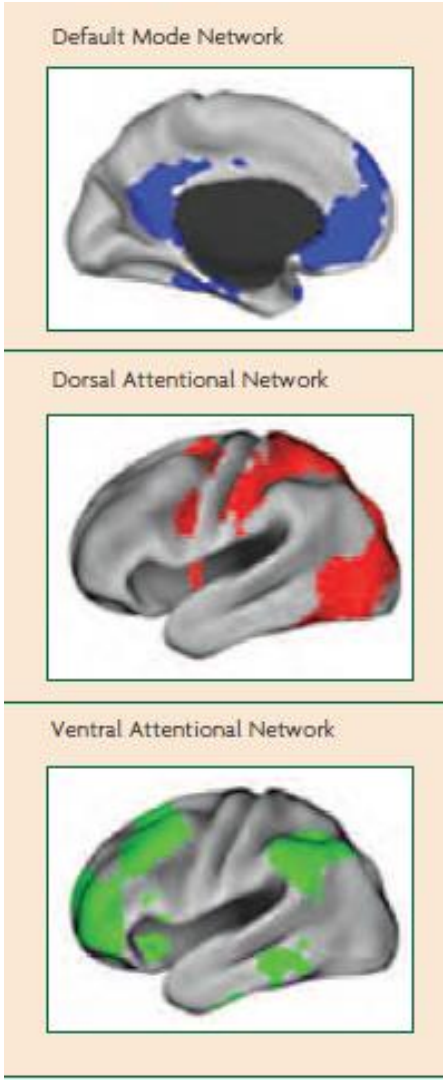


Cerebral activity and attention

Large scale networks involved in control of attention and arousal

3 main attentional Circuits:

- Default mode network (non-specific, self-reference)
  - Medial temporal cortex
  - Medial prefrontal cortex
  - Posterior cingulate gyrus
- Dorsal attentional network (orienting and processing)
  - Dorsolateral prefrontal cortex
  - Posterior parietal cortex
  - Corpus striatum
- Ventral attentional network (engagement and activation)
  - Basolateral amygdala
  - Lateral and inferior frontal cortex
  - Temporoparietal cortex
  - Ventral striatum



Shine JM, Lewis SJG (2013) ACNR 13:13-15

So why is neuroscience important?

We need to understand how the brain *functions* physiologically at a number of levels

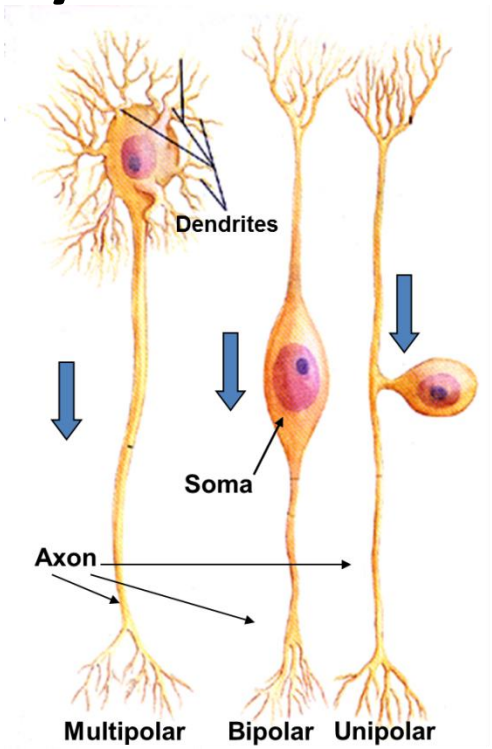
- Cellular/subcellular
- Communication
- Coordination
- Patterns
- Behaviour

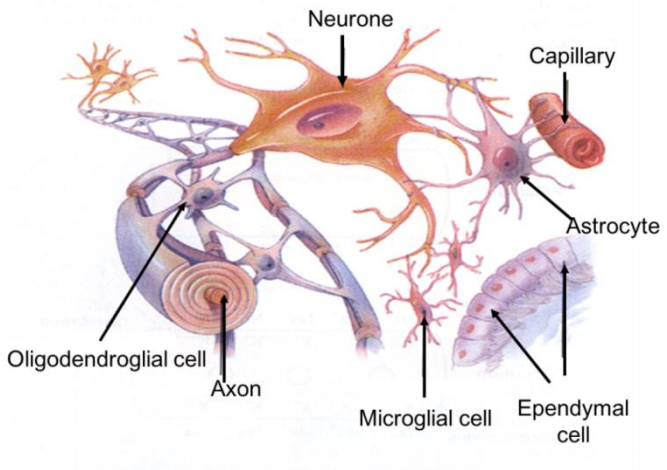
...To be able to apply this to disorders

...To develop effective treatments with minimal side-effects

Cell Types in the nervous system

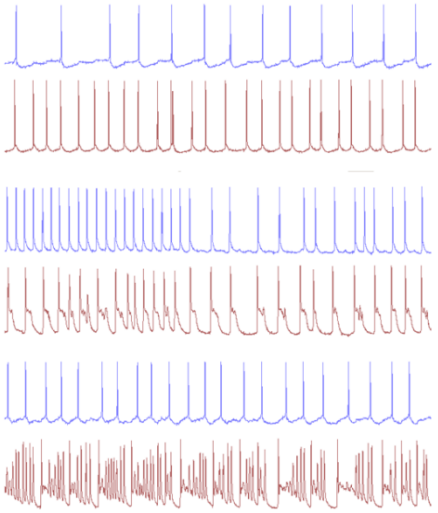
- **Neurons**
  - Principal cells
  - Interneurons
- **Glia**
  - Astrocytes
  - Ependymal cells
  - Microglia
  - Oligodendroglia
  - Schwann cells





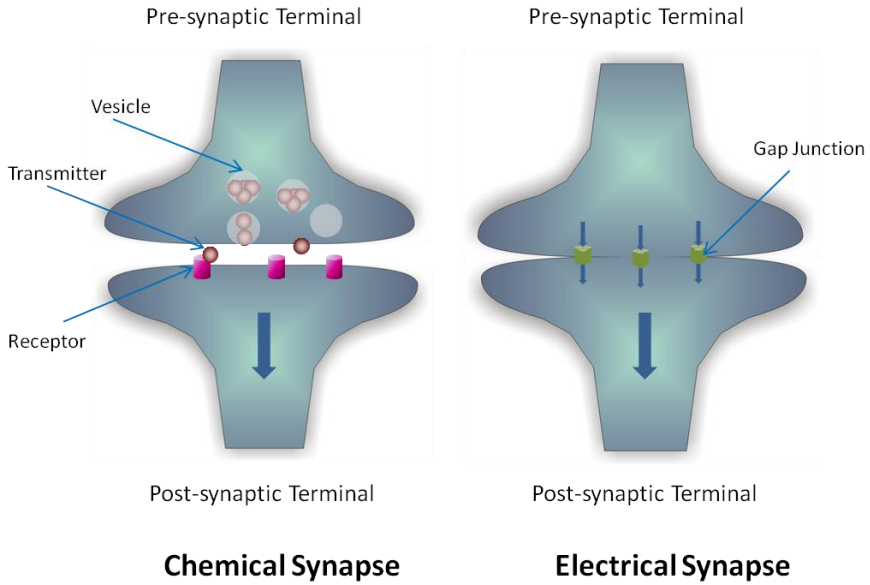
Modified from "Understanding Human Anatomy & Physiology" by S.S. Mader (1997)

Synapses



- Chemical
  - Vesicles releases from presynaptic terminal
  - Act on receptors in postsynaptic terminal
  - Major drug target

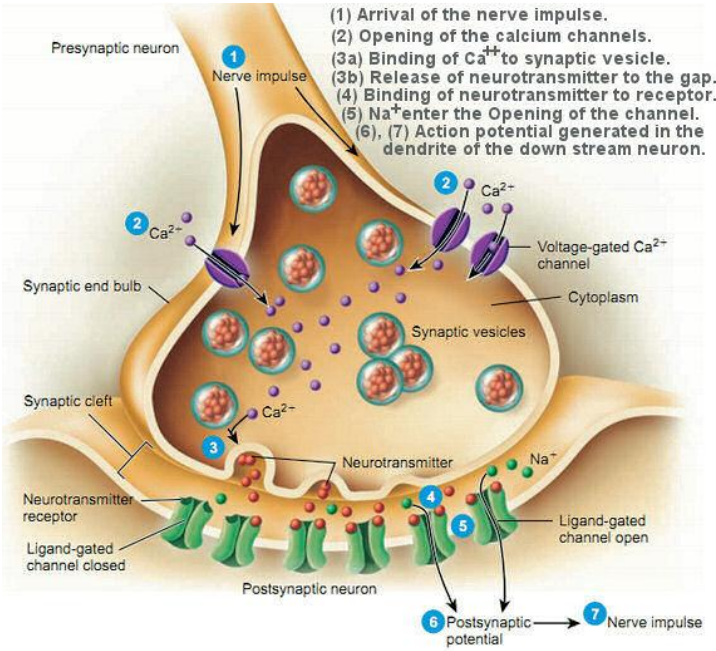
- Electrical
  - Gap junctions
  - Small molecules and current
  - ‘low-pass filter’
  - Synchrony
  - Up-and-coming drug target



Transmitters

- **Neurotransmitters**
  - Used by neurons for rapid cell-cell communication
  - Binds to receptor
  - Excitatory propagates the signal onward
  - Inhibitory blocks onward propagation
- **Neuromodulators** (and other modulatory substances):
  - Found in vesicles (or not), co-localised with NT
  - Act on receptors or membranes to indirectly alter neuronal activity
  - Changing sensitivity or kinetics of NT receptor
  - Also act on glial cells
- Most disorders linked to change in transmitter efficacy
- Some result from single transmitter alteration, usually more than one pathway will be affected

Neurotransmission in the nervous system		
Type	**Name**	**Main Role**
Neurotransmitter	Glutamate	Excitatory
	GABA	Inhibitory
	Aspartate	Excitatory
	Glycine	Inhibitory
	Acetylcholine	Neuro-muscular Junction
	Adrenaline	Stress/arousal
	Noradrenaline	Stress/arousal
	Dopamine	Motivation/Motor function
	5-HT (serotonin)	Homeostasis
	Histamine	Arousal
Neuromodulators	Neuropeptide Y	Appetite
	Substance P	Pain
	Vasopressin	Osmoregulation
	Somatostatin	Growth
	Anandamide	Endogenous Cannabinoid
Other transmitters	NO	Modulatory, not found in vesicles
	CO	Modulatory, not found in vesicles
	Adenosine	Modulatory, not found in vesicles
	ATP	Modulatory, not found in vesicles

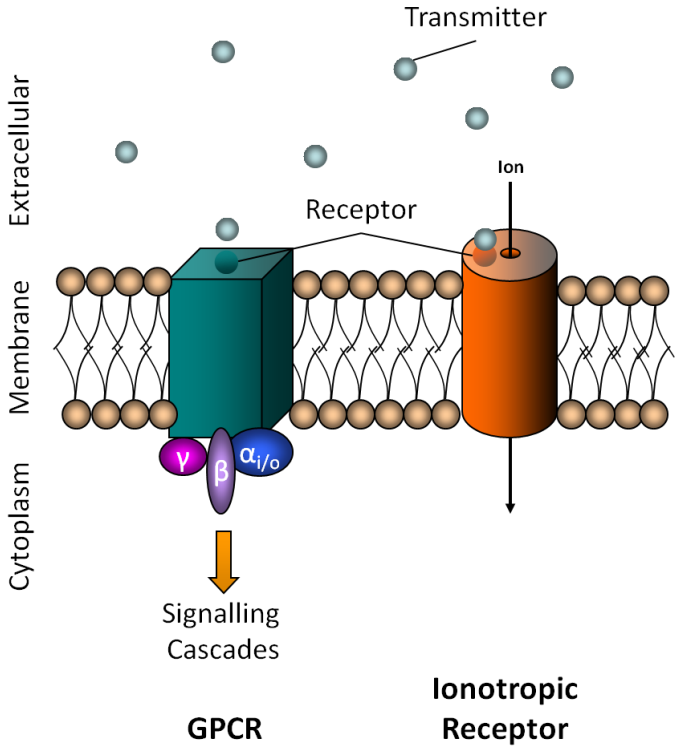


http://universe-review.ca/I10-75-synapse.jpg

Receptors in the nervous system

Ionotropic – linked to ion channels
Metabotropic – G-protein linked (aka GPCR)

- Receptors transmitter specific
- Some transmitters act on both types
- Drugs generally targeted at one specific subtype of receptor
- Drugs targeted at receptors sometimes too strong, now developing subunit specific agonists
- Polyvalent, non-selective (or 'dirty' drugs) act on multiple sites
- Think about where else the drug could be acting, that's where you'll see problems occurring



Excitation and Inhibition

Major Excitatory transmitter - **Glutamate**

Major Inhibitor transmitter – **GABA**

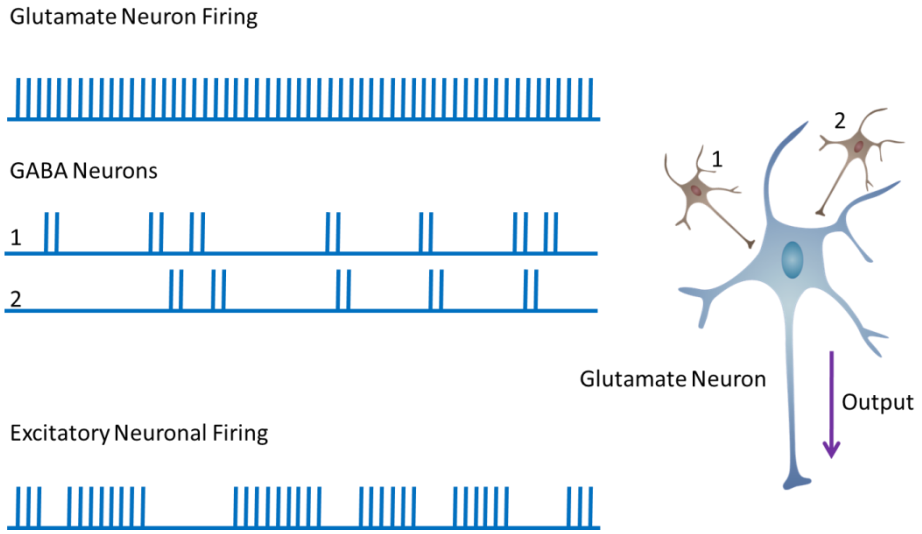
- Inhibition responsible for coding of activity

- Plasticity changes strength at neuronal level
- Synchrony gives strength at network level

Coding of Activity

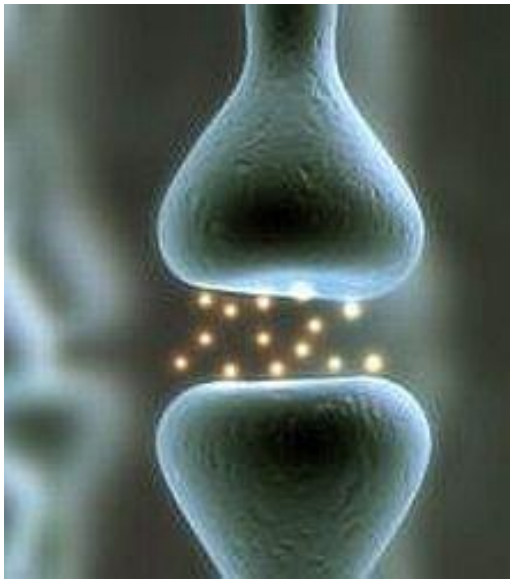
- Excitatory neurons have regular firing in absence of inhibition
- Inhibitory input sculpts this to give patterns (coding)
- Coding carries the information and can be read, like morse code

- Some drugs that increase firing can lead to loss of coding, and psychological side effects



What mechanisms are involved in pathogenesis of neuronal and psychological disorders?

- Altered neuronal activity
- Altered synchrony
- Cellular changes
- Subcellular change
- Genetic composition



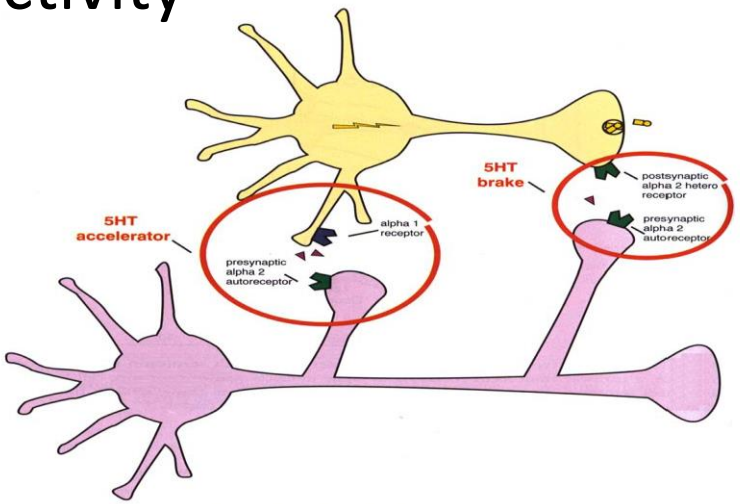
http://g.psychcentral.com/news/u/2010/09/neuron-mind-2.jpg

The aim is to restore balance!

Pathway Interactions

- Activation of one class of neuron often has knock-on effects on other pathways
  - NA levels can directly alter 5HT activity
  - 5HT levels can alter DA activity
  - DA levels can alter Ach Activity
  - Ach levels can alter GABA activity
  - And vice-versa for all!

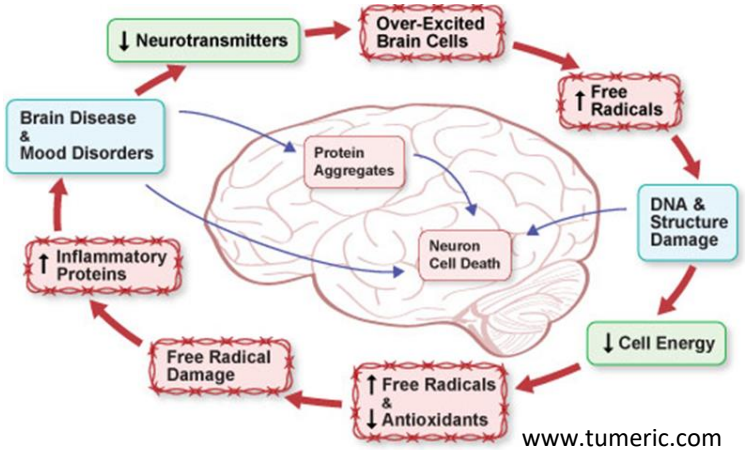
- It's a tangled web indeed!



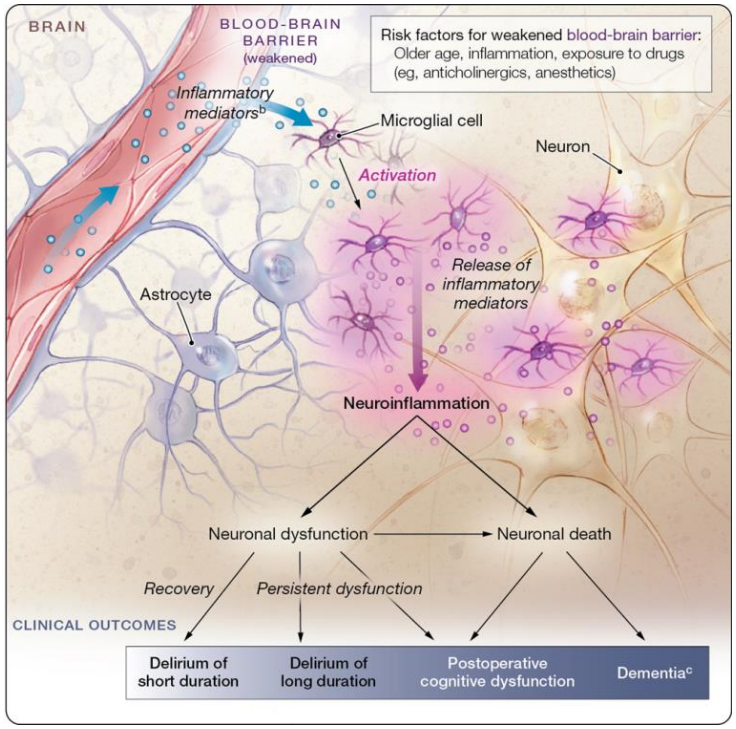
From Stahl: Essential Psychopharmacology

Inflammation

- Inflammatory mediators lead to:
  - Microglia activation
  - Cell dysfunction
  - Cell death



www.tumeric.com



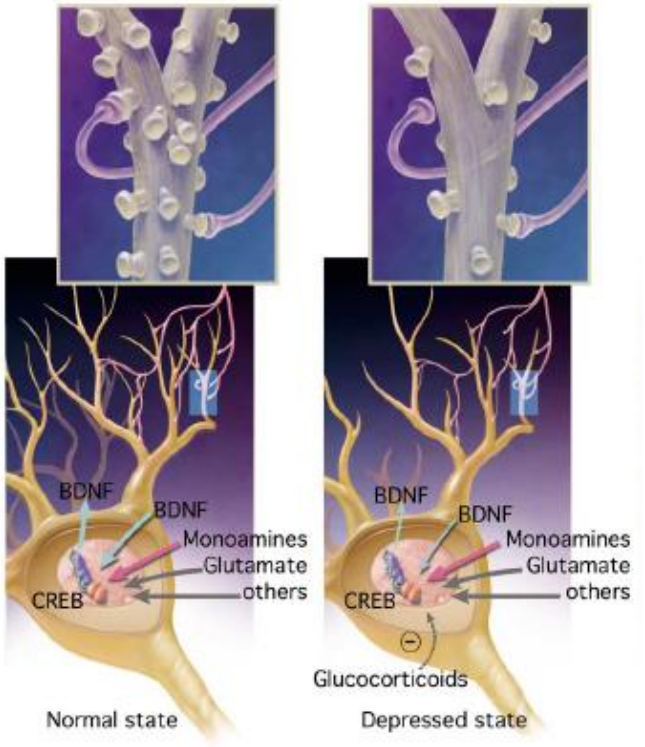
http://jama.jamanetwork.com/article.aspx?articleid=1172097

- Leads to spectrums of disorders

Pasternak et al. (2016) 'In vivo imaging of neuroinflammation in Schizophrenia.' Schiz. Res., 173, 200-212

Neurogenesis

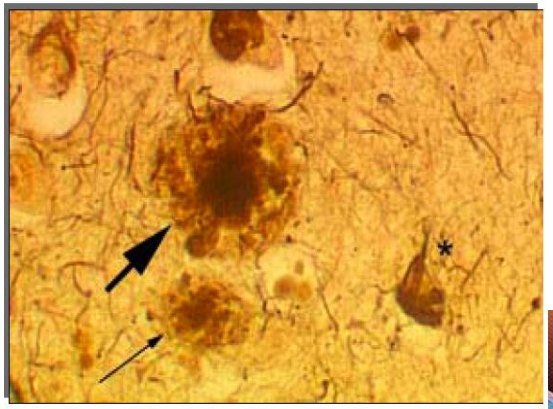
- Changes in arborisation
- Changes in synapse structure
- Altered receptor number
- Restored by drugs



Konarski et al (2008) Bipolar Disorders 10, 1–37

Neurodegeneration

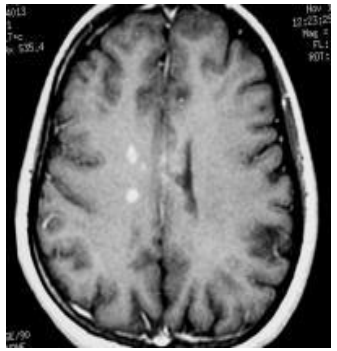
- Cellular – death of cell body (no regeneration possible
  - Parkinson's
  - Alzheimer's
  - ? Schizophrenia



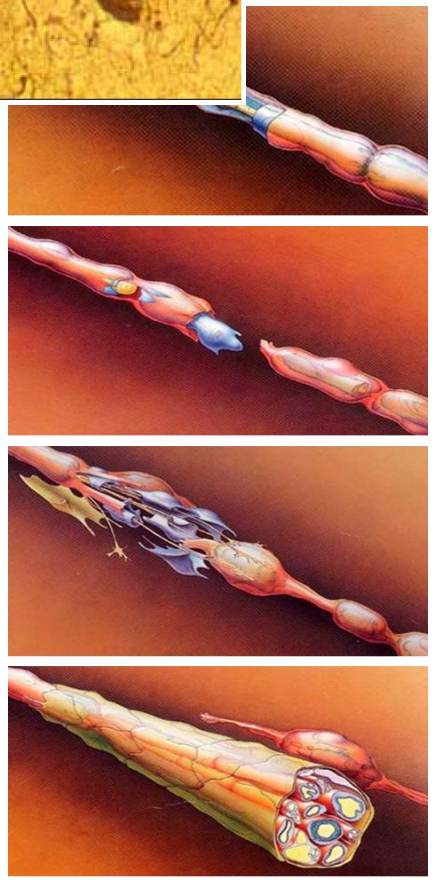
* Neurofibrilliary Tangle (tau)
↟ Neuritic Plaque (β-amyloid)
↑ Diffuse Plaque

- Axonal – dying back of axon proximal to cell body (some regeneration possible). Wallerian – distal degeneration of axon and myelin (generally trauma induced
  - Diabetic neuropathy
  - Nerve compression

- Myelin – loss of oligodenrdroglial/schwann cells affecting conduction velocity
  - Multiple Sclerosis (central)
  - Guillain Barré (peripheral)



Scan from MS patient

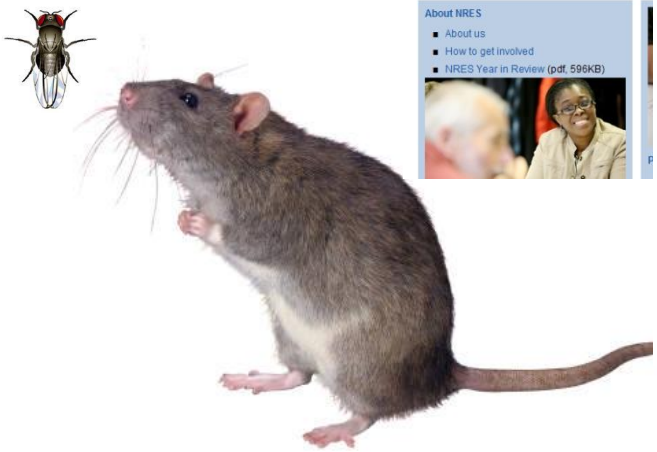


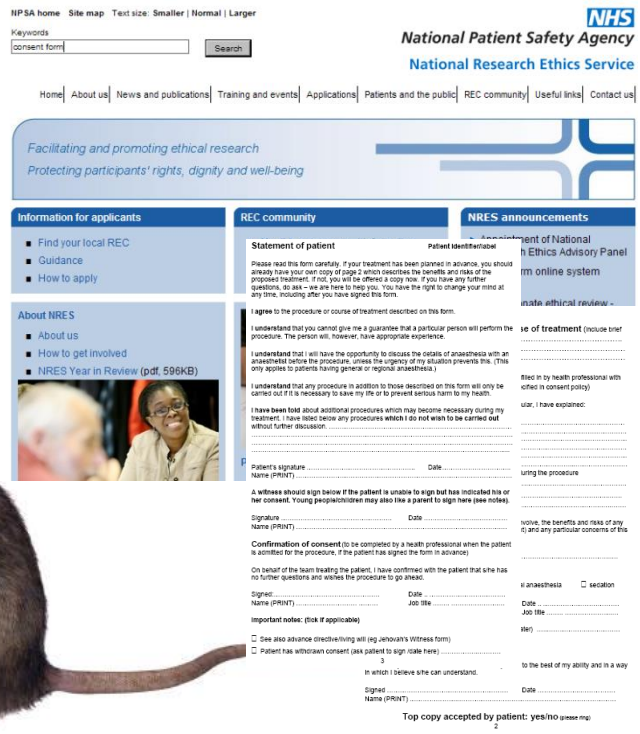
Stages of Wallerian Degeneration

How can you study Psychiatric disorders

- Human Studies

- Animal Studies
  - Behaviour
  - Electrophysiology
    - In vivo
    - In vitro
  - Molecular





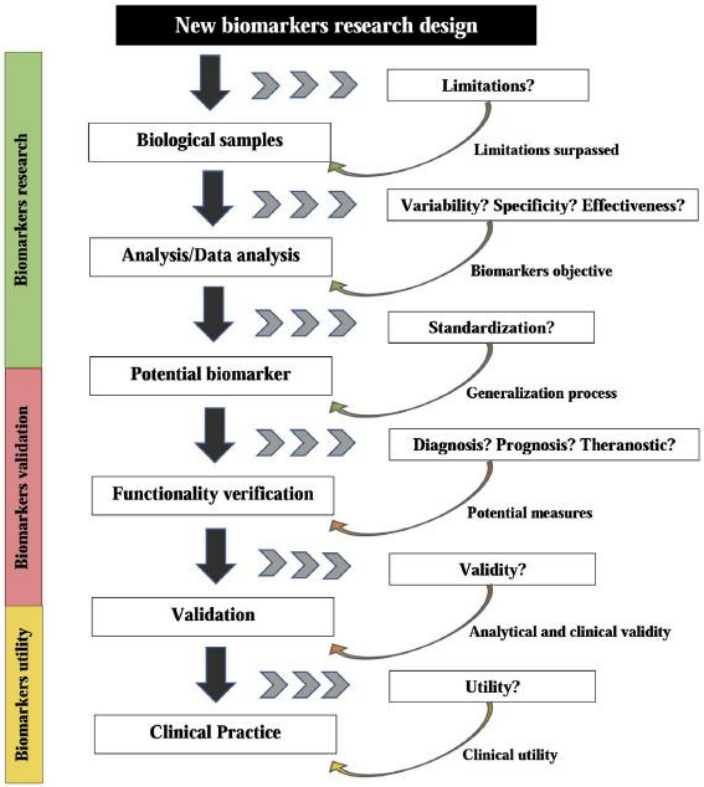
Cellular Research Techniques

- In-vitro
  - Receptor expression
  - Receptor modification
  - Pharmacology
  - Genetic modification
  - Subcellular mechanisms
- Quick turnaround
- Controllable

Totally Unrealistic

Biomarkers

- Aims to identify potential markers than can indicate predisposition to disorders
  - Activity – metabolic/neuronal
  - Genetic
  - Epigenetic
  - Protein



Rodrigues-Amorim et al. (2017) @Schizophrenia: a review of potential biomarkers.' J. Psych. Res., 93, 37-49.

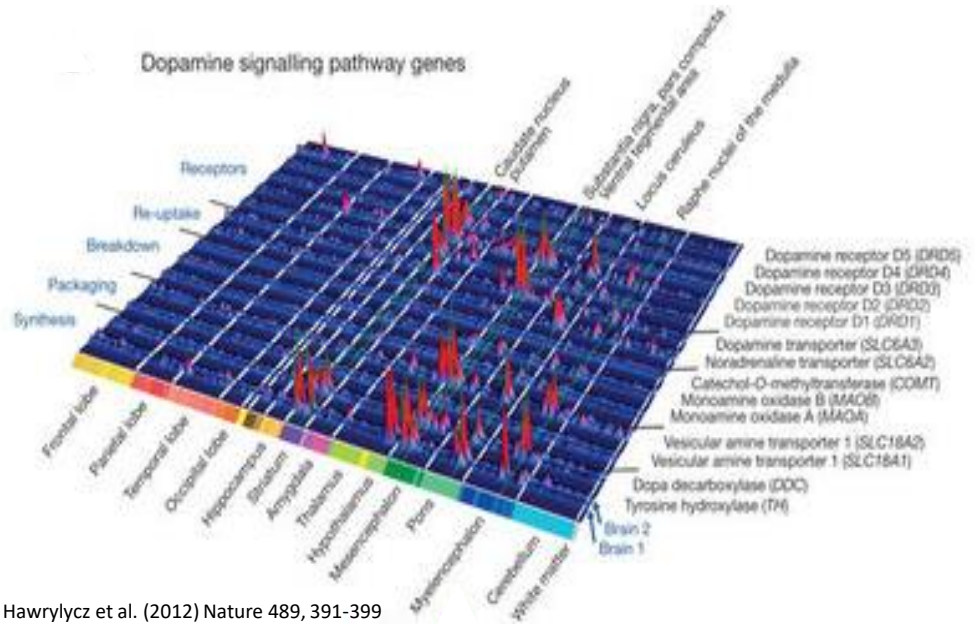
Genetic Profiling

Genetic composition may lead to predisposition for disorders

May also affect likelihood of response to treatment

Examples include:

- 5HT receptor subtypes
- DA receptor subtypes
- GABA receptor subunit variations
- GAD enzymes [synthesizes GABA]



Hawrylycz et al. (2012) Nature 489, 391-399

Inconclusive at present and can’t account for environmental factors

Current Drug R&D Targets

Reprofiling

NeuroTransmitters

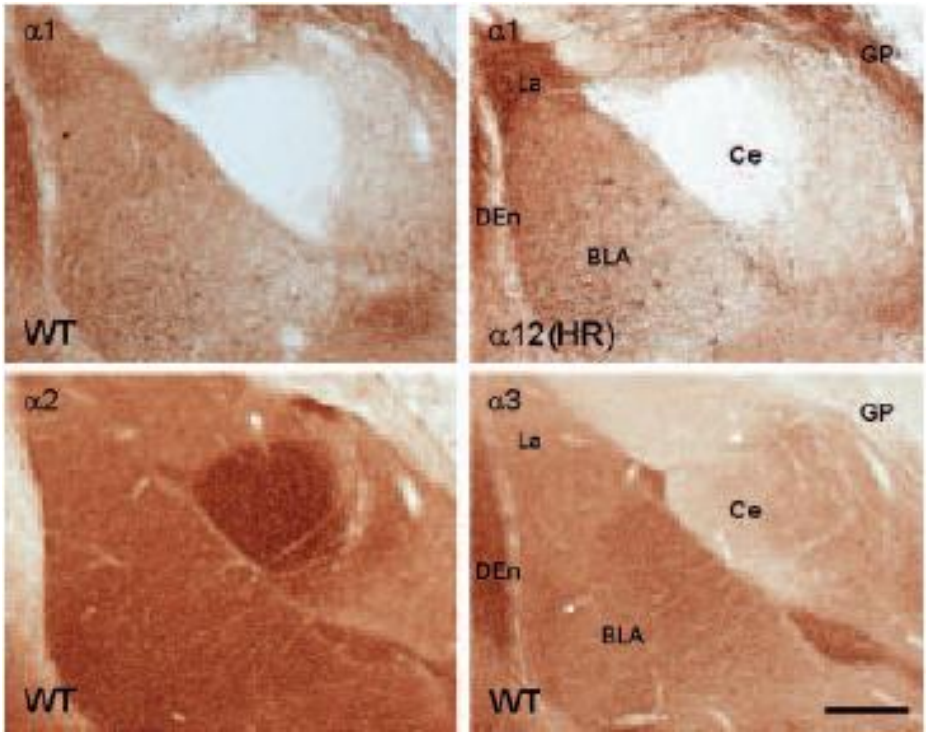
- 5HT
- Dopamine
- Noradrenaline
- Glutamate
- GABA

Neuromodulators

- Cannabinoids
- Peptides

Subunit specific drugs

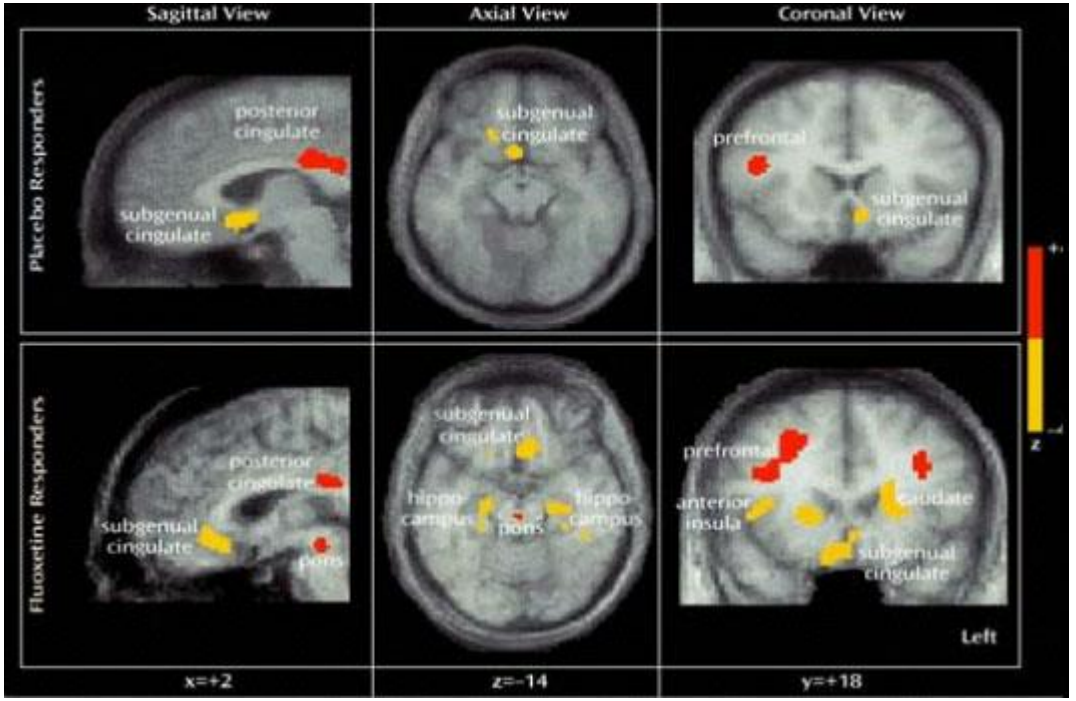
- Benzodiazepines



GABA$_A$ receptor subunit distribution in the amygdala. From: Marowsky et al (2004) European Journal of Neuroscience, 20, 1281–1289.

Placebo Effect

- 30% of patients respond to placebo
- Can change neuronal activity levels
- Different effects to ADs
- Works even if told!

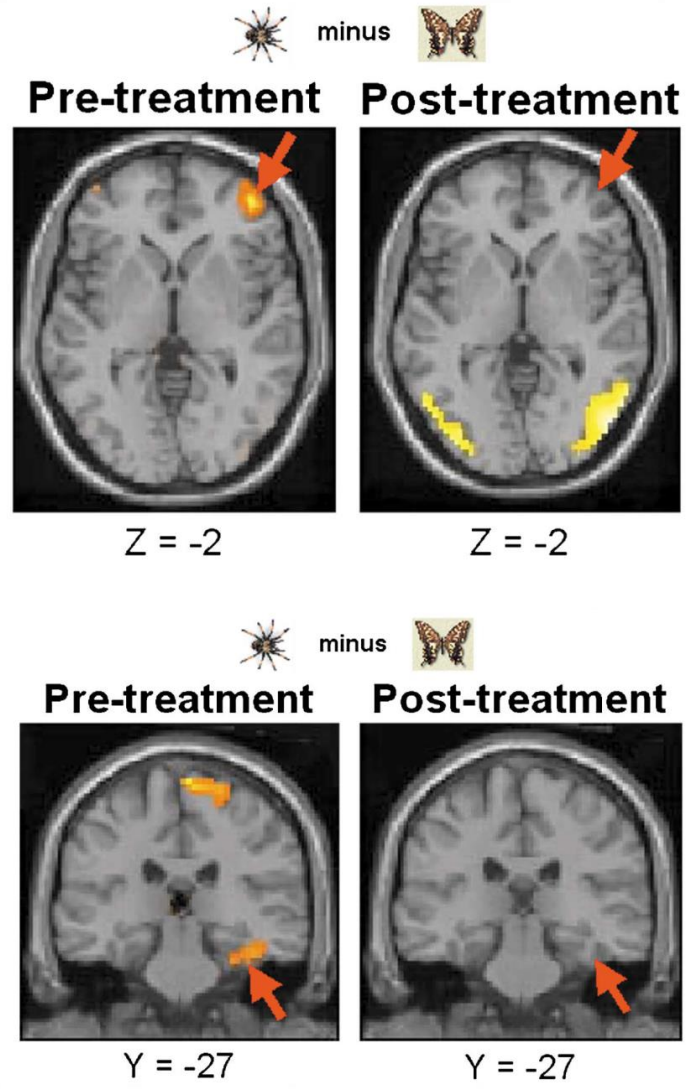


Mayberg, et al (2002) The Functional Neuroanatomy of the Placebo Effect,. Am J Psychiatry ,159: 728-737.

What's psychotherapy doing?

- New learning?
- Overwriting/depressing old learning?
- Altering brain activity frequencies?
- Desensitizing?

Or just coping?



CBT treatment of phobias

Psychosis

- Broad range of mental disorders (ICD F20-29: Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders) with symptoms including:
  - hallucinations (seeing, hearing, smelling, tasting or feeling things that are not there)
  - delusions (false and unshakable beliefs)
  - Serious defects in judgement (reasoning, evaluating objectively)
  - Disturbed cognitive processing (thinking)
- Symptoms may be constant or intermittent depending on the underlying cause
- Sufferers inhabit a world of their own making

- Schizophrenia most common and most severe form (c.1%)

http://www.healthtalk.org/peoples-experiences/mental-health/experiences-psychosis/onset-mental-distress

Hallucinations

Hallucinations are perceptions in the absence of external stimuli.

Common hallucinations include:

- Auditory hallucinations – hearing voices/sounds
- Tactile/somatic/gustatory hallucinations – feeling bodily sensations
- Visual hallucinations - seeing patterns/images
- Olfactory hallucinations - smelling a foul or pleasant odour

http://www.sleepcare.com/index.php/sleep-hallucinations/

Fuseli: The nightmare

https://www.ted.com/talks/oliver_sacks_what_hallucination_reveals_about_our_minds/transcript?language=en

Causes of Hallucinations

There are many causes of hallucinations, including:

- Delirium
- Dementia – e.g. Dementia with Lewy Bodies (DLB)
- **Psychiatric disorders, e.g. Schizophrenia and psychosis**
- Drugs, alcohol or medications
- Epilepsy – focal seizures
- Narcolepsy
- Visual impairment – Charles Bonnet syndrome

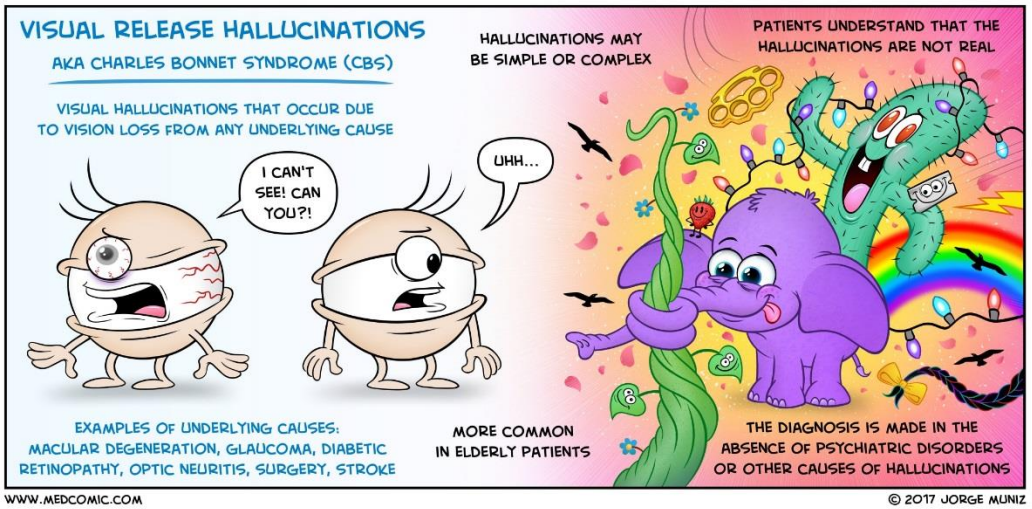
In some cases, hallucinations are normal:

- Part of the grief process
- Hypnagogic (falling asleep) and hypnopompic (waking) hallucinations

http://www.healthtalk.org/peoples-experiences/mental-health/experiences-psychosis/hearing-voices-seeing-things-and-unusual-beliefs

Charles Bonnet Syndrome

- Commonly seen in people with severe visual impairment
- Brain ‘filling in’ gaps
- Visual only
- Often animals and people
- Can be scary!
- Patient knows they are not real



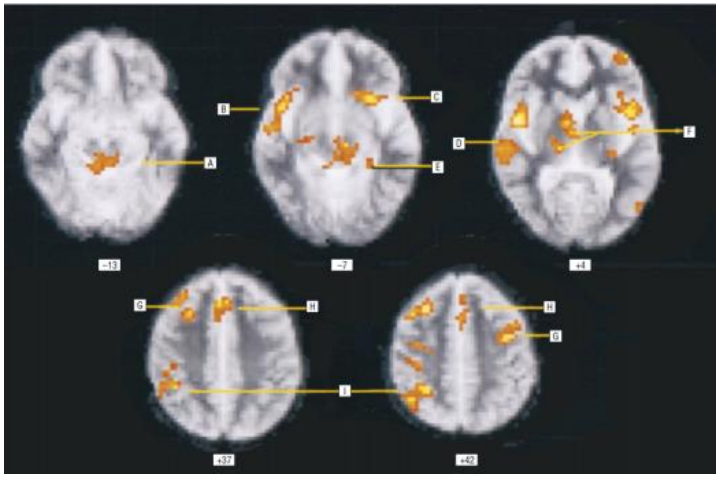
Cerebral Activity and Hallucinations

? Spontaneous activation of sensory centres

Activity in fMRI shows activity as if the hallucination is real

Hallucinatory activity overrides actual sensory input

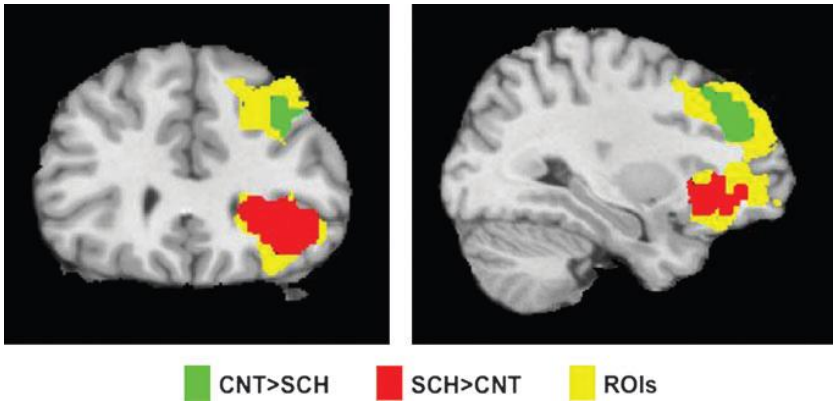
Temporary disconnect between cortical and thalamic regions



Auditory Hallucinations: Shergill et al. (2000) Arch. Gen. Psych., 57, 1033-1038

Circuit involved in Psychosis

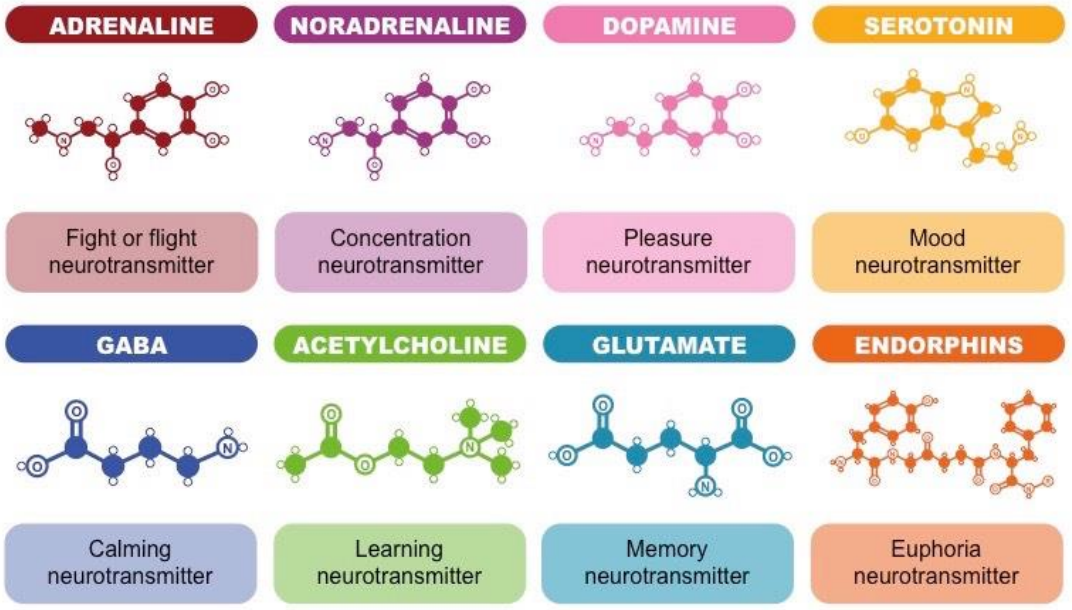
- Prefrontal cortex – dorsolateral and ventrolateral
- Anterior cingulate gyrus
- Basal ganglia – **striatum**
- Hippocampus
- Cerebellum



Gur et al. (2007) Schizophrenia Bull. 33, 4, 921–931.

Transmitters involved in psychosis

- Two main transmitters:
  - Dopamine
  - Acetylcholine
- Others include:
  - Serotonin
  - Glutamate
  - Histamine
  - Noradrenaline

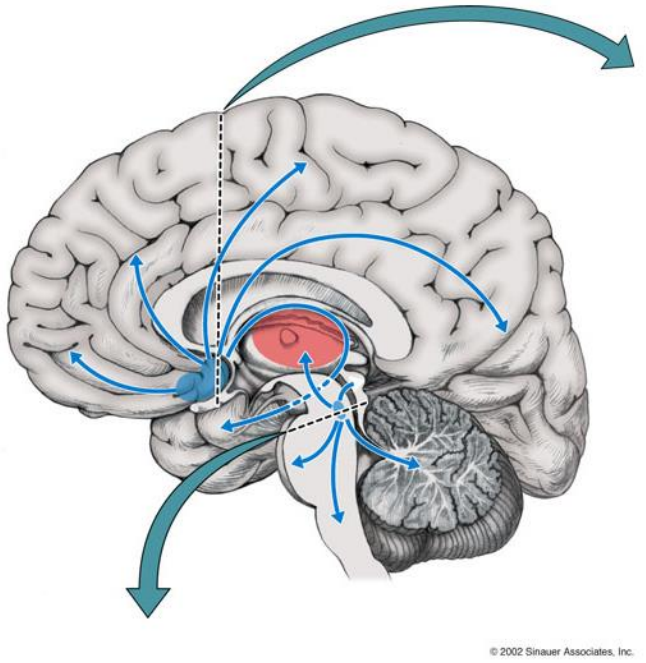


http://www.neuronanos.com

What role does Acetylcholine play in arousal?

- Peripherally controls ANS and muscle function (NMJ)

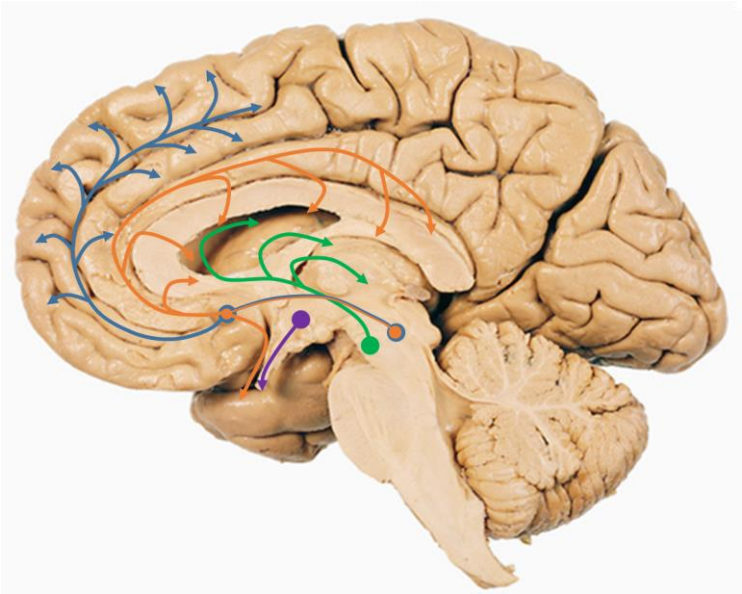
- Centrally involved in:
  - Alertness
  - Arousal
  - Attention
  - Sleep
  - Memory
  - Learning



- Acetylcholine (ACh) modulates a number of transmitter pathways, including dopamine

Dopamine Pathways

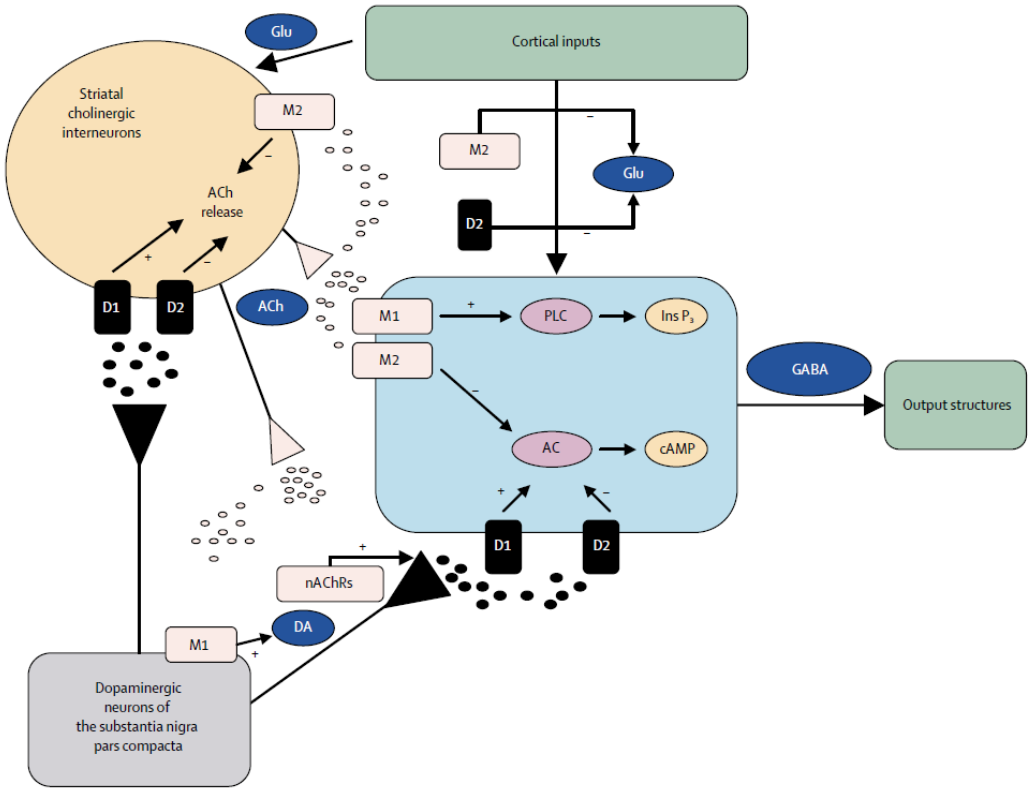
4 main pathways:



- **Nigrostriatal** - movement
- **Mesolimbic** – mood, memory
- **Mesocortical** – mood, higher cognition
- **Tubero-hypophyseal** – inhibits prolactin release

Link between DA and ACh

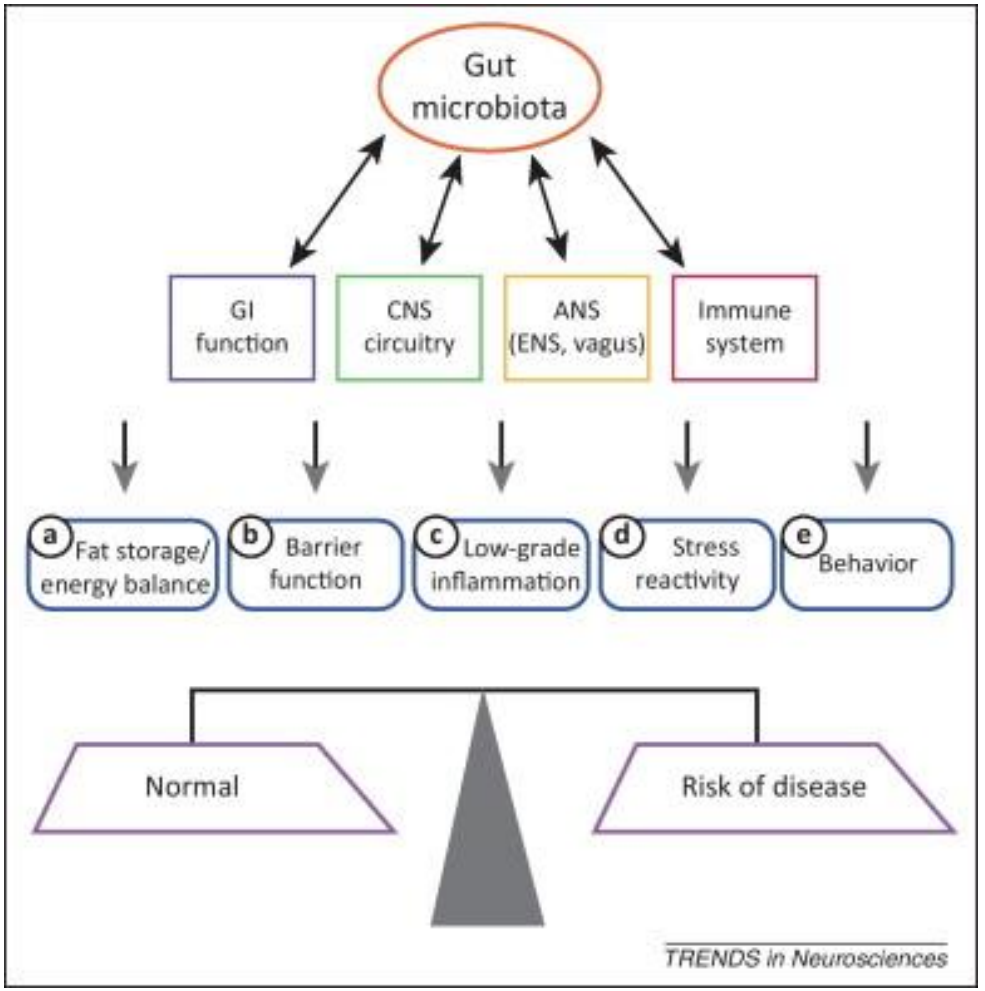
- ACh can modulate activity in dopamine pathways (and vice-versa)
- This will also have knock-on effects on other monoamines, NA and 5HT
- ACh and DA neurons in striatum modulate PFC and are abundant in the hippocampus



Weinstein et sl. (2016) 'Pathway-specific dopamine abnormalities in Schizophrenia.' Biol.Psych., 81, 31-42

And environmental factors?

- Gut-brain axis?
- Gut microbiome?
- Cannabis use
- Stress
- Combinations key!



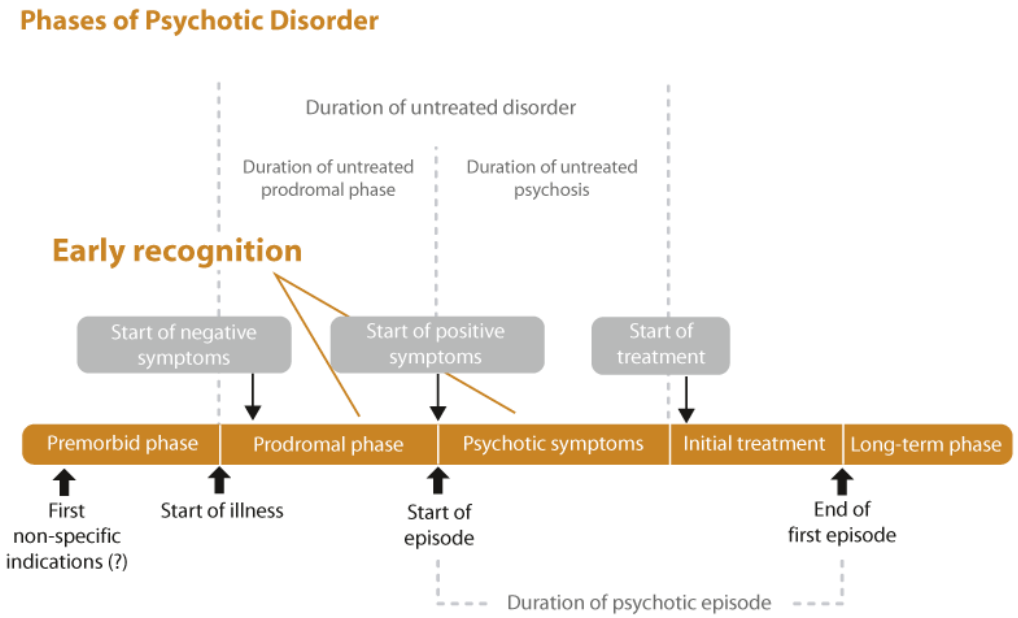
Moore et al. (2007) 'Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review.' Lancet, 370, 319–28.

Severance et al. (2016), Autoimmune disease, gastrointestinal disorders and the microbiome in schizophrenia: more than a gut feeling.' Schiz. Res. 176, 23-35

Foster and McVey Neufeld (2013) 'Gut–brain axis: how the microbiome influences anxiety and depression.' Trends Neurosci., 36, 305-312

Stages of Psychosis

- **Prodrome**: early signs of impending onset of psychosis, e.g. changes in feelings, thoughts, disconnection
- Any person exhibiting prodromal stage will develop psychosis

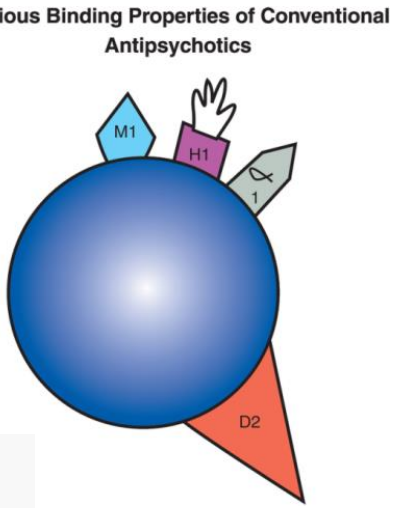


http://www.psychosis-bipolar.com/img/grafik_wp_10_gr.gif

Treatment of Psychosis

- Prodromal
  - Referral
  - **Specialist assessment**
  - Interventions to prevent onset
  - Psychological interventions
    - CBT
    - Family intervention
  - Interventions to treat anxiety/stress/PTSD and/or alcohol/drug misuse
- First episode
  - **Early intervention team**
  - Psychological interventions
  - Pharmacological interventions – oral antipsychotic, low dose trial 4-6wks
  - Regular monitoring
- Recurrent episodes
  - Psychological interventions
  - Pharmacological – antipsychotics and/or mood stabilisers
  - Regular health monitoring
  - Support network – self-help groups
- Acute episode
  - **Crisis resolution team**
  - Antipsychotics
  - Benzodiazepines (rapid tranquilisation only)

Antipsychotics

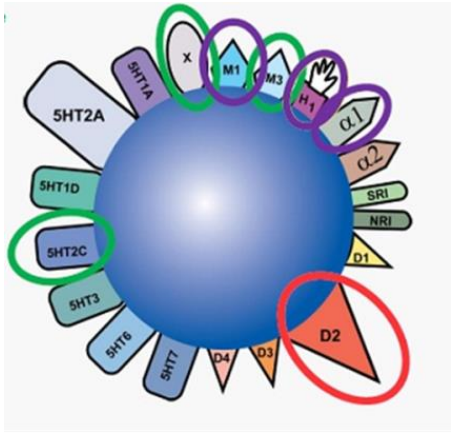


First and second generation

Need therapeutic dose to reach 60% occupancy at D_2 for effective response

<u>First Generation (aka classical/typical)</u>

- Primarily potent D_2 antagonists
- Extrapyramidal effects high
- Low efficacy
- 30% non-responders



Atypical antipsychotic

<u>Second Generation (aka atypical)</u>

- Primarily multiple actions $5HT_2$ & D_2 & others
- Reduced extrapyramidal effects
- Better at treating negative symptoms
- Higher efficacy

Drug	D_1	D_2	D_3	D_4	α_1	α_2	H_1	ACh	5-HT_1	5-HT_2	5-HT_{2A}
Clozapine	++	+	?	+	+++	+++	+++	++	+	++	+
Risperidone	+	+++	?	+	+++	+++	+	–	+	–	+++
Olanzapine	++	+++	+	+	++	+	+++	+	–	++	++
Quetiapine	+	++	+	–	+++	+	+++	–	–	+	+++
Aripiprazole	+	++++	?	?	–	–	–	–	++	?	+++
Ziprasidone	++	+++	++	?	++	–	+	–	++	?	+

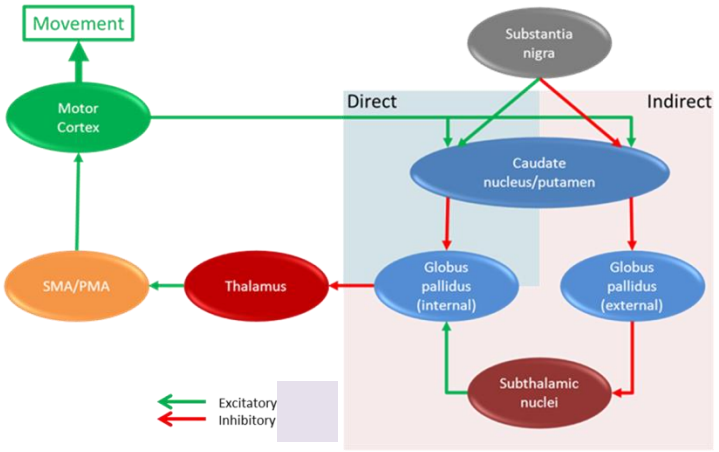
D=dopamine; α=alpha-adrenergic; H=histamine; ACh=acetylcholine; 5-HT=5-hydroxytryptamine (serotonin); ++++=very high affinity; +++=high affinity; ++=moderate affinity; +=low affinity; –=negligible affinity; ?=unknown affinity.

http://www.cnsspectrums.com/userdocs/ArticleImages/0805cns.acsupp02.gif

Side Effects

5 main groups of side-effects

- Extrapyramidal (EPS)
- Cardiovascular – increased QT interval
- Metabolic – weight gain/diabetes
- Hormonal – increased plasma prolactin
- Other – includes psychiatric



Extrapyramidal (~75% of cases):

- Parkinsonism symptoms

Also:

- Dystonias
- Akathisia
- Sedation
- Cardiovascular
- Prolactin elevation
- TARDIVE DYSKINESIA

2nd Generation

- Fewer EPS
- Cholinergic effects

	Extrapyramidal	Sedation	Weight gain	Hyperglycaemia	Anticholinergic	Orthostatic hypotension
Atypical antipsychotics						
Risperidone	●●	●● initially	●●	●●	●	●● initially
Quetiapine	●*	●●●	●●	●●●	●●	●●
Olanzapine	●	●●●	●●●	●●●	●●●	●
Clozapine	●	●●●	●●●	●●●	●●●	●●
Amisulpride	●●*	●	●	●	●	●
Aripiprazole	●	●	●	●	●	●
Ziprasidone	●	●●	●	●	●	●●
Typical antipsychotics						
Haloperidol	●●●	●	●●	●●	●	●
Chlorpromazine	●●	●●●	●●●	●●●	●●●	●●●

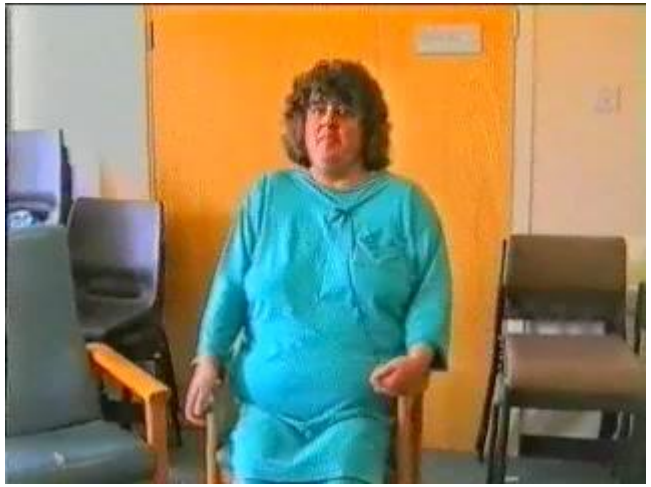
Approximate frequency of adverse effects: ● (<2%) = negligible or absent; ● (>2%) = infrequent; ●● (>10%) = moderately frequent; ●●● (>30%) = frequent. * rarely a problem at usual therapeutic doses

http://www.bpac.org.nz/bpj/2011/november/images/antipsychotics-img2.jpg

Tardive Dyskinesia

Typical symptoms

Disabling involuntary movements: tongue protruding, choreiform movements, grimacing, twisting



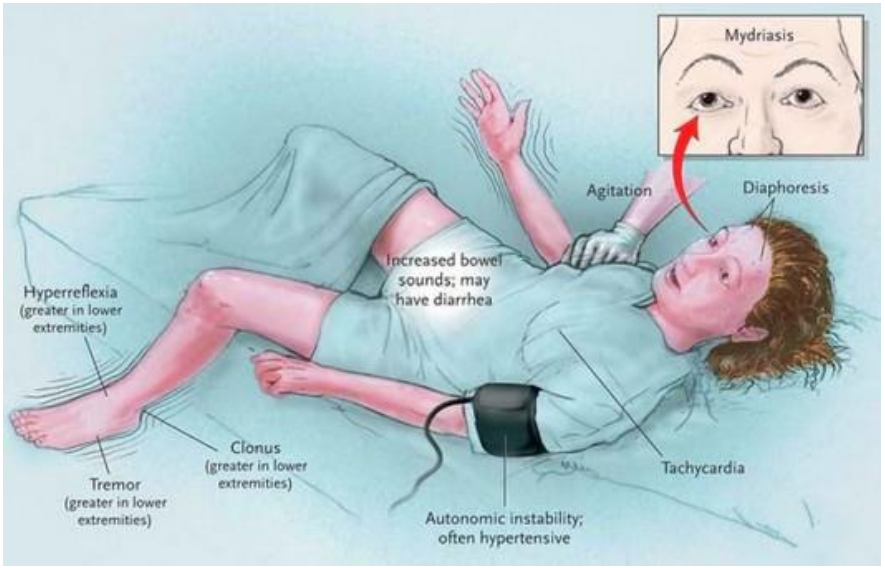
In many cases IRREVERSIBLE

- Occurrence ~25% of Cases
- Increases with length of exposure
- Remits spontaneously in ~30%
- Anticholinergic use stopped immediately
- Vitamin E & B6, Benzodiazepines, β-blockers can help
- Switch to 2nd generation antipsychotic

http://www.youtube.com/watch?v=t_NKRS8lLWA

Neuroleptic Malignant Syndrome

- Rare but potentially fatal side-effect
- Caused by over-activation of ANS/metabolic pathways:
  - Hyperthermia
  - Altered level of consciousness
  - Pallor
  - Sweating
  - Tachycardia
  - Fluctuating BP
  - Muscle rigidity
  - Urinary incontinence
- No effective treatment, try:
  - Stop antipsychotic use
  - Bromocriptine (dopamine agonist)
  - Dantrolene (muscle relaxant)



http://epomedicine.com/clinical-cases/neuroleptic-malignant-syndrome-nms-approach/

Benzodiazepines

Act on $GABA_A$ receptor (γ subunit) to increase activity

Reduces neuronal transmission by enhancing inhibition

Commonly used benzos:

- Diazepam (valium)
- Midazolam (sedative)
- Lorazepam (status epilepticus)
- Flumazenil (antagonist)

Benzodiazepines

Positive Allosteric Modulators (co-agonists) of $GABA_A$ receptors

Benzodiazepines, e.g. Midazolam, bind to the γ-subunit of $GABA_A$ receptors, working together with GABA to increase the opening of the channel allowing more chloride entry into the cell. This hyperpolarises the cell reducing the likelihood of action potential firing.

Summary

- Whilst we know a lot about the mechanisms underlying psychiatric disorders, treatments have not progressed as rapidly as the knowledge

- No one research models encompasses all of the human symptoms

- Human studies can be difficult and often inconclusive

- Assuming everyone is different means we'll probably never know the whole truth