INTRODUCTION TO NEUROLOGICAL DISEASE

Session #4
Learning in Retirement:
Epilepsy and Phantom Limbs
EPILEPSY
Lesson Overview

- Seizures VS Epilepsy
- What Causes Seizures?
- Types of Seizures
- Epilepsy
- Pathology
  - General
  - Cellular
  - Molecular
- Diagnosis
- Treatment
- Relevance
- Epilepsy Myths
- Sample Questions
Seizures VS Epilepsy

- Epilepsy ≠ Seizure
- Epilepsy describes a condition of the brain that causes seizures
- Seizures are bursts of abnormal, highly synchronous, electrical activity in the brain
- This abnormal activity leads to alterations in consciousness, and often convulsions as well (involuntary muscle spasms)
- Seizures:
  - Come on suddenly
  - Vary in duration and severity
  - May occur only once, or be a recurring event
What Causes Seizures?

- The brain is most susceptible to seizures when it is inactive and in times of transition (i.e. sleep → wake)
- About 50% of seizures are symptomatic, or have a known, specific cause
  - Tumour (accounts for 10% of all seizures)
  - Infection
  - Trauma
  - Toxic Chemicals
  - Drugs
- About 50% of seizures are idiopathic, or have no known cause
  - Appear spontaneously in the absence of identifiable CNS disease
Types of Seizures

• Several factors may **precipitate** a seizure
  • E.g. drugs, emotional stress, fever, hormonal changes, hyperventilation, sleep deprivation

• Two major groups of seizures, which differ in how/where they start

• **Focal onset seizures** start at a precise spot (at a focus) on one side of the brain, then may (or may not) spread to surrounding regions

• **Generalized onset seizures** affect both sides of the brain (or groups of cells on both sides) at the same time

**Focal onset seizures** may or may not affect awareness, while **generalized onset seizures** always involve impaired awareness.
Focal Onset Seizures

- **Focal onset seizures** can be further classified based on individual’s awareness
  - **Aware**: person is awake and aware during seizure; usually remembers/has some idea what happened
    - Usually involves small area of the brain
    - Patient may experience strange sensations (i.e. strange odours), but may also involve jerking movements (if neurons affecting muscle groups are affected)
    - Usually unilateral (wouldn’t typically cause fall)
  - **Impaired awareness**: person is confused/awareness is otherwise impaired during seizure
Generalized Onset Seizures

- **Bilateral**: involve both hemispheres

- Focal onset seizures can also quickly become generalized seizures (if this occurs, called **focal onset bilateral** seizure)

- Types of generalized seizures:

<table>
<thead>
<tr>
<th>TONIC</th>
<th>CLONIC</th>
<th>MYOCLONIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>- muscles become stiff/flexed</td>
<td>- violent muscle contractions (convulsions)</td>
<td>- small muscle twitches</td>
</tr>
<tr>
<td>- person may fall (backward)</td>
<td></td>
<td>- short, but can be many in a short period of time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATONIC</th>
<th>TONIC-CLONIC</th>
<th>ABSENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- muscles become limp</td>
<td>*most common type of generalized seizure</td>
<td>- period of impaired awareness or consciousness (only observable sign is that person appears ‘spaced out’)</td>
</tr>
<tr>
<td>- person may fall (forward)</td>
<td>- tonic phase followed by clonic phase</td>
<td></td>
</tr>
</tbody>
</table>

- **TONIC-CLONIC**: *most common type of generalized seizure* - tonic phase followed by clonic phase
Epilepsy

- **Epilepsy** is a seizure disorder
- Patients with epilepsy have unpredictable and recurring seizures
- Someone is said to have epilepsy if they have two or more unprovoked seizures separated by at least 24 hours
  - OR
- After experiencing one seizure with high risk for experiencing more
Pathology: General

• Highly synchronous electrical activity (of neurons) in the brain
• Can begin at a focus or be widespread
• Symptoms vary (as discussed, many types of epilepsy), and depend on seizure severity and location, and which neurons are affected
• Clusters of neurons temporarily become impaired, and begin sending out massive amounts of excitatory signals over and over
Pathology: Cellular

- In epilepsy, too much excitation or too little inhibition is allowing neurons to fire excessively.

- Ion channels opening and closing (and thus allowing ions to pass through) determines whether or not a neuron will depolarize.

- If a neuron depolarizes, it releases NTs – when these bind to their post-synaptic Rs, they will either promote or inhibit the opening of the ion channels:
  - Glutamate promotes (by allowing Ca\textsuperscript{2+} ions to enter pre-synaptic neuron).
  - GABA inhibits (by allowing Cl\textsuperscript{-} ions to enter pre-synaptic neuron).
Pathology: Molecular

- **NMDA receptors** are the primary receptor type that glutamate (excitatory) binds to; when Glu binds to NMDA receptor, Ca\(^{2+}\) open, which tells neuron to fire
  - Some patients with epilepsy have fast or long-lasting activation of NMDA receptors

- **GABA receptors**, when activated, allow Cl\(^-\) ions to enter the cell, which leads to hyperpolarization
  - Some patients with epilepsy have **genetic mutations** that render their GABA receptors dysfunctional (cannot inhibit signals)

Important: Both NMDA and GABA receptors may be influenced by things like infection, brain tumour, or trauma. Neurological exams and brain imaging used to help clarify cause of seizure
Diagnosis

- **Electroencephalogram (EEG)** is the most common test used to diagnose epilepsy.

- Electrodes placed on the patient’s scalp record electrical activity of neurons.

- Even when not having a seizure, individuals with epilepsy generally show abnormal patterns of neural activity.

- **High-density EEG** is a variant of EEG that spaces electrodes much closer together – used to help localize seizure activity more precisely.

- **Neurological exam** and medical history helps determine type of epilepsy.

- **Blood Tests** help identify infections, genetic conditions/other conditions that may be causing seizures.
Treatment

- **Anti-epileptic medications**: most people with epilepsy are able to live seizure-free by taking one anti-epileptic medication.
- Others may be able to reduce the frequency and severity of their seizures by taking a combination of medications.
- If medication isn’t doing it, doctor may recommend surgery to remove affected area (if it is a small, focal region).
- Nerve stimulation – **vagus nerve** (thought to influence NT release), helps in 20-40% of cases.
- In extreme cases of widespread and severe seizures that do not respond to anti-epileptic medications, **callosotomy** may be considered.
Treatment

- Anti-epileptic medications come in 3 main categories (all are **anti-convulsants**)

1) **Na⁺ and Ca²⁺ channel inhibitors**
   - Reduces inward positive current
   - Prevents NT release

2) **Drugs that increase GABA activity**
   - Increases inhibition (promotes hyperpolarization of neuron)
   - Receptor agonists
   - Breakdown inhibitors

3) **Drugs that decrease glutamate activity**
   - Decreases excitation (inhibiting depolarization)
   - Receptor antagonists
Relevance

• Although genetic factors have been identified in some cases of epilepsy, the majority of cases are idiopathic.
Epilepsy Myths

• You can swallow your tongue during a seizure
  • It is physically impossible to swallow your tongue

• You should force something into the mouth of someone having a seizure
  • No!! Roll individual on side, place something soft under head to prevent injury

• You should restrain someone who is having a seizure
  • Never. Seizure will run its course and cannot be stopped
Sample Question 1:

• NAME THAT TYPE OF EPILEPSY!

• Joey has epilepsy. His seizures involve his muscles going completely limp, and he falls forward to the ground.

• Based on Joey’s symptoms, what would you name this type of epilepsy?

Name of Epilepsy = Onset Type + Symptoms Observed

• Generalized onset
• Symptoms: Atonia

Generalized Onset
Atonic Seizure
Sample Question 2:

- NAME THAT TYPE OF EPILEPSY!

- Roman has epilepsy. When he experiences a seizure, he stays awake and usually remembers what has happened.

- Based on Roman’s seizures, what would you name this type of epilepsy?

Name of Epilepsy = Onset Type + Symptoms Observed

- Focal onset (generalized always involves impaired awareness)
- Symptoms: Recall of events (awareness)

Focal Onset Aware Seizure
Sample Question 3:

• NAME THAT TYPE OF EPILEPSY!

Sally has epilepsy. When she experiences a ‘fit’, it always occurs the same way. First, she smells a strange odour and sometimes other odd sensations. Then, her muscles first stiffen, causing her to fall backward. Finally, she experiences 30-60 seconds of convulsions.

Based on Sally’s symptoms, what would you name this type of epilepsy?

Focal Onset Bilateral Tonic-Clonic Seizure

Name of Epilepsy = Onset Type + Symptoms Observed

• Focal onset (strange sensations)
• ...becomes generalized (so we don’t worry about classifying awareness): ‘Bilateral’
• Symptoms: Tonic, then clonic (tonic-clonic)
PHANTOM LIMBS
Lesson Overview

- Neuroplasticity
- Phantom Limbs
- V.S. Ramachandran – TED Talk
  - Capgras Syndrome
  - Phantom Limbs
  - Synesthesia
- Phantom Limb Pathology
  - General
  - Cellular
  - Molecular
- Treatment and Relevance
Neuroplasticity

• Describes the brain’s ability to reorganize itself by forming new neural connections
• Allows neurons to respond to changes and adjust their activity in response to new situations or changes in the environment
• Gives the brain a way to _____________ for dysfunction caused by disease or injury
Neuroplasticity

• “Neurons that wire together, fire together” – Donald Hebb

• Neural networks are like roads – the thoughts, emotions and behaviours we engage in often (our habits) are like well-traveled roads

• Each time we think a certain way/feel a certain emotion/perform a certain task, that path/road gets strengthened
Phantom Limbs

- Following the loss of a limb, many people experience vivid sensations where the limb used to be, as if it were still there.
- Some can voluntarily move this ‘phantom limb’, while in others, it is paralyzed.
- For many, the paralyzed phantom can be very painful (e.g. fist clenched, nails digging into palm, muscle spasms, unable to relieve).
- V.S. Ramachandran is a famous neuroscientist who is known for his work in behavioural neurology – notably, for his work in patients with phantom limb pain.

- Phantom limb pain is a sensation of pain that feels like it’s coming from a body part that is no longer there.
Phantom Limb Pain

- Phantom limb pain is just one example of a real sensory experience produced by the brain’s adaptation to its environment
  - The cause(s) of phantom limb pain are unclear
  - One hypothesis is that since the brain and SC no longer receive sensory input from the limb, they may react in unpredictable ways – and send the basic ‘something is not right here’ signal = PAIN.

- V.S. Ramachandran believes that individuals who can voluntarily move their phantom limb can do so because signals are sent from the motor cortex to the phantom limb, telling it to 'move!'

- Over time though, the limb becomes paralyzed, because no visual or proprioceptive feedback to show that commands to 'move!' are being obeyed

- In 2011, *Time* magazine listed V.S. Ramachandran as one of the most influential people in the world on the “Time 100 List”
Phantom Limb Pain

- Cortical remapping can occur in the sensory homunculus following amputation of a limb.

- Areas adjacent to the limb may ‘take over’, and patients may feel as though their *phantom limb* is being touched when their *cheek* is touched, for example.

- Since this represents another scenario of ‘tangled wires’, the result can be pain.

- This is an example of *maladaptive plasticity*.
TED Talk – V.S. Ramachandran 😍
Pathology: General

- Severed nerves in the periphery cause changes in the CNS
  - E.g. Cortical remapping, efferent motor commands with no visual/proprrioceptive feedback

- Other factors are thought to contribute to pain, including damaged nerve endings and scar tissue at site of amputation

- Memory of painful limb pre-amputation may also contribute to phantom limb pain – a well traveled ‘road’ if arm was immobile/painful for any length of time
Pathology: Cellular

- Cortical remapping involves **synaptic plasticity**
- Compensatory axonal sprouting/reinnervation
- Centrally, this refers to regions of the somatosensory cortex taking over region where limb was previously represented on homunculus
- Peripherally, this could contribute to heightened sensations of pain (reinnervation of stump)

*Nature Reviews Neuroscience (2006)*
Pathology: Cellular

- Cortical remapping involves **synaptic plasticity**
- **Long-term potentiation:** Describes a persistent increase in synaptic strength due to increased activity between neurons
  - Opposite is **long-term depression**, an activity-dependent reduction in the efficacy of synapses
- Neurotransmitter changes
  - Changes in numbers of receptors
  - Changes in quantities of NT released
- In the context of memory – good!
- Bad in the context of pain 😞

**LTP: An illustration**

1. A synapse is repeatedly stimulated
2. ↑ dendritic Rs
3. ↑ NTs
4. Stronger link between neurons
Pathology: Molecular

• Disinhibition of SC
  1 – Decreased activity of GABA and glycine in SC
    • Neurons using GABA and glycine may be damaged as a result of axotomy
  2 – Increased sensitivity of N-methyl-D-aspartate (NMDA) receptors to the NT glutamate
    • Caused by inflammation
    • Abnormal firing → pain sensation
    • This combination results in SPINAL HYPEREXCITABILITY

• Cortical Changes
  • Complex, and under investigation

Without proper inhibition, neurons in the SC can go wild
Phantom Limb Pain: Treatment

• Generally, multi-modal

  • Primarily **pharmacotherapy**
    • Analgesics, antidepressants, anti-convulsants, glutamate antagonists

  • Behavioural therapies/Combinations of medical and **neurobehavioural techniques**
    • Mirror therapy
    • Acupuncture
    • Massage
Relevance

- Therapies like the mirror-box can change lives – people previously debilitated by pain can function once more.

- Research done by V.S. Ramachandran and others shows us that the mere visual feedback provided by a mirror can relieve a spasm in a non-existent limb.

- Information saying phantom limb is moving travels through visual systems to somatosensory areas of brain, and with enough practice, the phantom limb can even be successfully ‘amputated’ – this is pretty incredible.