



Biological Psychology

M5X00908 Brain, Behaviour, and Cognition (BBC)

Lecture 7: Brain Damage and Neuroplasticity

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Brain Damage



Studying brain damaged individuals is important:

- 1. It helps us understand how the brain should work in a healthy individual**
 - 2. Serves as basis for the development of new treatment.**
- Causes of Brain Damage:**
 - Brain tumors**
 - Cerebrovascular disorders**
 - Closed-head injuries**
 - Infections of the brain**
 - Neurotoxins**
 - Genetic factors**





Brain Tumors

- A tumor (**neoplasm**) is a mass of cells that grows independently of the rest of the body – a cancer
- 20% of brain tumors are **meningiomas** – grow between the meninges (the 3 membranes that cover the CNS)
- All meningiomas are encapsulated: they grow within their own membranes (picked-up on CT)
- Usually benign, surgically removable, little risk
- However: Most brain tumors are infiltrating (grow diffusely through surrounding tissue)
- Usually malignant, difficult to destroy.
- About 10% of brain tumors are **metastatic** – originate elsewhere (usually lungs), & are carried to brain by bloodstream.

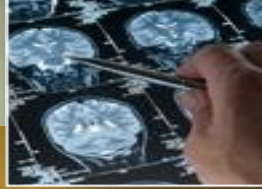
Cerebrovascular Disorders



- **Stroke:**

- Sudden-onset cerebrovascular event causing brain damage
- Leading cause of death in U.S. & cause of adult disability
- Symptoms depend on area of brain affected but common consequences are amnesia, aphasia (language deficits), paralysis, & coma.
- Area of dead/dying tissue is called an infarct.
- Area surrounding infarct is called the penumbra.
- Two major types:
 - **Cerebral hemorrhage** (bleeding in the brain)
 - **Cerebral ischemia** (disruption of blood supply)

Cerebrovascular Disorders



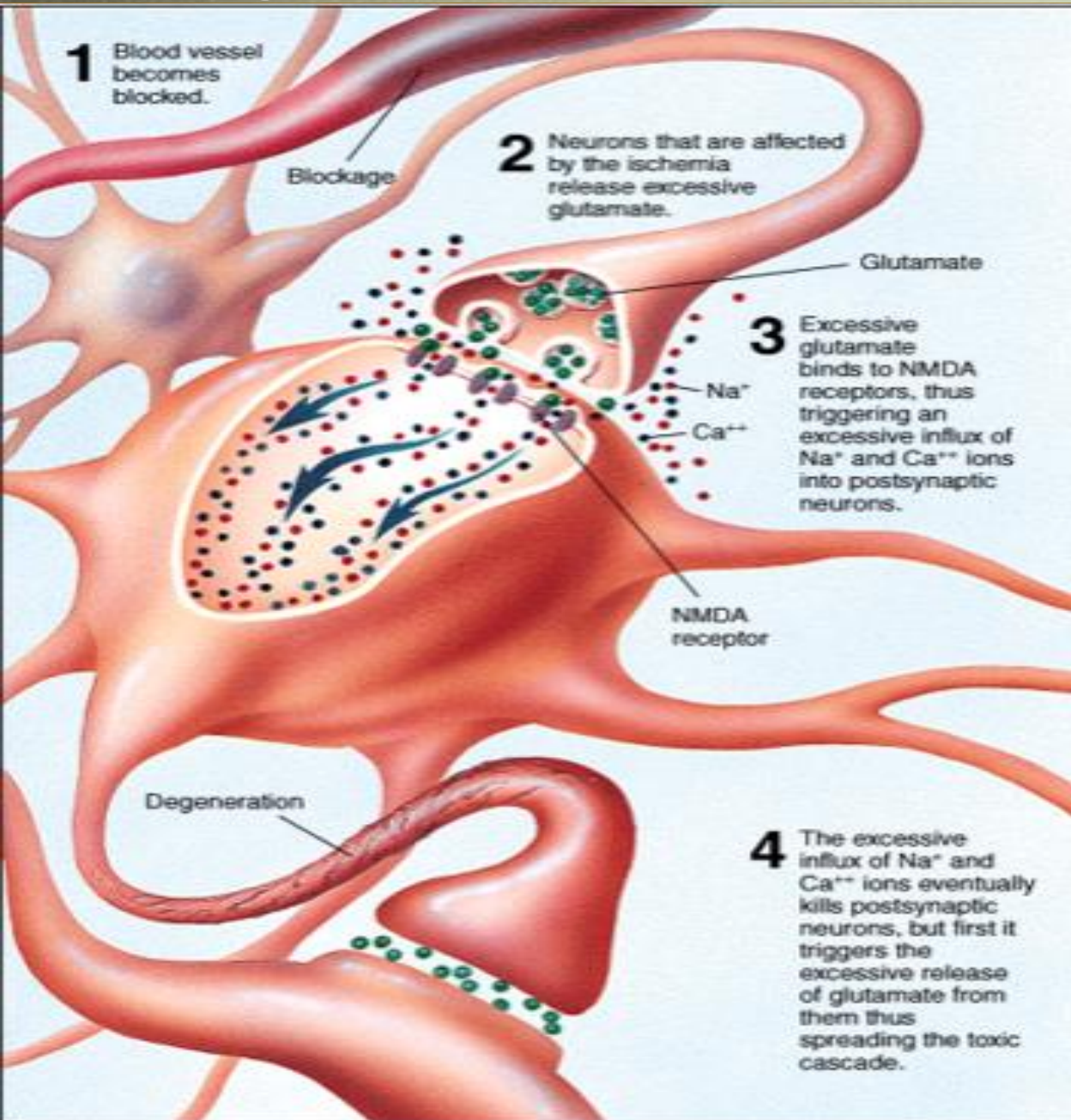
- **Cerebral hemorrhage (bleeding in the brain)**
 - Occurs when cerebral blood vessel ruptures and blood seeps to surrounding tissue.
 - **Aneurysm** – balloon-like dilation that forms in wall of an artery at a point where elasticity of artery wall is defective; may be congenital (present at birth) or due to poison/infection.
- **Cerebral ischemia (disruption of blood supply)**
 - **Thrombosis** – a plug forms in the brain, blocking flow
 - **Embolism** – a plug forms elsewhere and moves to the brain
 - **Arteriosclerosis** – wall of blood vessels thicken, usually due to fat deposits creating narrow channels.

Damage Due to Cerebral Ischemia



- Does not develop immediately (takes ~ 2 days)
- Most damage is a consequence of excess neurotransmitter release – especially glutamate:
 - most prevalent excitatory neurotransmitter.
- Blood-deprived neurons become overactive and excessively release glutamate.
- Glutamate over-activates its receptors, especially N-methyl-D-aspartate (NMDA) receptors leading to an influx of Sodium (Na^+) and Calcium (Ca^{2+}) ions
- Influx of Na^+ and Ca^{2+} triggers
 - More release of glutamate, which spreads toxic cascade
 - A sequence of internal reactions ultimately kill neuron

Damage Due to Cerebral Ischemia



- Ischemia-induced brain damage:
 - takes time
 - does not occur equally in all parts of the brain
 - mechanisms of damage vary with the brain structure affected

The cascade of events by which the stroke-induced release of glutamate kills neurons



Closed-Head Injuries

- **Brain injuries due to blows that do not penetrate the skull: brain collides with the skull**
 - **Contrecoup injuries** – contusions are often on the side of the brain opposite to the blow
- **Contusions** – closed-head injuries that involve damage to the cerebral circulatory system; damage produces internal hemorrhaging, which results in a hematoma (localized collection of clotted blood where a bruise forms).
- **Concussions** – when there is disturbance of consciousness following a blow to the head and no evidence of structural damage.
 - While there is no apparent brain damage with a single concussion, multiple concussions may result in a dementia referred to as “punch-drunk syndrome”



Infections of the Brain

- **Encephalitis** – the resulting inflammation of the brain by an invasion of microorganisms
- Two common types of brain infection:
 - **Bacterial infections**
 - Often lead to abscesses, pockets of puss
 - May inflame meninges, creating meningitis
 - Treat with penicillin and other antibiotics
 - But does not reverse brain damage
 - **Viral infections**
 - Some preferentially attack neural tissues
 - Others attack neural tissue but do not have a preference for it over other tissue.
 - Some can lie dormant for years

n eurotoxins

- Nervous system can be damaged by exposure to variety of toxic chemicals.
- These may enter general circulation from the Gastrointestinal tract or lungs, or through the skin.
- **Toxic psychosis** – chronic insanity produced by a neurotoxin
- The Mad Hatter – hat makers often had toxic psychosis due to mercury exposure when preparing the felt used to make hats
- Some antipsychotic drugs in the 1950s produced a motor disorder called **tardive dyskinesia**
- Some neurotoxins are endogenous (produced by the body)
 - e.g., auto-immune disorders

Genetic Factors

- Accidents during cell division can result in a fertilized egg ending up with an abnormal chromosome or an abnormal number of chromosomes.
- Most neuropsychological diseases of genetic origin are associated with recessive genes passed from parent.
- **Down syndrome:**
 - 0.15% of births, probability increases with advancing maternal age of mother
 - Extra chromosome 21 created in the egg during ovulation – when fertilized 3 instead of 2 of this chromosome exists
 - Characteristic disfigurement, mental health and other health problems result.



Programmed Cell Death



All six causes of brain damage produce damage, in part, by activating **apoptosis.**

This can be of benefit, otherwise if damage cells were just left in the brain they could swell, break off and travel around causing other problems.

Neuropsychological Diseases



So far discussed causes of human brain damage.

What about diseases associated with brain damage.

- **Epilepsy**
- **Parkinson's disease**
- **Huntington's disease**
- **Multiple sclerosis**
- **Alzheimer's disease**



Epilepsy



- **Primary symptom is seizures, but not all who have seizures have epilepsy**
- **Epileptics have seizures generated by brain dysfunction**
- **Affects about 1% of the population**
- **Difficult to diagnose due to the diversity and complexity of epileptic seizures**

Epilepsy



- Types of seizures
 - **Convulsions** – motor seizures: involve tremors, rigidity, loss of balance and consciousness.
 - However, others involve merely subtle changes of thought, mood, or behavior
- Causes
 - Brain damage
 - Faulty Genes – over 70 have been linked so far
 - Faults at inhibitory synapses, particularly GABA where neurons end up just firing in synchronized bursts.
- Diagnosis
 - EEG – **electroencephalogram**
 - Why?.....Seizures are associated with high amplitude EEG spikes during an attack.

Epilepsy



- Some epileptics experience psychological changes before a convulsion – known as auras
 - Such as a smell, hallucination, or feeling
 - Aura's nature suggests the epileptic focus
 - Warns epileptic of an impending seizure
- Once diagnosis is given, it's usual to assign the epilepsy to one of 2 categories:
 - Partial epilepsy – does not involve whole brain
 - Generalized epilepsy – involves the entire brain

Partial Seizures are divided into:



Simple

- Symptoms are primarily sensory or motor or both
- Known as Jacksonian seizures after neurologist Hughlings Jackson
- Symptoms spread as epileptic discharge spreads

Complex

- Often restricted to the temporal lobes (temporal lobe epilepsy)
- Patient engages in compulsive and repetitive simple behaviors (automatisms)
- More complex behaviors seem normal & although conscious they do not have recollection of seizure.

Generalized Seizures can be:

- **Grand mal**

- Loss of consciousness
- Loss of Equilibrium
- Violent Tonic-clonic convulsions
 - Rigidity (tonus)
 - Tremors (clonus)

- **Petit mal**

- Not associated with convulsions
- Instead there is a disruption of consciousness associated with cessation of ongoing behavior
- The EEG of a petit mal seizure is different from other types: it is a bilateral symmetrical 3 per second spike and wave discharge.



Parkinson's Disease



- A movement disorder of middle and old age affecting about .5% of the population (about 2.5 times more prevalent in males).
- Tremor at rest is the most common symptom of the full-blown disorder, muscular rigidity, difficulty initiating movement.
- Shows Cognitive deficits but Dementia is not typically seen
- No single cause (faulty genes, brain damage)
- Associated with degeneration of the substantia nigra; these neurons release dopamine to the striatum of the basal ganglia
- Almost no dopamine in the substantia nigra of Parkinson's patients
- Autopsies often reveal **Lewy bodies** (protein clumps) in the substantia nigra
- Treated temporarily with L-dopa (synthesis of dopamine)
- Linked to about 10 different gene mutations
- **Deep brain stimulation** of **subthalamic nucleus** reduces symptoms, but effectiveness slowly declines over months or years

Multiple Sclerosis



- A progressive disease that attacks CNS myelin, leaving areas of hard scar tissue (sclerosis).
- Typically attacks young individuals.
- It is an autoimmune disorder.
- Nature and severity of deficits vary with the nature, size, and position of sclerotic lesions.
- Periods of remission are common.
- Symptoms include visual disturbances, muscle weakness, numbness, tremor, and loss of motor coordination (ataxia).
- Can include cognitive and emotional change.
- Evidence for genetic and environmental causes – particularly an interaction between the two.
- Role of vitamin D implicated.

Alzheimer's Disease



- **Most common cause of dementia – likelihood of developing it increases with age**
- **Progressive, with early stages characterized by confusion and a selective decline in memory.**
- **Can also involve deficits in attention, personality changes, and as progresses involves irritability, anxiety, deterioration of speech, to such a point where the person cannot do simple things like swallowing or controlling their bladder.**

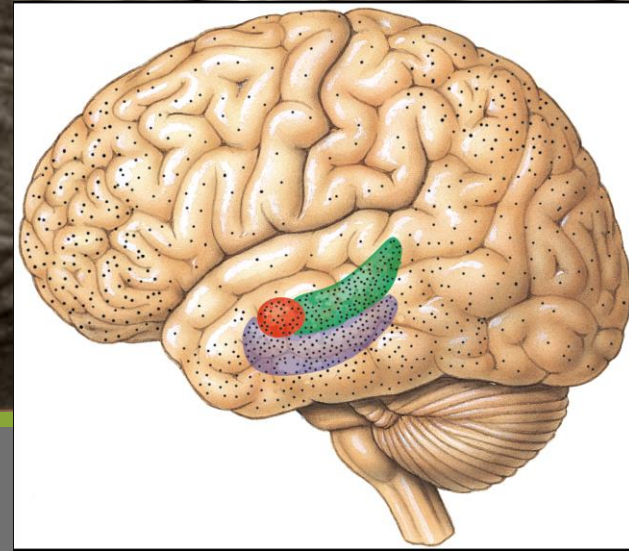
Alzheimer's Disease



- **Definitive diagnosis only at autopsy – must observe neurofibrillary tangles & amyloid plaques.**
 - **Neurofibrillary tangles:** threadlike tangles of protein in the neural cytoplasm
 - **Amyloid plaques:** clumps of scar tissue composed of degenerating neurons and a protein called amyloid
 - **Both are often prevalent in medial temporal lobe structures such as amygdala and hippocampus, which are involved in memory.**
 - **They are also prevalent in the inferior temporal cortex, posterior parietal cortex, and prefrontal cortex, which are involved in complex cognitive functions.**

Alzheimer's Disease

- Thought to have a major genetic component, so research focuses on the rare early onset form with specific gene mutations associated.
- Early-onset AD synthesizes amyloid or tau, a protein found in the tangles.
- Which comes first, amyloid plaques or neurofibrillary tangles? **Genetic research on early-onset AD supports amyloid hypothesis (amyloid first)**
- Decline in acetylcholine levels is one of the earliest signs of AD
- Effective treatments not yet available
 - Immunotherapy (amyloid vaccine) is promising in animal models



Animal Models of Human Neuropsychological Diseases



- Experiments regarding neuropathology are not usually possible with human subjects
- Animal models are often utilized, for example:
- Kindling model of epilepsy
 - Experimentally induced seizure activity
- Transgenic mouse model of Alzheimer's
 - Mice producing human amyloid
- MPTP model of Parkinson's
 - Drug-induced damage comparable to that seen in PD



Kindling Model of Epilepsy



- A series of periodic brain stimulations eventually elicits convulsions: **the kindling phenomenon**
 - Neural changes are permanent - an animal that has been kindled and then left unstimulated for several months can still respond to low levels of stimulation.
 - Produced by stimulation distributed over time
- Convulsions are similar to those seen in some forms of human epilepsy – but they only occur spontaneously if kindled for a very long time
- Kindling phenomenon is comparable to the development of epilepsy (epileptogenesis) seen following a head injury
- Kindling also used to look at behavior between seizures.

Transgenic Mouse Model of Alzheimer's Disease

- **Promising area in Alzheimer's disease research is the development of several transgenic models....**
 - **Transgenic: placing genes of one species in to another.**
- **Only humans & some related primates develop amyloid plaques, therefore.....**
 - **Genes that accelerate the synthesis of human amyloid are injected in to newly fertilized mouse eggs.**
 - **When the mice grow up, their brain will have amyloid plaques like those in human Alzheimer's patients.**
 - **The mice tend to show neural loss & memory disturbances**
 - **Limitation: they do not show up neurofibrillary tangles, which is critical if they are primary symptom in human Alzheimer's disease.**



MPTP Model of Parkinson's Disease



The Case of the Frozen Addicts:

- Main animal model of Parkinson's disease originally came from cases of humans who had taken synthetic heroin which led to irreversible Parkinson's symptoms
- Eventually the synthetic heroin they had taken had been tracked down and the agent within it causing the problem was identified as MPTP.
- MPTP causes cell loss in the substantia nigra, like that seen in Parkinson's Disease.
 - which is the brain's major source of dopamine
 - So, not surprising that dopamine is greatly reduced in the MPTP model.
- Animal studies led to the finding that deprenyl, which is a monoamine agonist that blocks the effect of MPTP in an animal model can slow the progression of PD

Neuroplastic Responses to Nervous System Damage



- **Degeneration – deterioration**
- **Regeneration – regrowth of damaged neurons**
- **Reorganization**
- **Recovery**

Neural Degeneration



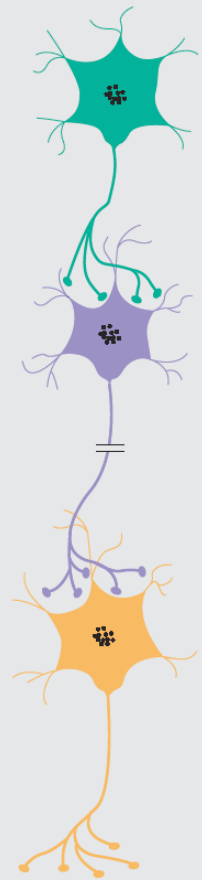
Cutting axons (axotomy) = common way to study response to neural damage

From this 2 types of neural degeneration follow.....

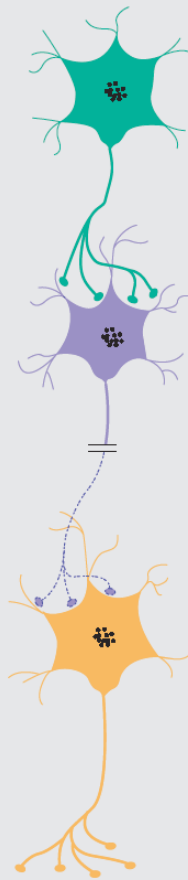
Anterograde: degeneration of the distal segment – between the cut and synaptic terminals

Retrograde: degeneration of the proximal segment between cut & cell body.

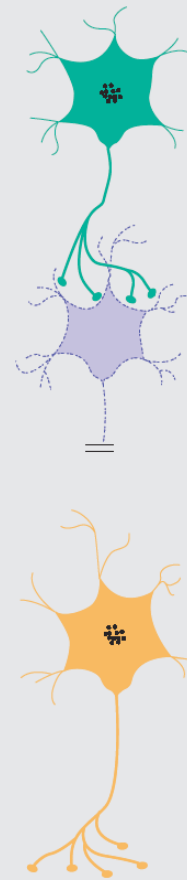
Finally, degeneration can spread from damaged neurons to other neurons linked by synapses: called trans neuronal degeneration



1 Axotomy:
The axon of a neuron is cut.



2 Anterograde Degeneration:
Then, the distal portion of the damaged neuron degenerates.



3 Retrograde Degeneration:
Then, the proximal portion of the damaged neuron may degenerate.



4 Transneuronal Degeneration:
Then, neurons that synapsed on the damaged neuron may degenerate (i.e., retrograde transneuronal degeneration) and so too may neurons on which the damaged neuron synapsed (i.e., anterograde transneuronal degeneration).

Neural Regeneration

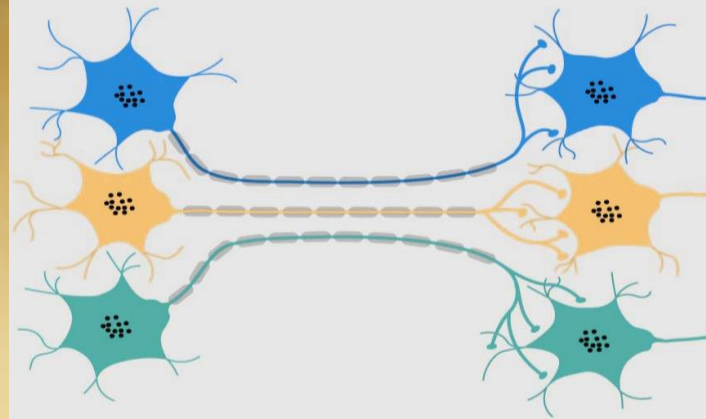
- On the other hand neural regeneration involves the regrowth of damaged neurons.
- Does not proceed successfully in mammals and other higher vertebrates – capacity for accurate axonal growth is lost in maturity.
- Regeneration is virtually nonexistent in the CNS of adult mammals and unlikely, but possible, in the PNS.



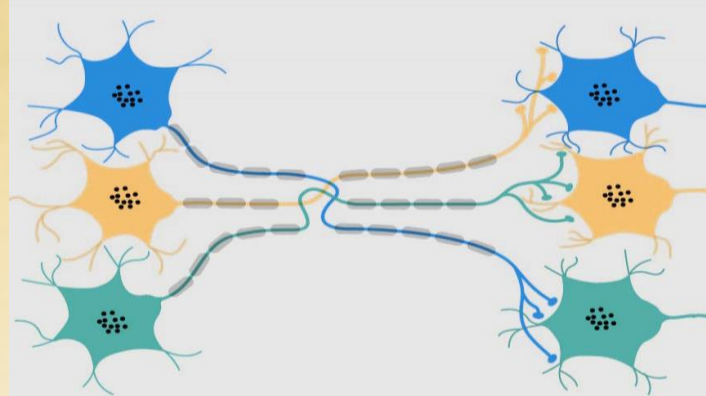
Neural Regeneration in the PNS



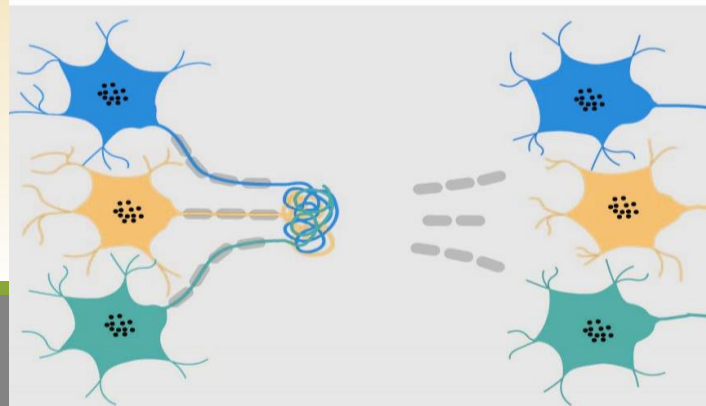
- If the original Schwann cell myelin sheath is intact, regenerating axons may grow through them to their original targets.
- If the nerve is severed and the ends are separated, they may grow into incorrect sheaths.
- If ends are widely separated, no meaningful regeneration will occur.



When a nerve is damaged without severing the Schwann cell sheaths (e.g., by crushing), individual axons regenerate to their correct targets.



When a nerve is damaged and the severed ends of the Schwann cell sheaths are slightly separated, individual axons often regenerate up incorrect sheaths and reach incorrect targets.



When a nerve is damaged and the severed ends of the Schwann cell sheaths are widely separated, there is typically no functional regeneration.

Neural Reorganization



Reorganization of primary sensory and motor systems has been observed in **laboratory animals** following

- Damage to peripheral nerves
- Damage to primary cortical areas

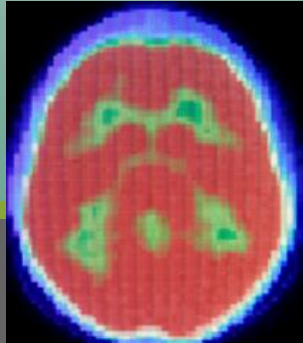
Lesion one retina and remove the other – V1 neurons that originally responded to lesioned area now responded to an adjacent area – remapping occurred within minutes

Studies show large scale of reorganization possible

Cortical Reorganization Following Damage in Humans



- Cortical reorganization in animals prompted research to search for similar effects in humans
- Studies have used brain-imaging to examine the cortices of blind individuals.
- These studies indicate there is continuous competition for cortical space by functional circuits.
- Because there is no visual input to the cortex in those who are blind the auditory and somatosensory cortex therefore expand and info regarding sound or touch is then processed in former visual areas



Mechanisms of Neural Reorganization



- How does this neural reorganization work?
- Two mechanisms have been proposed.....

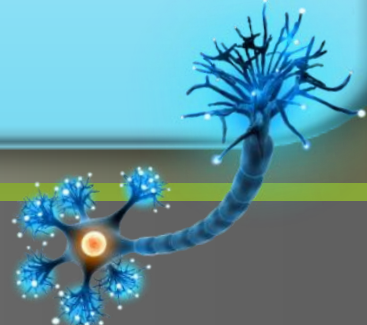
The human brain

1. Strengthening of existing connections

- Support for this comes from 2 observations:
 - A. Reorganization happens too quickly to be explained by new growth
 - B. Rapid reorganization does not involve changes of more than 2 millimeters across the cortical surface.

2. Establishment of new connections

- Indirect evidence from fact that magnitude of long-term reorganization can be too great to be explained by changes in existing connections.



Recovery of Function after Brain Damage

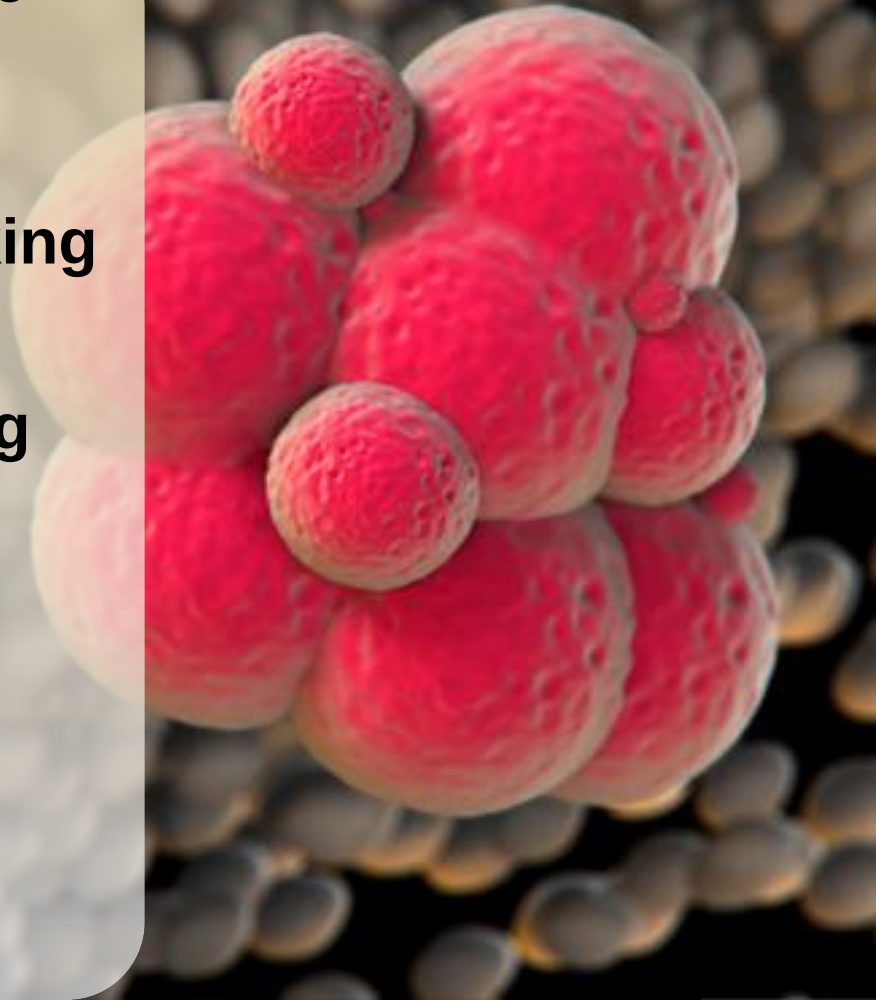


- Difficult to conduct controlled experiments on populations of brain-damaged patients.
- Cannot distinguish between true recovery and compensatory changes of the brain
- Cognitive reserve: the education and intelligence of a patient – thought to play an important role in any observed improvement – may permit cognitive tasks to be accomplished in new ways
- Recovery of function is also complicated by fact that damage to one area can cause widespread changes elsewhere
- Adult neurogenesis may play a role in recovery



Neuroplasticity and the Treatment of Nervous System Damage

- So what sort of treatments can be administered following brain damage?
- Reducing brain damage by blocking neurodegeneration
- Promoting recovery by promoting regeneration
- Promoting recovery by transplantation
- Promoting recovery by rehabilitative training



Reducing Brain Damage by Blocking Neurodegeneration



- **Various neurochemicals can block or limit neurodegeneration**

**Apoptosis
inhibitor protein**

**Nerve growth
factor**

Estrogens

- **Neuroprotective molecules tend to also promote regeneration**

Promoting CNS Recovery by Promoting Regeneration



- While regeneration does not normally occur in CNS, experimentally it can be induced, directing growth of axons by:
 - Schwann cells
 - Olfactory ensheathing cells



Promoting Recovery by Neurotransplantation



- **Transplanting fetal tissue:**

- From donor, then integrated in receivers brain tissue
- Fetal substantia nigra cells have been used to treat MPTP in the monkey model of Parkinson's disease
- Treatment in monkeys was successful
- But limited success with humans

- **Transplanting stem cells**

- e.g. Embryonic stems cells implanted into damaged rat spinal cord
- Once injected they can develop and replace the damaged neurons or myelin.
- Rats with spinal damage had improved mobility

Promoting Recovery by Rehabilitative Training



- Successful in monkeys with a lesion to the hand area of the motor cortex following an induced stroke.
- 5 days after damage, monkey participated in hand training by plucking hundreds of tiny food pellets, which reduced cortical damage in surrounding areas.
- Following this a rehabilitative program called Constraint-induced therapy was created based on the idea that neurons compete with each other for synaptic sites and neurotrophins with the loosing neurons dying.
- The procedure involves tying down functioning arm of a stroke patient for 2 weeks while impaired arm receives intensive training, which creates a competitive situation that leads to recovery from the increase in the area of motor cortex that controls that arm.



Promoting Recovery by Rehabilitative Training

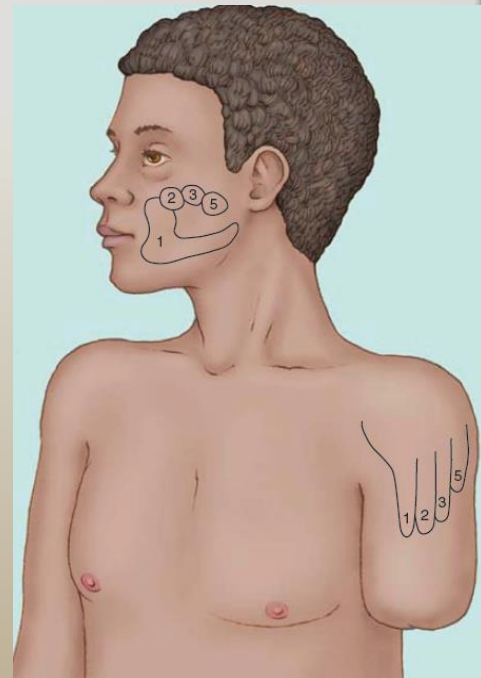


- On this principle the benefits of cognitive and physical exercise have shown:
- Correlations in human studies between physical/cognitive activity and resistance or recovery from neurological injury and disease
- Rodents raised in enriched environments are resistant to induced neurological conditions (epilepsy, models of Alzheimer's, Huntington's, etc.)
- Physical activity promotes adult neurogenesis in rodent hippocampus.



Phantom Limbs: Neuroplastic Phenomena

- Phantom limb: amputees continue to have the experience of limb that has been amputated.
- Ramachandran's hypothesis: phantom limb caused by reorganization of the somatosensory cortex following amputation
- Amputee feels a touch on his face and also on his phantom limb (due to their proximity on somatosensory cortex)
- Amputee with chronic phantom limb pain gets relief through visual feedback: view in mirror intact hand unclenching as seen in mirror box



Next Week....



Drug Addiction and the Brain's Reward

Essential Reading:

Pinel, J. P. J – Biopsychology.
Chapter 15