Topic 8 – Motor Neuron Disorders
& Spinal Cord Injury

1. Terminology
2. "Upper motor neuron" injury
3. Mechanisms of damage
4. Some disorders

Motor System Disorders - Terminology

• Muscle Strength
  • Paralysis / Paresis
  • hemi-, para-, or tetra (quad)- plegia

• Muscle Bulk
  • atrophy – disuse or neurogenic

Motor System Disorders - Terminology

• Upper motor neurons
  • Originate in "higher" regions of brain such as motor cortex
  • Corticospinal tract

• Lower motor neurons
  • Directly innervate skeletal muscles

Motor System Disorders - Terminology

• Hypotonia - abnormally low resistance to stretch
  • cerebellar disorders
  • LMN lesions
  • acute UMN lesions

• Hypertonia - abnormally strong resistance to stretch
  • chronic UMN lesions
  • 2 types = spastic and rigid

Motor System Disorders - Terminology

• Spastic Hypertonia
  • resistance to passive movement is velocity sensitive

• Rigidity
  • resistance to passive movement remains constant regardless of velocity
  • Decorticate / Decerebrate

Decerebrate Rigidity
Decerebrate - upper brainstem or lower midbrain

Decorticate - severe lesion superior to midbrain

Overall muscle tone is determined by
1. Intrinsic elastic properties of muscle
2. Neural input

Decorticate Rigidity

Topic 8 – Motor Neuron Disorders & Spinal Cord Injury
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Stretch reflex -
- contraction in response to lengthening
- receptor is muscle spindle (Ia afferent fiber)
- descending pathways modify gain of reflex
Hoffmann Reflex

- stimulate Ia afferents (and motor neurons)
- measure "M-wave" and "H-wave" using EMG

"Spinal shock" -
- Complete absence of reflexes
- Maybe from sudden withdrawal of descending input
- Reflexes recover (weeks – months) and become oversensitive…

"Hyperactive" reflexes
- 'spasm-like' muscle bursts in response to mild stimuli
- Loss of descending inhibition
- Increased resistance to stretch -
  - Velocity-dependent hypertonia

Treatment -
- administration of baclofen to spinal cord
- GABA B receptor agonist
- inhibition of synapse between Ia fibers and motor neurons

Babinski’s Sign
- stroking across plantar surface of foot normally causes flexion of toes
- Upper motor neuron damage can reverse this response

Summary of "UMN" Injury Effects

<table>
<thead>
<tr>
<th>Trauma</th>
<th>Lack of descending inhibition</th>
<th>Lack of descending excitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased tone and reflexes</td>
<td>Modified segmental relations</td>
<td>Weakness</td>
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<tr>
<td>Spasms</td>
<td>Impaired voluntary motor control</td>
<td></td>
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<tr>
<td></td>
<td>Coordination</td>
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</tbody>
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**Topic 8 – Motor Neuron Disorders & Spinal Cord Injury**

1. Terminology
2. ”Upper motor neuron” injury
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4. Some disorders

**Primary Injury –**
mechanical damage to neuronal apparatus

**Secondary Injury –**
occurs over hours post-injury

---

**Glutamate - Excitotoxicity**

- GLU binds to R and opens Na⁺ channels
- ↑ Na⁺, draws water into the cell = edema
- ↑ Ca²⁺, activates proteases, lipases that degrade components of cell, may initiate apoptosis

**Neuroprotective strategies**

- block glutamate receptors
- antioxidants
- block Na⁺ channels

---

**Na⁺ Channel Blockers**

BBB = measure of locomotor function

- Riluzole
- Control

**Na⁺ Channel Blockers**

• effects on integrity of descending spinal tracts

---


**Na⁺ Channel Blockers – Tissue Loss**

![Graph showing Na⁺ Channel Blockers – Tissue Loss](source)


**Wallerian Degeneration**

**Axotomy - transection of the axon by cutting or crushing**

Can result in degeneration of pre-/post-synaptic cells and glia.

![Wallerian Degeneration](source)


**Possible Therapies**

- Regeneration of damaged axons
- Remyelination – Schwann cell transplants
- Cell replacement – stem cells

**Topic 8 – Motor Neuron Disorders & Spinal Cord Injury**

1. Terminology
2. "Upper motor neuron" injury
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**Poliomyelitis**

- poliovirus
- acute infection of ventral horn of spinal cord
- Selectively destroys lower motor neurons – denervates muscle

![Poliomyelitis](source)

Poliomyelitis

Amyotrophic Lateral Sclerosis (ALS)
- degeneration of "upper" and "lower" motor neurons
- neurogenic atrophy of muscles
- correlated with mutation in chromosome 21

Multiple Sclerosis

Axonal Conduction Block
- normally, voltage gated K+ channels are present in the internodes and v-g Na+ channels are densely packed in region of node
- after demyelination, electrical properties of axon change
- Conduction slows or may become blocked

End of topic 8

Topic 9 - Parietal Association Cortex
1. Sensory-to-motor transformations
2. Activity in parietal association cortex and the effects of damage
**Sensory to Motor Transformation**

Sensory information (visual, somatosensation etc.) is integrated and used to generate an appropriate motor output.

**PPC association area**

- PPC is neither purely sensory nor purely motor ("association cortex")
- Important for integration of sensory information
- Sends information to motor areas (e.g. premotor and M1)
- Important for "sensory-to-motor" transformation

**Cells have "preferred postures"**

- Provides info about how body segments are positioned

**Topic 9 - Parietal Association Cortex**

1. Sensory-to-motor transformations
2. Activity in parietal association cortex and the effects of damage

Source: MacKay, Neuro 101, Sefalotek Ltd., 1999

Visual information is also important

General Take-Home Message!

PPC is involved in transforming sensory cues into info regarding:
- the locations of objects in the environment
- the location of our limbs in the environment
- relative location of body segments

→ helps provide a "reference frame" for the world around us.

Lesions of parietal association cortex produce complicated deficits...

Astereognosis
- inability to recognize objects by touch alone

Personal neglect syndrome
- lack of awareness of a body part
Optic Ataxia
"dorsal" and "ventral" streams

Dorsal stream
Optic Ataxia
Primary visual area (V1)
Ventral stream


Optic Ataxia
The inability to accurately reach for visible objects

Ideomotor Apraxia
Loss of ability to perform previously learned motor tasks

Dorsal vs. Ventral Streams

Dorsal vs. Ventral Streams

Disorders in Action and Perception

Milner & Goodale, 1995
Ventral Stream

- Object identification
- Relational metrics
- Long term representation
- ‘Conscious’

Dorsal Stream

- Visual control of motor output
- Absolute metrics
- Moment-to-moment computations
- ‘Unconscious’


Why study lesions?

Advantages

- Provides insight into normal functioning of the brain.
- Tells you which areas are necessary for which functions

Disadvantages

- Lesions are rarely focal


PPC Functions

- Sensori-motor integration
- Early, abstract planning of movements
- Attention
- Language

Neglect

- Mostly found with right lesions in the IPL.
- May be in the superior temporal cortex – site in monkeys that is associated with spatial awareness.
- Some subcortical damage: basal ganglia and thalamus.

Neglect

- Lack of awareness of personal and extra-personal space contralateral to lesioned hemisphere, e.g.
  - patient may believe the left side of body is someone else’s.
  - patient eats only the food in the right half of plate.
  - patient may only dress or shave on side.

Neglect

- Attention Deficits

Yves Rossetti, INSERM 534, France

Neglect

Mattingley et al., Brain, 1992

Neglect

- Visuo-motor deficits.

Yves Rossetti, INSERM 534, France
Neglect

- Extinction

- Anosognosia- The loss of recognition or awareness of a disease.
  - Most people with neglect are also unaware that they have the disorder.

Balint’s syndrome

- Visuomotor and visuospatial disorders
- Bilateral damage to posterior parietal lobes
  - Simultanagnosia – inability to interpret the visual field as a whole
  - Ocular apraxia – deficit of visual scanning
  - Optic ataxia – inability to reach accurately under visual guidance

Simultanagnosia

- Difficulty copying/drawing/writing because they can’t see the end of the pen and what is on the paper at the same time.
- Spatial disorientation: unable to discern spatial properties of objects e.g. distance and size.
- Difficulty describing complex scenes (e.g. Boston cookie theft)
Ocular Apraxia

- Impaired visual scanning (moving the eyes voluntarily)
  - Not an oculomotor deficit
  - Reflexive movements are spared
  - Eye movements toward auditory stimuli are spared
  - Gaze restricted to narrow band, right of midline (similar to neglect)

Optic Ataxia

- Visuomotor deficits - errors in visually-guided movements
  - No other perceptual or motor deficits
  - Two types of optic ataxia patients

Unilateral Optic Ataxia

Bilateral Optic Ataxia

Vighetto, 1980

Healthy Field

Ataxic Field

Vighetto, 1980

Healthy Field

Ataxic Field

Vighetto, 1980
Unilateral Optic Ataxia

Optic Ataxia
Bilateral Optic Ataxia

Bilateral Optic Ataxia

Optic Ataxia Patient

Bilateral Optic Ataxia

Immediate

Delayed


Milner et al., 1999; 2001; 2003

IT Functions

- Object perception, recognition, memory
- Face perception
Visual Agnosia

- Inability to recognize objects from sight
- Deficient shape perception
- Famous case D.F.
  - Can’t recognize or copy drawings of common objects (such as an apple or a key) but can draw from memory
  - Can’t estimate size, distance of objects

Prosopagnosia

- Inability to recognize faces by sight,
  - Even themselves
  - Can by recognize by voice
- Can recognize faces as faces and name parts
- Can discriminate faces (tell two faces apart)
  - Based on feature comparison not global recognition

Summary

Dissociation between ventral and dorsal streams

**Parietal Damage**

- Can recognize objects
- Can judge relative distance, size
- Cannot make accurate visual guided actions e.g. saccades, pointing, grasping
- Lack of attention of space

**Inferior Temporal Damage**

- Cannot recognize objects, faces
- Cannot judge relative distance, size
- Can make accurate visually guided action (taking shape into account)
- Aware of space

End of Topic 9

Topic 10 - Basal Ganglia

1. Motor circuit of BG
2. Disorders
The Basal Ganglia
- group of subcortical nuclei (4 main parts)
- influence movement by modulating activity in "upper motor neurons"

1. Striatum (caudate and putamen),
2. Globus Pallidus (external and internal segments),
3. Substantia Nigra (pars compacta and pars reticulata),
4. Subthalamic nucleus

Input to Basal Ganglia -
From most of cerebral cortex (and other regions)
--> to striatum - i.e caudate and putamen (main input areas)

Output from Basal Ganglia
To motor areas via the thalamus
--> from Globus Pallidus (int.)
and
To eye mvt areas of brainstem
--> from substantia nigra (pars reticulata)

BG Circuits
Multiple loops between cortex and basal ganglia -
1. Motor - voluntary movements
2. Limbic - "emotional behaviour"
3. Executive - "cognitive processes"

Motor Circuit
- Involved in initiation of voluntary movements
- Motor circuit has a general somatotopic organization throughout projections

Tonic inhibitory outflow from BG -
- During rest, BG continuously inhibit motor areas (tonic)
**Tonic inhibitory outflow from BG**
- During rest, BG continuously inhibit motor areas (tonic)
- This inhibition must be removed before movements can be initiated
- 2 main pathways ("Direct" and "Indirect" - from striatum to output nuclei) within the BG modulate tonic inhibitory output

**"Direct" and "Indirect" pathways**
2 main groups of projection neurons in striatum
- one group projects to GP(int) and SN pars reticulata
  - = direct pathway (decreases tonic inhibitory output from BG)
- other group projects to GP(ext)
  - = indirect pathway (increases tonic inhibitory output from BG)

**"Direct Pathway" disinhibits the thalamus which facilitates movement**
--> from striatum to GP(int)

**Disinhibitory circuit of direct pathway**

**"Indirect Pathway" further inhibits thalamus (inhibits movement)**

**Dopaminergic input from SN(po) decreases inhibitory output from BG**
--> inhibits indirect & excites direct pathway
--> differential effects of DA (because of different R types)
Topic 10 - Basal Ganglia

1. Motor circuit of BG

2. Disorders

Hypokinesia
- decrease in the amount and speed of movements

Hyperkinesia
- unwanted movements

Parkinson's Disease
- Cell death in substantia nigra (unknown cause)
- Loss of dopamine
- Disrupts normal modulations of BG output

Parkinson Disease
Loss of dopamine-producing cells in SNc
- Akinesia – difficulty initiating movement voluntarily
- Bradykinesia – once started, movements very slow
- Resting tremor in distal limbs (4-6 Hz) from oscillator properties of pallidal cells

Loss of acetylcholine-producing cells in pedunculopontine nucleus
- Rigidity - unable to inhibit reticulospinal and vestibulospinal tracts

PD Treatments - Pallidotomy

**PD Treatments - STN lesion**

Parkinson's Disease (hypokinetic)

- Degenerated Substantia nigra pars compacta
- Increased Striatal to external segment
- Diminished Caudate/pallidum
- Increased Subthalamic nucleus
- Increased Tonic inhibition
- Decreased excitation

**PD Treatments - L-DOPA (Dopamine precursor)**

Parkinson's Disease (hypokinetic)

- Degenerated Substantia nigra pars compacta
- Increased Striatal to external segment
- Diminished Caudate/pallidum
- Increased Subthalamic nucleus
- Increased Tonic inhibition
- Decreased excitation

**PD Treatments - Deep Brain Stimulation**

Huntington's Disease

- Preferential loss of striatal neurons comprising the indirect pathway (neurons from striatum to external segment of GP)
- Hyperkinetic

**Huntington's Disease**

- Preferential loss of striatal neurons comprising the indirect pathway (neurons from striatum to external segment of GP)
- Hyperkinetic
Hemiballism
uncontrolled, involuntary flinging of limbs on side contralateral to lesion
STN lesion - stroke
↓ output of Gpi

End of Topic 10

Topic 11 – Cerebellum

1. Theories of Function
2. Neuroanatomy
3. Basic circuitry and dysfunction

Cerebellum - Introduction

Cerebellum - Multiple Roles in Voluntary Movement
- Timing and spatial accuracy of movements
- Motor learning
  - acquisition new motor skills
- "Comparator"
  - compares sensory feedback with intended movement (receives a copy of the intended "motor plan" in the form of "efference copy").

Cerebellum - Introduction

- Approx 10% of total brain volume
  - But contains about half of brain's neurons!
- Can remove cerebellum without loss of perception or muscle weakness.
- Regulates movement indirectly by adjusting output of major descending motor systems
Topic 11 – Cerebellum

1. Theories of Function
2. Neuroanatomy
3. Basic circuitry and dysfunction

Anatomy

- 2 hemispheres divided by vermis
- 3 lobes – anterior, posterior, flocculonodular
- Cerebellar cortex over white matter

Connected to brain stem through 3 peduncles

- Superior – output to cortex via thalamus
- Middle – input/output via pons
- Inferior – input/output with brain stem/spinal cord

Functional Organization

1. Fastigial
2. Interposed (globose and emboliform)
3. Dentate

Cerebrocerebellum (lateral hemisphere)

Spino cerebellum (vermis and intermediate)

Vestibulocerebellum (flocculonodular lobe)
**Functional Organization**

Most output from cerebellar cortex goes through a deep nucleus - All connections are inhib. (GABA):
- Cerebrocerebellum -> dentate
- Spinocerebellum -> interposed, fastigial
- Vestibulocerebellum -> lateral vestibular nucleus

**Somatotopic maps in cerebellum**

Different parts of cerebellar cortex are concerned with different parts of body.

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**Topic 11 – Cerebellum**

1. Theories of Function
2. Neuroanatomy
3. Basic circuitry and dysfunction

---

**Basic circuitry -**

All output from cerebellar cortex (to deep nuclei) is via Purkinje cells - inhibitory (GABA)

**Afferent input:**

1. **Mossy fibers**
   - synapse directly with deep cerebellar nuclei
   - synapse indirectly with Purkinje cells via granule cell parallel fibers
2. **Climbing fibers**
   - synapse directly with deep cerebellar nuclei and Purkinje cells

**Cerebellar cortex**

- Parallel fiber
- Purkinje cell
- Granule cell
- Molecular layer
- Deep cerebellar nuclei
- To thalamus (motor cortex)
### Complex / Simple Spikes

- **Mossy Fibers** – result in simple spikes
- **Climbing Fibers** – result in complex spikes

(Intracellular recordings from Purkinje cells)

*Source: Kandel et al., Principles of Neural Science, McGraw Hill, 2000*

### Interneurons modulate inhibitory activity of P-cells

- Golgi cells
-stellate cells
-basket cells

This "Basic circuit" is repeated throughout the cerebellum.

*Source: Kandel et al., Principles of Neural Science, McGraw Hill, 2000*

### Purkinje Cells as “Relaxation Couplers”

Circuitry enables temporal control of output (i.e. Coordination)

*Source: MacKay, Neuro 101, Sefalotek Ltd., 1999*

### Cerebellar Ataxia

- lack of coordination among limb / body segments

*Source: Kandel et al., Principles of Neural Science, McGraw Hill, 2000*
End of Topic 11

Topic 12 - Premotor Cortex

1. General
2. Medial regions
3. Lateral regions

Premotor Cortex

Premotor areas - Introduction
- Concerned with planning movements
- active during preparation of movement
- uses info from other regions to select movements appropriate to context of a required action
- extensive connections with M1 and direct projections to spinal cord

- a set of interconnected areas in the frontal lobe (rostral to M1)
- divided into "lateral" and "medial" regions


Topic 12 - Premotor Cortex

1. General

2. Medial regions

3. Lateral regions

Medial premotor areas
- Supplementary motor area (SMA)
- Cingulate motor areas (CMA)

Source: http://www.driesen.com/secondary_motor_cortex.htm
SMA is involved in performing learned sequences of movements


Damage to SMA interferes with movement sequence production

Source: Getzke et al. (2003) Neuropsychologia. 40: 1364-1404

SMA and Basal Ganglia are highly interconnected


Patients with BG damage have trouble performing sequences of movements.


"Pre-SMA" is involved in learning motor sequences

Source: http://www.med.tohoku.ac.jp/room/124/english.html

Cingulate Motor Areas (CMA)
CMA may be involved in the "emotional" aspects of movements

Topic 12 - Premotor Cortex
1. General
2. Medial regions
3. Lateral regions

Lateral Premotor Cortex

Medial areas - internally initiated movements
Lateral areas - externally cued movements

Dorsal premotor area (PMD)
- Involved in learning associations between a particular sensory input and a specific motor output.
- Role in selection of action based on learned associations.

Subjects had to learn correct associations between different colour cues and hand postures.

Patients with frontal lesions (incl. PMd) could not learn associations as well as controls.

PMv is involved in choosing hand shapes appropriate for a given task.

Mirror Neurons in PMv
- Respond when animal performs an action or views the same action being performed by another.

End of Topic 12

Topic 13 - Cortical Networks
1. Subcortical White Matter
2. Cortical networks for movement

Source: http://www.pbs.org/wgbh/nova/sciencenow/
Functional regions of the brain don't work independently of one another.

- Different regions work together in cortical networks.

Subcortical White Matter

3 categories of white matter fibers:

1. Projection
2. Association
3. Commissural

Projection – between subcortical & cortical

Almost all projection fibers travel through the internal capsule.

Association – between cortical regions within one hemisphere

- Short association fibers ("U" shaped fibers)
- Long association fibers
Commissural – between hemispheres

Connect homologous areas of the cerebral hemispheres.

Commissural fibers
Corpus callosum

Anterior commissure

Source: Lundy-Ekman, Neuroscience: Fundamentals for Rehabilitation, Saunders, 2002

Commissural – between hemispheres

Corpus Callosum, body
Corpus Callosum, genu
Corpus Callosum, splenium
Corpus Callosum, rostrum
Anterior commissure
Posterior commissure

Source: http://retina.anatomy.upenn.edu

Topic 13 - Cortical Networks

1. Subcortical White Matter

2. Cortical networks for movement

Disruption of connections between homologous areas can lead to deficits in motor control.

Source: Lundy-Ekman, Neuroscience: Fundamentals for Rehabilitation, Saunders, 2002

"Alien Hand Syndrome" - Involuntary but seemingly purposeful unilateral limb movements
- Sometimes observed after damage to corpus callosum and medial motor areas

"Corpus Callosotomy ("split brain")"
6 months post-stroke: - left medial frontal lesion extending into corpus callosum

The "Dual Premotor systems" Hypothesis:
Lateral Premotor regions - externally cued movements
Medial Premotor regions - internally-generated movements
Alien Hand Syndrome may result from imbalance between lateral and medial premotor systems

Medial areas - internally initiated movements
Lateral areas - externally cued movements

"Left hand apraxia" after CC lesion
- Can't pantomime object use from verbal command or visual presentation of object.
Lateralization of function (ie. localization of a function to the left or right side of brain) could be a factor in production of this deficit.

Evidence of Lateralization in Motor Areas e.g. M1
- Right M1 is mainly activated during movement of left hand
- Left M1 is activated during movement of either hand (regardless of handedness)
Other examples of lateralization in motor regions -

- Left-brain dominance for motor planning?
- Lateralization during performance of complex sequences in premotor and parietal regions?


Importance of Parieto-Frontal Connections

Premotor regions select behaviours and muscle synergies based on information supplied by posterior half of the brain

→ this info is used by premotor regions to relate target to body position in order to act on it

→ premotor regions also integrate cognitive information (last lecture), rules for movement

Regions within the Intraparietal Sulcus (IPS)

VIP = ventral intraparietal area
MIP = medial intraparietal area
AIP = anterior intraparietal area
LIP = lateral intraparietal area


Anterior Intraparietal region -

AIP neuron activity varies depending on object grasped.
- Neurons "prefer" some shapes to others.
Anterior Intraparietal region -

Some AIP neurons respond to purely visual info.


Examples of highly selective "object-type visual-dominant" AIP neurons during visual fixation of different objects.


PMv might use info about size, shape and orientation of objects from AIP to choose hand shapes appropriate for a given task.


Areas active in human brain during object manipulation.

Anterior region of IPS

PMv


Human Anterior Intraparietal region also responds to pictures of "graspable" objects (hammer, house, lion, face)


- MIP / area 5 provides info about how body segments are positioned (cells have "preferred postures")
- PMd might use info about current posture from MIP neurons to plan movements

PMD cells are active during the delay period when the rules are needed to make the appropriate movement to a given cue (discussed last lecture)

The nervous system must also deal with ‘higher order’ relationships

Biomechanical / kinetic information provided in primary motor area
Parietal (area 5) cells vs. MI cells

Reflects emg/force profiles

Doesn’t reflect emg/force profiles

Summary: What part of the brain is active for a simple movement?


Functional network active during a "simple" reaching movement -

Take-Home Message

Many regions of the brain must work together in a network to generate even "simple" motor outputs.

End of Topic 13

Topic 14 - Stroke

1. Blood supply to the brain
2. Types of stroke
3. Treatment of acute stroke
Blood supply to the brain

- The brain has high metabolic rate and oxygen requirements:
  
  Human brain is ~2% of total body weight but consumes ~20% of oxygen used by entire body.

- "Autoregulation" helps maintain a constant supply of blood to brain tissues.

Energy is needed to maintain resting potential, synthesize, remove and recycle NT’s etc…

- Most energy is obtained from glucose oxidation.
- Brain requires a constant flow of blood rich in glucose and O2.

**Anterior cerebral artery**

**Internal carotid artery**

**Bulbar artery**

**Vertebral artery**

**Anterior cerebral artery**

**Middle cerebral artery**

**Posterior cerebral artery**

**Circle of Willis**


**Territories supplied by anterior, middle and posterior cerebral arteries.**


**Topic 14 - Stroke**

1. Blood supply to the brain
2. Types of stroke
3. Treatment of acute stroke

**Stroke**

- a.k.a. "cerebrovascular accident" or "brain attack"
- Sudden onset of neurologic deficits due to disruption of blood supply to brain.
STROKE - Statistics

Deaths
• 4th leading cause of death in Canada
• approx. 16,000 Canadians die each year

Prevalence
• 40,000-50,000 strokes in Canada each year (500,000 in US)
• approx every 10-12 minutes

STROKE
2 major causes of a stroke:

1) Ischemic
- Blockage of a blood vessel caused by a blood clot

Ischemic Stroke
Region of decreased blood flow
Interruption of blood supply (blood clot)

Source: Haines et al., Fundamental Neuroscience, Churchill-Livingstone, 2002
Source: http://wwwوضح.org

Lacunar Infarcts

Source: Lundy-Ekman, Neuroscience: Fundamentals for Rehabilitation, Saunders, 2002

Hemorrhagic Stroke

2) Hemorrhagic
- rupture of a blood vessel

Source: Haines et al., Fundamental Neuroscience, Churchill-Livingstone, 2002

Source: Lundy-Ekman, Neuroscience: Fundamentals for Rehabilitation, Saunders, 2002
**Watershed Lesions**

Source: Haines et al., Fundamental Neuroscience, Churchill-Livingstone, 2002

**Umbra** region (ischemic core)

**Penumbra** region (surrounding region)

Source: Haines et al., Fundamental Neuroscience, Churchill-Livingstone, 2002

**Neural Effects**

1. **Energy failure**
   - Ischemia (deficiency in blood flow) results in hypoxia (deficiency in oxygen) and decreased glucose availability.


2. **Excitotoxicity** - excessive exposure to glutamate may kill neurons

   - **Astrocyte**
     - Glutamate
     - Glutamine
     - Transport of glutamate out of synaptic cleft

   Source: MacKay, Neuro 11, Selkirk Ltd., 1999

   - **Glutamate - Excitotoxicity**
     - ↑ Na⁺, draws water into the cell
     - Changes in cell volume can lead to osmotic lysis (particularly in umbra region)
     - ↑ Ca²⁺, activates proteases, lipases that degrade components of cell, may initiate apoptosis

Stroke outcome depends on regions effected -

Source: Haines et al., Fundamental Neuroscience, Churchill-Livingstone, 2002

Topic 14 - Stroke

1. Blood supply to the brain
2. Types of stroke
3. Treatment of acute stroke

Treatment of acute stroke

Decreased blood flow in areas supplied by posterior cerebral artery.

Intracranial hemorrhaging.

Thrombolytics – dissolve clots
- Tissue Plasminogen Activator (t-PA)
- ~ 3 hour time window
- 33% more likely to recover from stroke with little or no disability
- Risks include hemorrhage

Acute Treatment for Ischemic Stroke

TIME IS BRAIN!!!!

Acute Treatment

Neuroprotective strategies -
- Glutamate antagonists
- Ca++ and Na+ blockers
- Antioxidants (scavengers of free radicals)

May extend time window for thrombolytics.

Hypothermia as a Neuroprotective strategy?

- Lowered body temperature by 1.3 degrees Celsius during acute phase of stroke
- Patients who were cooled were 2x more likely to survive 6 months post-stroke

Hypothermia may decrease infarct volume

Infarct volume after thromboembolic stroke


End of Topic 14

Topic 15 - Recovery from Stroke

Motor Recovery Post-Stroke - Spontaneous

Recovery Post-Stroke

At least 3 separate but interactive processes associated with recovery

1) Resolution of diaschisis, inflammation etc..
2) Behavioural compensation
3) Neuroplasticity

Diaschisis

- Loss of function in remote areas anatomically connected to region of lesion
- Possibly from disruption of afferent excitatory input from lesioned area to other brain regions.

Some initial improvement also likely corresponds to resolution of tissue inflammation.

- Early stage inflammation starts a few hours after onset of ischemia
- Microglia and leukocyte involvement
Recovery Post-Stroke
At least 3 separate but interactive processes associated with recovery

1) Resolution of diaschisis, inflammation etc..

2) Behavioural compensation

3) Neuroplasticity

Behavioural compensation

E.g.
- Use unaffected arm
- Learn to walk with a cane

Mechanisms of Neuroplasticity Implicated in Stroke Recovery

1) Redundancy – alternate pathways take over lost function

2) Unmasking - activation of normally inhibited pathways

3) Long-term potentiation - increasing efficiency of synaptic connections and formation of new synapses.

1) Redundancy – alternate pathways take over lost function


Cortical Activity During Index Finger Tapping

1) Redundancy – alternate pathways take over lost function

2) Unmasking – activation of normally inhibited pathways

Model of intracortical connections in M1 -

Inhibitory interneuron prevents excitatory connections from whisker area from activating forelimb area.


Adjacent cortical regions expand when preexisting lateral excitatory connections are unmasked by decreased intracortical inhibition.


Reduction in GABA Receptors throughout cortex after focal ischemic lesion.


Cortical activation during finger tapping with right hand

Control subjects

Patients with ischemic lesion (left internal capsule)

Redundancy and unmasking.


3) Long-term potentiation

- Increasing efficiency of synaptic connections.

- Formation of new synapses.

- A means of modifying neural circuitry

Increase in Ca2+ in post-synaptic cell is critical trigger for induction of LTP

Ca2+ ions activate postsynaptic protein kinases

→ result is increased synaptic strength

**LTP may arise from rapid insertion of AMPA receptors**

LTP may increase size and number of synaptic contacts

New dendritic spines begin to form approx 1 hour after induction of LTP

Long-term depression - weakening of a synaptic connection

End of Topic 15
**Topic 16 - Rehabilitation After Stroke**

1. Rehab techniques
2. Pharmacological approaches

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**Forced Use / Constraint-Induced Training**

Patients practice using affected limb while other limb is restrained.

- ~6 hours/day for several weeks
- Can increase patient's ability to use affected limb.

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**Constraint-induced rehab training enhances cortical reorganization**

The representation of the unconstrained limb increased.

- Induced lesion in part of hand representation area in M1.
- Without post-stroke rehab digit representation in non-lesioned regions also diminished.

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Rehabilitative Training

- Post-lesion training is important for optimizing plastic change.
- An absence of training can lead to a further reduction in representation of the affected limb.

Other approaches...

"Observation" therapy - patient observes someone else moving with intent to imitate movements --> may involve "mirror neuron" system

Other approaches...

"Mirror-box" therapy - movements of patient's unaffected arm appear to be made by patient's impaired limb.


Topic 16 - Rehabilitation After Stroke

1. Rehab techniques
2. Pharmacological approaches

Amphetamine Enhances Recovery ??


Fluoxetine Enhances Recovery ??

Source: Dam et al. (1996) Stroke. 27: 1211-1214.
**Stem Cell Therapy**

**Stem cells** are cells with the ability to divide indefinitely and, under the right conditions, give rise to many different cell types.  
- Potential to replace damaged tissues

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**Human Blastocyst**

[Image: Human Blastocyst](Photo Credit: Mr. J. Conaghan)

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**Lateral ventricular walls of adult human brain contain stem cells.**

"Activation" of these cells could allow the brain to heal itself.


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**Adapted from:** Chu et al. (2004) Brain Res. 1016: 145-153.

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**Summary - Stroke Management Strategies**

- **Acute treatment**
  - Reperfusion and neuroprotection
  - Time window: hours
  - Target: ischemic core and penumbra
  - Limitations: time window, risks

- **Recovery and Rehabilitation**
  - Time window: days, weeks, months, years
  - Target: the “rest” of the brain
  - Development of innovative rehabilitation techniques and “stroke recovery drugs”

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**End of Topic 16**

(and lecture material!)

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