INTRODUCTION

What is neuroscience?

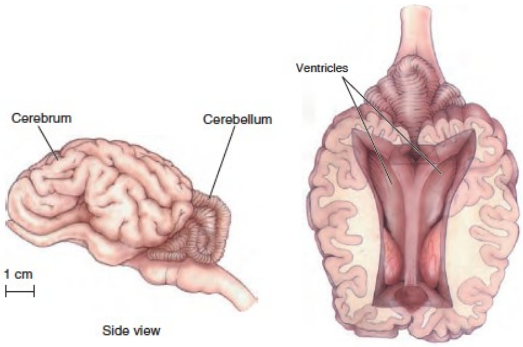
- Study of the nervous system –
  - brain
  - spinal cord
  - nerves

ORIGINS OF NEUROSCIENCE

- Pre-historic ancestors knew brain was vital to life
- Evidence of skull surgeries ('trepanation')
- Ancient Egyptians thought heart (not brain) was:
  - seat of the soul
  - repository of memories (*discarded brain after death*)

Views of the brain: Roman Empire

- Galen was Greek physician to gladiators
- He was aware of:
  - cerebrum
  - cerebellum
  - ventricles



Views of the brain: Renaissance to 19th C

- **Renaissance**: brain seen as machine
  - **Descartes**: brain only controls beast-like behaviour
    - mind controls uniquely human behaviour
- **17th & 18th C**: observed white and gray matter in brain
- **End of 18th C**: observed bumps (*gyri*) and grooves (*sulci & fissures*) on brain

VIEWS OF THE BRAIN: 19TH C

Nerves as wires

- Found muscles twitched when nerves stimulated electrically
- Nerves are 'wires' - conduct electrical signals to/from brain
- **Bell & Magendie**: spinal roots carry info in diff. directions
  - ventral roots contain only motor fibres
  - dorsal roots contain only sensory fibres

Localisation of specific functions to different parts of brain

- **Bell**:
  - cerebellum is origin of motor fibres
  - cerebrum is origin of sensory fibres
- **Marie-Jean-Pierre Flourens**:
  - used experimental ablation method
    - parts of brain destroyed to determine function
  - cerebellum plays role in coordination of movement
- **Franz Joseph Gall**:
  - correlated structure of head with personality traits (*phrenology*)
- **Broca**:
  - had patient who couldn't speak
  - found a lesion in left frontal lobe of brain
  - concluded this region of cerebrum responsible for speech
- **Others**:

Evolution of nervous system

- **Charles Darwin**: theory of natural selection
  - different species evolved from common ancestor
  - behaviour is heritable trait that can evolve
    - mammals have same reaction when scared: big pupils
- Infer that the nervous systems of different species evolved from common ancestors and may have common mechanisms
  - rationale for animal experiments

The neuron: the basic functional unit of the brain

NEUROSCIENCE TODAY

Neuroscientists

- Years of education and training required
- Two types of research:
  1) **clinical**:
     - conducted by physicians
       - neurologists
       - psychiatrists
       - neurosurgeons
       - neuropathologists
     - study effects of brain damage
     - study benefits/risks of treatments
  2) **experimental**:
     - conducted by M.D.s or Ph.D.s
       - neuroscientists
       - neurobiologists
       - neuroanatomists
       - neurochemists

The cost of ignorance

- Research is expensive
- Cost of ignorance about brain is greater
- Disorders that affect nervous system:
  - **Alzheimer's**: degenerative disease of brain
  - **cerebral palsy**: motor disorder
  - **depression**: mood disorder

- occipital lobe required for vision

NEURONS AND GLIA

INTRODUCTION

Neurons and glia
- Types of cells in the nervous system:
  1) neurons
  2) glia
- More glia than neurons in brain
  - BUT neurons more important for functions of brain

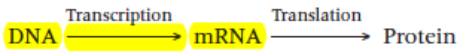
Neurons
1) **sense** changes in environment
2) **communicate** changes to other neurons
3) **command** body's responses to sensations

Glia
1) **insulate**
2) **support** - neurons
3) **nourish**

THE PROTOTYPICAL NEURON
- Parts of neuron:
  1) **soma**
  2) **dendrites**
  3) **axon**
- Inside of neuron separated from outside by **neuronal membrane**
  - circus tent draped on internal scaffolding

THE SOMA
- Spherical central part of neuron
- Within the soma are the organelles:
  1) **nucleus**
  2) **rough ER**
  3) **smooth ER**
  4) **golgi apparatus**
  5) **mitochondria**

Nucleus
- Contains chromosomes (DNA)
- The following occur in the nucleus:
  1) **gene expression**: reading of DNA
  2) **transcription**: assembling piece of mRNA
     - mRNA carries instructions for protein assembly from nucleus to cytoplasm



Rough ER
- Stacks of membrane
- Dotted with globular structures: **ribosomes**
- Major site of protein synthesis in neuron

Smooth ER
- Rough ER without ribosomes
- Processes protein molecules
- Regulates internal conc. of substances
  - e.g. calcium in muscle

Golgi apparatus
- Stack of membrane-enclosed disks
- Farthest from nucleus
- Sorts newly synthesised proteins for delivery

Mitochondria
- Sausage-shaped structures
- Site of cellular respiration
- When mitochondria "**inhale**":
  1) they pull inside pyruvic acid and O_2 from cytosol
  2) pyruvic acid enters Krebs cycle
  3) products of Krebs cycle enter electron-transport chain
  - yields ATP
- When mitochondria "**exhale**" - ATP released

THE NEURONAL MEMBRANE
- Barrier to enclose cytoplasm in neuron
- 5nm thick
- Studded with proteins
- Protein composition varies
  - depends on whether it is in the soma, dendrites or axon

THE CYTOSKELETON
- Internal scaffolding
- Gives neuron its shape
- Three "bones":
  1) microtubules
  2) microfilaments
  3) neurofilaments

THE AXON
- All axons have:
  1) beginning: **axon hillock**
  2) middle: **axon proper**
  3) end: **axon terminal**

Axon differs from soma (structure and function)
- ER doesn't extend into axon
  - no protein synthesis
- Different proteins in axon membrane
  - enables it to serve as "telegraph wire" – send info

Axon terminal
- Where axon comes in contact with other neurons
- Point of contact called **synapse**
- Cytoplasm of axon terminal differs from that of axon:
  1) doesn't have microtubules
  2) has synaptic vesicles
  3) has abundance of proteins
  4) has numerous mitochondria (needs energy)

The synapse
- Has 2 membranes (indicates direction of info. flow):
  1) **presynaptic**: axon terminal
  2) **postsynaptic**: dendrite/soma of another neuron
- **Synaptic cleft**: space between membranes
- **Synaptic transmission**: transfer of info at synapse
  - Signals: electrical ⏤ chemical ⏤ electrical

DENDRITES
- Extend from the soma
- Resemble tree branches
- Covered with synapses ⏤ function as antennae of neuron
- Membrane has receptors for neurotransmitters

CLASSIFYING NEURONS

Based on number of neurites that extend from soma
- **Neurites:** axons and dendrites

Based on dendrites

- Classification often unique to parts of brain
  - 2 classes in cerebral cortex:
    1) **stellate**: star-shaped
    2) **pyramidal**: pyramid-shaped
- Some have spines, some don't
  - **Spiny**: spines
  - **Aspinous**: no spines

Based on connections

- **Primary sensory neurons:** connect with sensory surfaces
- **Motor neurons:** connect with muscles
- **Interneurons:** connect with other neurons

Based on axon length

- **Golgi type 1**: long axons
  - extend from one part of the brain to the other
- **Golgi type 2**: short axons
  - do not extend beyond cell body

Based on neurotransmitter

- **Cholinergic**: release acetylcholine at synapse

GLIA

Astrocytes

- Most numerous glia in brain
- Influence whether neurites can grow/retract
- Regulate chemical content of fluid around neurons ('extracellular space')

Myelinating glia

- Oligodendroglial and Schwann cells
- Provide myelin sheaths around axons in brain & spinal cord
- Mylelin sheath interrupted at nodes of Ranvier

Other non-neuronal cells

- **Ependymal cells**: line fluid-filled ventricles in brain
- **Microglia**: phagocytes – remove debris (dead neurons/glia)
- **Vasculature of brain**: arteries, veins, capillaries

ALZHEIMER'S

- Loss of brain function
- Due to disruption of neuron cytoskeletons in cerebral cortex

First described by Alzheimer (1907)

- 51 year old patient
- First symptom: jealousy towards husband
- Then had memory impairment, confusion etc.
- After she died, Alzheimer examined her brain
- Noted changes in neurofibrils

Neurofibrillary tangles

- Major component of tangles: **Tau protein**
  - usually forms bridge between microtubules in axons
  - ensures they run straight and parallel
- In Alzheimer's, Tau detaches from microtubules and accumulates in soma
  - causes axons to wither
  - impedes information flow in neurons

What causes neurofibrillary tangle formation?

- Abnormal secretion of amyloid by neurons
- Possible therapy: reducing amyloid in brain
  - Unipolar: 1 neurite
  - Bipolar: 2 neurites
  - Multipolar: 3+ neurites

MENTAL RETARDATION AND DENDRITIC SPINES

- Mental retardation:
  - sub-average cognitive functioning
  - IQ < 70 (mean is 100)
  - 2-3% of humans
- Causes:
  1) genetics
     - e.g. Down syndrome (extra chromosome 21)
  2) accidents during pregnancy and childbirth
  3) poor nutrition during pregnancy
  4) environmental impoverishment
- Due to changes in dendritic structure
  - Fewer dendritic spines
  - Spines long and thin
- Dendritic spines important target of synaptic input
- Good news: deprivation-induced changes are reversible

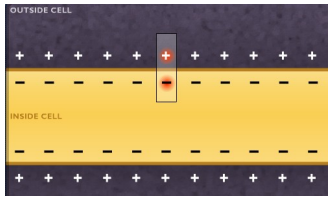
THE ACTION POTENTIAL

THE NERVE IMPULSE

- Electrical current that travels along neuron
- Due to ions moving through voltage-gated channels in the neuron's plasma membrane

NEURON AT REST

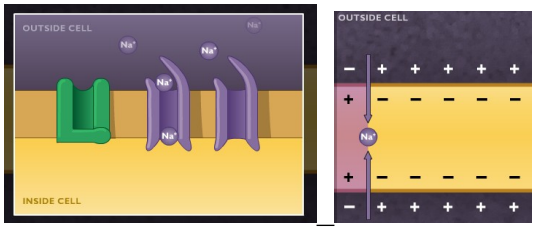
- Charge difference between inside and outside of cell
- Maintained by active transport using Na^+-K^+ pumps
  - Send Na^+ out and bring K^+ in
- Other channels allow flow of K^+ out of cell
  - But Na^+ cannot get back in to replace lost +ve charges
- Overall result: inside of cell more -ve than outside
  - Different in charge = **resting membrane potential**
  - -65mV in neuron



THE ACTION POTENTIAL

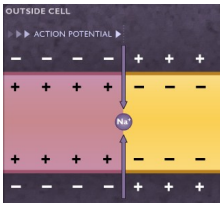
Depolarisation

1) stimulus disturbs plasma membrane on dendrite
2) voltage-gated Na^+ channels open
3) Na^+ flows into cell
   - depolarises the membrane
   - local region inside of cell more +ve than outside



Movement of depolarisation

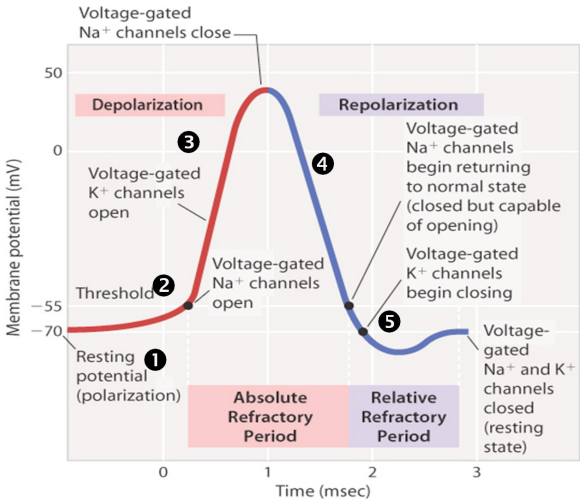
4) neighbouring voltage-gated Na^+ channels open
5) depolarisation moves along membrane ('AP')



Restoring resting membrane potential

6) changes occur behind the AP:
   - voltage-gated Na^+ channels close
   - voltage-gated K^+ channels open
7) K^+ flows out of cell
   - repolarises the membrane
   - inside of cell more –ve than outside
   - hyperpolarises the membrane

PHASES OF ACTION POTENTIAL



PROPERTIES OF ACTION POTENTIALS

"All or none"

- If threshold potential reached – AP is generated
- If threshold potential reached – no AP is generated

Absolute refractory period (1msec)

- AP cannot be generated, regardless of stimulus intensity

Relative refractory period (several msecs)

- AP can be generated, but only with high-intensity stimulus

CONDUCTANCE OF ACTION POTENTIALS

- Movement of AP along neuron

Continuous conduction

- Occurs along unmyelinated axons
- AP moves in series of tiny steps

Saltatory conduction (*saltare* = leaping)

- Occurs along myelinated axons
- Myelin blocks flow of ions across membrane
- AP jumps from one Node of Ranvier to another
- Much faster than continuous conduction

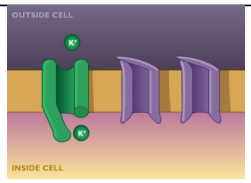
Rate of conduction determined by

1) **Myelination**
   - ***Myelinated*** axons conduct APs more quickly
2) **Axon diameter**
   - ***Large*** axons conduct APs more quickly
3) **Temperature**
   - ***Warm*** axons conduct APs more quickly

STUDYING ION CHANNELS

Patch clamp electrophysiology

- Measures current flowing through ion channel



8) Na^+/K^+ pumps establish proper concentrations of Na^+ & K^+ inside and outside the cell
- restores resting membrane potential

SYNAPTIC TRANSMISSION

WHAT IS IT?

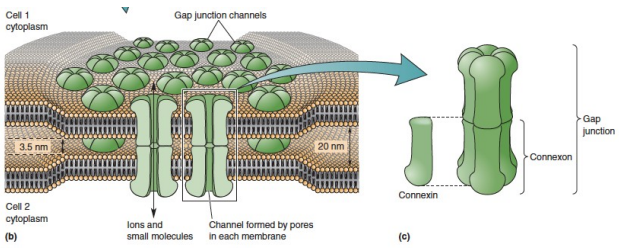
- Transfer of information from one neuron to another
  - information flows in one direction
- At 'synapse' (named by **Charles Sherrington** – 1897)

Debate: chemical or electrical synapses?

- Chemical: **Otto Loewi** (1921)
  - neurotransmitters transfer info.
- Electrical: **Edwin Furshpan** & **David Potter** (1959)
  - electrical current transfers info.

ELECTRICAL SYNAPSES

- Occur at **gap junctions**
  - gap is spanned by clusters of connexin proteins
  - 6 connexins combine to form channel: **connexon**
  - 2 connexons combine to form a **gap junction channel**
  - Channel allows ions to pass between cells
- Cells connected by gap junctions are **'electrically coupled'**
- Transmission is fast
- When neurons are electrically coupled:
  - AP in one neuron causes current to flow into 2nd neuron
  - causes **postsynaptic potential (PSP)** in 2nd neuron
  - the PSP generated by single electrical synapse is small
    - not enough to trigger an AP in the 2nd neuron
  - several PSPs occurring at same time can trigger an AP



CHEMICAL SYNAPSES

- Most synapses are chemical
- Different types, but have universal characteristics

Universal characteristics

- Neurons at chemical synapse separated by **synaptic cleft**
- Axon terminal of presynaptic neuron has **synaptic vesicles**
- Synaptic vesicles store **neurotransmitter**
  - used to communicate with postsynaptic neuron

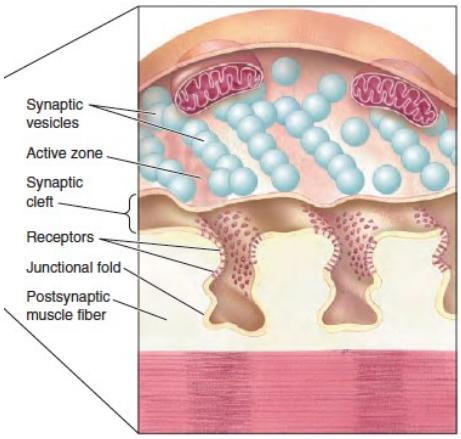
CNS synapses

- Classified based on **what forms synapse**:
  1) ***Axodendritic***: axon + dendrite
  2) ***Axosomatic***: axon + cell body
  3) ***Axoaxonic***: axon + axon
  4) ***Dendrodendritic***: dendrite + dendrite
- Classified based on **membrane differentiations**:
  1) ***Grays type 1***: asymmetrical and excitatory
  2) ***Grays type 2***: symmetrical and inhibitory

Neuromuscular junction

- Chemical synapse between:
  - axons of motor neurons of spinal cord
  - skeletal muscle
- One of the largest synapses in the body
- Presynaptic terminal has **active zones**
- Postsynaptic membrane ('motor end plate') has **folds**
- Active zones line up with folds
  - neurotransmitter released onto receptors

Note: NMJ more accessible researchers than CNS synapses



PRINCIPLES OF CHEMICAL SYNAPTIC TRANMISSION

Basic requirements of chemical synaptic transmission

1) neurotransmitter synthesised
2) neurotransmitter packed into synaptic vesicles
3) vesicles spill contents into synaptic cleft in response to AP
4) response to neurotransmitter in postsynaptic neuron
5) neurotransmitter removed from synaptic cleft

Neurotransmitters

- >40 important neurotransmitters discovered
- Categories:
  1) **amino acids & amines**
     - small organic molecules
     - stored and released from synaptic vesicles
  2) **peptides** (amino acid chains)
     - large molecules
     - stored and released from secretory granules

Amino acids	Amines	Peptides
GABA	ACh*	Dynorphin
Glutamate	Dopamine (DA)	Enkephalins (Enk)
Glycine	Serotonin (5-HT)	Cholecystokinin (CCK)

* ACh was first neurotransmitter to be identified

NEUROTRANSMITTER SYNTHESIS AND STORAGE

Amino acids and amines

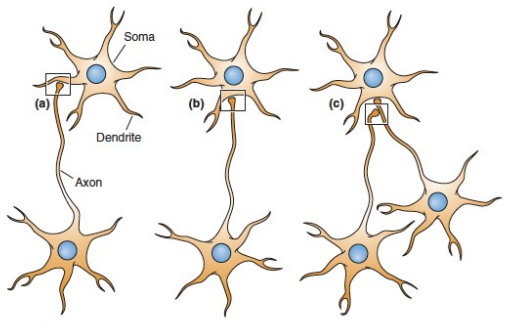


FIGURE 5.5
Synaptic arrangements in the CNS. (a) An axodendritic synapse. **(b)** An axosomatic synapse. **(c)** An axoaxonic synapse.

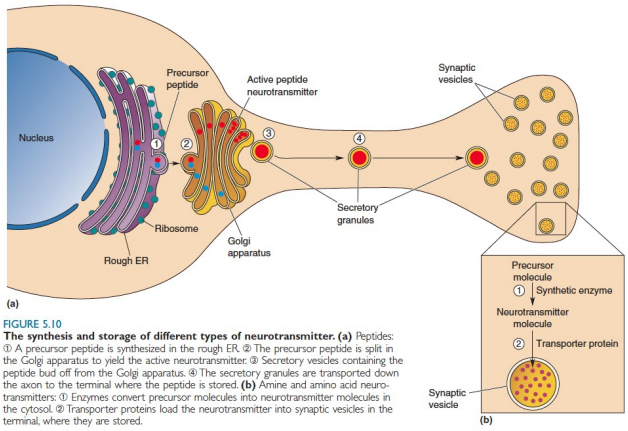
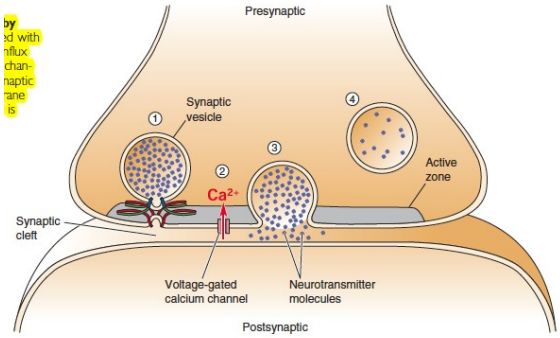


FIGURE 5.10
The synthesis and storage of different types of neurotransmitter. (a) Peptides: ① A precursor peptide is synthesized in the rough ER. ② The precursor peptide is split in the Golgi apparatus to yield the active neurotransmitter. ③ Secretory vesicles containing the peptide bud off from the Golgi apparatus. ④ The secretory granules are transported down the axon to the terminal where the peptide is stored. **(b)** Amine and amino acid neurotransmitters: ① Enzymes convert precursor molecules into neurotransmitter molecules in the cytosol. ② Transporter proteins load the neurotransmitter into synaptic vesicles in the terminal, where they are stored.

NEUROTRANSMITTER RELEASE

1) AP arrives at axon terminal
2) Influx of Ca^{2+} through voltage-gated Ca^{2+} channels
3) Synaptic vesicles release contents into synaptic cleft by **exocytosis** (vesicle membrane & presynaptic membrane fuse)
4) Synaptic vesicle recycled by **endocytosis**



NEUROTRANSMITTER RECEPTORS & EFFECTORS

- >100 different neurotransmitter receptors
- Can be classified as:
  1) transmitter-gated ion channels
  2) G-protein coupled receptors

Transmitter-gated ion channels

- Membrane-spanning proteins
- 4/5 subunits come together to form pore
- Less ion selectivity than voltage-gated channels
  - ACh-gated ion channel at NMJ permeable to Na^+ & K^+

If channel permeable to Na^+ (ACh, glutamate-gated channels)

- Na^+ will depolarise postsynaptic membrane
- Brings membrane potential towards AP threshold
- Causes **excitatory post synaptic potential (EPSP)**
- Enzymes convert precursors into neurotransmitter in cytosol
- Neurotransmitter transported to synaptic vesicles in terminal

Peptides

- Precursor peptide synthesised in rough ER
- Precursor is split in Golgi apparatus
  - yields active neurotransmitter
- Secretory granules containing peptide transported to terminal

NEUROTRANSMITTER RECOVERY & DEGRADATION

- Ways neurotransmitters are cleared:
  1) **diffusion** away from synaptic cleft
  2) **diffusion and reuptake** into presynaptic axon terminal
     - most amino acid and amine neurotransmitters cleared this way
  3) **enzymatic destruction** in synaptic cleft
     - ACh destroyed by AChE at NMJ
- Important that neurotransmitter is cleared
  - can cause **desensitisation**
  - e.g. despite presence of ACh, ACh-gated channels close - neuromuscular transmission fails

NEUROPHARMACOLOGY

- Study of effects of drugs on nervous system tissue

Receptor antagonists

- Bind to receptors and block action of neurotransmitter
- e.g. Curare (arrow-tip poison used to paralyse)
  - blocks action of ACh

Receptor agonists

- Bind to receptors and mimic actions of neurotransmitter
- e.g. Nicotine
  - binds to and activates ACh receptors in skeletal muscles

Defective neurotransmission

- Root cause of many neurological and psychiatric disorders

SYNAPTIC INTEGRATION

- The output of a single neuron is not enough to cause a postsynaptic neuron to fire or prevent it from firing
- The postsynaptic neuron must combine potentials from many neurons to fire
- These potentials are combined at the axon hillock in 2 ways:
  1) **spatial summation**
     - combines potentials occurring simultaneously at different locations on the dendrites and cell body
  2) **temporal summation**
     - combines potentials arriving a short time apart

Summation of EPSPs and IPSPs

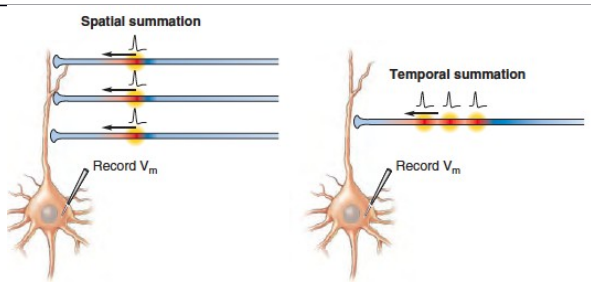
- Summation combines EPSPs so AP more likely to occur
- Summation combines IPSPs so AP less likely to occur
- When both excitatory and inhibitory impulses arrive on a neuron, they will also summate, but algebraically

If channel permeable to Cl^- (glycine, GABA-gated channels)

- Cl^- will hyperpolarise postsynaptic membrane
- Brings membrane potential away from AP threshold

G-protein coupled receptors

- Slower, longer-lasting, more diverse postsynaptic actions
- 3 steps:
  1) neurotransmitter binds to receptor proteins in membrane
  2) receptor proteins activate G-proteins in cell
  3) activated G-proteins activate 'effector' proteins
- Effector proteins can be:
  a) ion channels in membrane
  b) enzymes that synthesise second messengers



NEUROTRANSMITTERS

NEUROTRANSMITTER PRINCIPLES

Dale's principle

- A neuron will store/release only 1 neurotransmitter
- Exceptions: peptide-using neurons
  - GABAergic neurons secrete glutamate & GABA
    NB: *ergic* = use

1 NT may be ligand for no. of different receptors

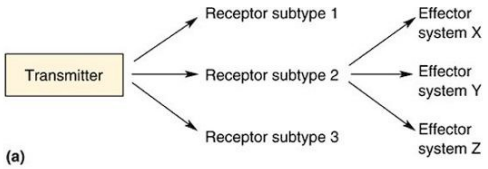
- BUT no 2 NTs bind to same receptor

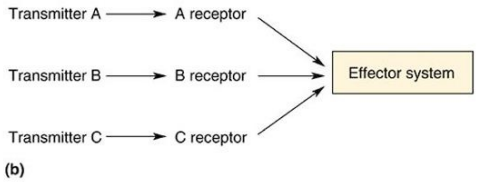
Co-transmitters

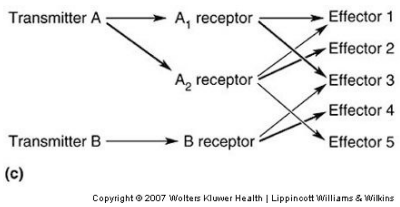
- 2+ NTs released from 1 nerve terminal

Divergence vs. convergence

- **Divergence**:
  - 1 NT
  - Many effector systems
- **Convergence**:
  - Many NTs
  - 1 effector system







NEUROTRANSMITTER RESEARCH

Immunocytochemistry

- Localise specific molecules to particular cells

***In situ* hybridisation**

PHASES OF ACTION POTENTIAL

-

- Confirm that cells synthesises a particular protein
- Needs autoradiography

Brain slices *in vitro*
- Study release of chemicals when particular synapse stimulated

Neuropharmacalogical analysis
- Investigate receptors by studying action of drugs

RECEPTOR SYSTEMS

ACh (cholinergic) receptors
- Nicotinic – skeletal muscle
- Muscaranic – heart

Glutamate receptors
- AMPA
- NMDA
- Kainite

NE (adrenergic) receptors
- NEα – smooth muscles (involuntary)
- NEβ – heart, lung, skeletal muscle (voluntary)

NEUROTRANMITTER CHEMISTRY

Cholinergic (ACh) neurons

Catecholaminergic neurons

Serotonergic neurons

Amino acidergic neurons

RECEPTOR TYPES

Ionotropic: ligand gated channels
- Nicotinic ACh
- $GABA_A$ receptors
- Glutamate receptors

How it works
- Ligand binding opens channel

Metabotropic: G-protein coupled receptors
- Muscarinic ACh
- Adrenoceptors

How it works
- Ligand binds to receptor
- Receptor linked to intracellular G-protein
  - has 3 subunits: α (binds GTP), βγ
- Binding of ligand activates G protein
  - GTP replaces GDP on α subunit
- G-protein dissociates
- 2 subunits interact with effectors
  - enzymes, proteins, ion channels
- Effectors activate 2nd messengers
  - cAMP, Ca^{2+}, phosphoionsitides

SOMATIC SENSATION – TOUCH

INTRODUCTION TO SOMATIC SENSATION

- Responsible for touch and pain
- Enables body to feel, ache, chill
- Different from other systems:
  - receptors widely distributed
  - responds to many types of stimuli

TOUCH

Skin

- Types:
  1) **hairy**
  2) **glabrous** (hairless)
- Layers:
  1) outer: **epidermis**
  2) inner: **dermis**
- Functions:
  - Protective
  - Prevents evaporation of body fluids
  - Provides direct contact with world

MECHANORECEPTORS OF SKIN

- Most somatosensory receptors are mechanoreceptors
- Sensitive to physical distortion (e.g. bending, stretching)
- Types of mechanoreceptors (**named after histologists**):
  - Pacinian corpuscle
  - Ruffini's endings
  - Meissner's corpuscles
  - Merkel's disks
  - Krause end bulbs
- Mechanoreceptors **vary in**:
  - **receptive field sizes**
    - small: Meissener's (*small = meezly*)
    - large: Pacinian (*large = packet*)
  - **adaptation rate**
    - rapidly adapting: response to stimuli does not persist (e.g. Meissener's & Pacinian)
    - slowly adapting: response to stimuli persists

Two-point discrimination

- Ability to discriminate features of stimulus varies across body
  - e.g. fingertip better able to discriminate than elbow
- Depends on:
  - density of mechanoreceptors
  - size of receptive fields
  - amount of brain tissue devoted to sensory info
  - special neural mechanisms

PRIMARY AFFERENT AXONS

- Enter spinal cord through dorsal roots
  - cell bodies lie in dorsal root ganglia
- Axons from skin sensory receptors (in size order):
  - Aα
  - Aβ (mediates touch)
  - Aδ
  - C (mediates pain and temperature)

THE SPINAL CORD

- Most peripheral nerves communicate w/ CNS via spinal cord
- Spinal cord encased in bony vertebral column

Segmental organisation of spinal cord

- 30 spinal segments divided into 4 groups:
  - cervical (**C**) 1-8
  - thoracic (**T**) 1-12
  - lumbar (**L**) 1-5

Dermatome

- The area of skin innervated by a single spinal segment

Shingles

- Infection of nerves
- Increases excitability of sensory neurons
- Leads to low thresholds of firing
- Pain: burning and stabbing

Sensory organisation of spinal cord

- Spinal code composed of:
  - inner core of **gray matter**
  - thick covering of **white matter**
- Each half of spinal gray matter divided into:
  1) dorsal horn
  2) intermediate zone
  3) ventral horn
- Myelinated Aβ axons (touch) enter dorsal horn and branch:
  1) synapses in deep part of dorsal horn
  2) ascends to brain

SOMATOSENSORY PATHWAYS TO BRAIN

- Different pathways for:
  - touch
  - pain and temperature

DORSAL COLUMN-MEDIAL LEMNISCAL PATHWAY

- Major route for touch

Steps:

1) Axon 1 enters **dorsal column** of spinal cord
2) Axon 2 ascends to **dorsal column nuclei**
   - at junction of spinal cord and medulla
3) Axon 3 ascends to ventral posterior (**VP) nucleus** of thalamus
   - through medial lemniscus (white matter tract)
4) Axon 4 projects to primary somatosensory cortex (**S1**)

TRIGEMINAL TOUCH PATHWAY

- Route for somatosensory information from face

Steps:

1) Axon 1 (of trigeminal nerve) ascends to **trigeminal nucleus**
2) Axon 2 ascends to **VP nucleus** of thalamus
3) Axon 3 projects to primary somatosensory cortex (**S1**)

SOMATOSENSORY CORTEX

- Somatosensory processing occurs here
- Most of somatosensory cortex is in **parietal lobe**
- **Brodmann's area** (3b or S1): primary somatosensory cortex
  - lies on post-central gyrus
- Other areas that process somatic sensory info:
  - **3a, 1 & 2** (post-central gyrus)
  - **5 & 7** (posterior parietal cortex)

Brodmann's area (3b or S1)

- Primary somatic sensory cortex because:
  1) receives dense inputs from VP nucleus of thalamus
  2) its neurons are very response to somatosensory stimuli
  3) lesions here impair somatic sensation
  4) electrical stimulation causes somatic experience

Areas 1 & 2

- Receive input from area 3b
  - **3b ⊔ 1**: info about **texture**
  - **3b ⊔ 2**: info about **size** and **shape**

- sacral (**S**) 1-5 ***cut the lamb shanks***

Cortical somatotopy

- Mapping of body's surface sensations onto structure in brain
- Uses electrical stimulation of S1
- Somatotopic map called **homunculus**
  - not continuous (hand separates face and head)
  - not scaled to human body (looks like caricature)
- Size of body part related to importance of sensory input
  - hands big – used to identify objects
  - mouth big – used for speech and taste
- Importance of body part varies in species
  - rodents: facial vibrissae (whiskers) take up a lot of S1

Cortical map plasticity

- Changes in brain as a result of one's experiences
- Example – violinists:
  - continually finger strings with left hand
  - amount of cortex devoted to fingers of left hand enlarged
- Owl monkey experiment:
  - cut off monkey's finger
  - cortex originally devoted to that finger responded to stimulation of adjacent fingers

Posterior parietal cortex

- Involved in:
  1) somatic sensation
  2) visual stimuli
  3) movement planning
- Damage to posterior parietal areas can cause:
  - **agnosia**: inability to recognise objects, though simple sensory skills seem normal
  - **astereognosia**: inability to recognise common objects by feeling them
  - **neglect syndrome**: part of body/world is ignored

SOMATIC SENSATION – PAIN

NOCICEPTORS

- Free, branching, unmyelinated nerve endings
- Activated by stimuli that could cause tissue damage:
  - strong mechanical stimulation
  - temperature extremes
  - oxygen deprivation
  - chemicals
- Stimuli causes ion channels on nociceptor membrane to open

Example: stepping on thumbtack

- Ion channels open due to:
  - stretching/bending of nociceptor membrane
  - release of substances by damaged cells at site of injury
    - proteases (break down kininogen to bradykinin)
    - ATP
    - K^+

TYPES OF NOCICEPTORS

- **Mechanical**: respond to strong pressure
- **Thermal**: respond to extreme heat/cold
- **Chemical**: respond to chemicals (e.g. histamine)
- **Polymoidal**: respond to all of the above

ALTERED PAIN SENSITIVITY

- **Hyperalgesia**: increased sensitivity to pain
- **Hypoalgesia**: reduced sensitivity to pain
- **Analgesia**: absence of pain
- **Hyperpathia**: exaggerated pain
- **Paresthesia**: unpleasant sensations (e.g. burning, prickling)
- **Dysesthesia**: distortion of senses
- **Alloydnia**: pain after non-noxious stimulis

NERVE FIBRES THAT CARRY PAIN IMPULSES

Aδ fibres

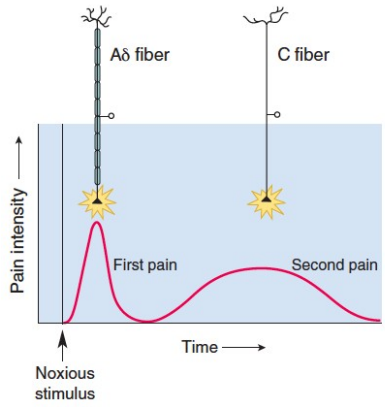
- Large, myelinated fibres
- Impulses travel quickly ('fast pain')
- Release glutamate at synapse w/ spinal neuron

C fibres

- Small, unmyelinated fibres
- Impulses travel slowly ('slow pain')
- Release glutamate & substance P at synapse w/ spinal neuron

First and second pain

- Aδ & C fibres bring info to CNS at different rates
- Activation of nociceptors produces 2 perceptions of pain:
  1) fast, sharp ***first pain*** (Aδ)
  2) dull, long-lasting ***second pain*** (C)



ASCENDING PAIN PATHWAYS

Differences between touch and pain pathways

1) **nerve endings in skin**
   - touch - specialised structures in skin
   - pain - free nerve endings
2) **diameter of axons**
   - touch - fat Aβ fibres
   - pain - thin Aδ and C fibres
3) **connections in spinal cord**
   - touch - ascends ipsilaterally (same side of body)
   - pain - ascends contralaterally (opposite side of body)

Brown-Sequard syndrome

- Sensory & motor signs following damage to 1 side of body
- Damage to left side will cause:
  - loss of touch in left side
  - loss of pain in right side

Trigeminal pain pathway

- Route for pain information from face and head

Steps

1) Axon 1 (of trigeminal nerve) ascends to **trigeminal nucleus**
2) Axon 2 ascends to **trigeminal lemniscus** of thalamus
3) Axon 3 projects to cerebral cortex

NEURAL PATHWAY FOR PAIN

First-order neuron:

- In dorsal root ganglia
- Transmits sensory info. to dorsal horn of spinal cord

Second-order neuron:

- In dorsal horn of spinal cord
- Axons cross-over and ascend
- Spinothalamic pathway ▭ thalamus ('**neospinothalamic'**)
  - identify pain location, intensity etc.
- Spinoreticular pathway ▭ reticular formation ('**paleospinothalamic'**)
  - arouse organism in response to pain

Third-order neuron: in thalamus of brain

- Relay information from thalamus to cerebral cortex

THE REGULATION OF PAIN

Afferent regulation

- Pain evoked by activity in nociceptors can be reduced by simultaneous activity in mechanoreceptors (Aβ fibres)
- Why it feels good to rub skin around bruise
- **Gate theory of pain** explains these phenomena

Descending regulation

- Strong emotion, stress or determination can suppress pain
- Several brain regions implicated in pain suppression
  - **Periaqueductal gray matter** (PAG)
  - Electrical stimulation of PAG induces analgesia

Endogenous opiates

- Opioids produce analgesia
- Brain makes morphine-like substances ('**endorphins**')

DESCRIBING PAIN

By origin

- **Cutaneous**: from stimulation of skin and superficial tissues

By qualities

- **Referred**: pain perceived at wrong location
  - signals from diff. areas of body ascend using same route
  - signals get mixed
  - visceral pain (from organs) often felt in skin
    - e.g. angina - get pain in chest and left arm

NEUROPATHIC PAIN

- Chronic pain caused by damage to nerves

Neuropathic syndromes

- **Trigeminal neuralgia**
  - shooting neck and facial pain
  - treatment:
    - anti-convulsants (e.g. *carbamazepine*)

- **Post-herpetic neuralgia**
  - complication of shingles
  - pain persists after condition cleared
  - treatment:
    - topical anaesthetics (e.g. *lidocaine*)
    - tricyclic anti-depressants (e.g. *amitriptyline*)

- **Complex regional pain syndrome (CRPS)**
  - pain in limbs after injury or trauma
  - treatment:
    - analgesics

- **Phantom limb pain**
  - pain in amputated limb
  - incidence: 70% amputees
  - treatment:
    - hypnosis

- **Deep somatic**: from stimulation of ligaments and bones
- **Visceral**: from stimulation of receptors in internal organs

BRAIN RHYTHMS/EPILEPSY

ELECTROENCEPHALOGRAPHY (EEG)

- Measure of electrical activity of brain
- Caton (1875) used EEG on animal brains
- Berger (1929) used EEG on human brains
  - Found waking and sleeping EEG different

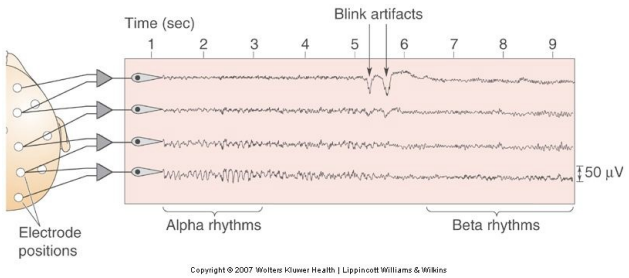
Uses

- Study sleep patterns
- Diagnose disease
- Locate tumors
- Study drug effects
- Determine brain death

How it works

- Non-invasive electrodes attached to scalp
  - international 10-20 system of electrode placement
  - can compare EEG activity from different subjects
- Records voltage produced by currents given off by brain **pyramidal cells**
- Can look at different regions of brain

Normal EEG



BRAIN WAVES

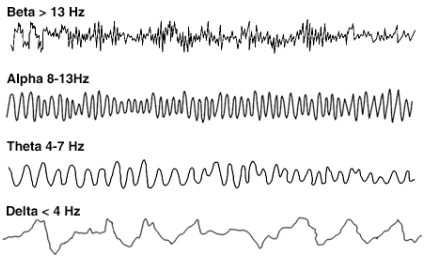
- Waves of electrical activity
- EEG measures wave:
  - amplitude (height)
  - frequency (cycles/sec)

Amplitude related to synchronisation of neuron activity

- Each neuron receives many synaptic inputs
- If inputs fire irregularly:
  - pyramidal cell responses not synchronised
  - summed activity has small amplitude
- If inputs fire regularly:
  - pyramidal cell responses synchronised
  - summed activity has large amplitude

Categorisation based on frequency

- **Beta** (13-24) – awake, alert
- **Alpha** (8-12) – awake, quiet, resting
- **Theta** (4-7) – light sleep, REM sleep
- **Delta** (<4) – deep sleep
  - Large amplitude



Brain waves change with:

- Sensory stimuli
- Age
- Brain disease
- Chemical state

Generation of synchronous rhythms

- Synchronous rhythms can be:
  - **a)** led by a **pacemaker** (thalamus)
    - thalamic neurons have voltage-gated ion channels
    - allow each cell to generate rhythmic AP discharges
    - coordinated rhythms passed to neurons in cortex
  - **b)** arise from the **collective behaviour of neurons**

SEIZURES

- Extreme form of synchronous brain activity
- Neurons in cortex fire with abnormal synchrony
  - Seizures case large EEG patterns

Epilepsy

- Repeated seizures

Generalised seizures: entire cerebral cortex (both hemispheres)

- **Tonic-clonic** ('grand mal'): loss of consciousness + muscle contraction
  - **Status epilepticus:** recurrent episodes of tonic-clonic
- **Absence** (petit mal): abrupt loss of consciousness
  - fluttering eyelids
  - twitching mouth
- **Myoclonic**: muscle jerks
- **Atonic:** loss of muscle tone

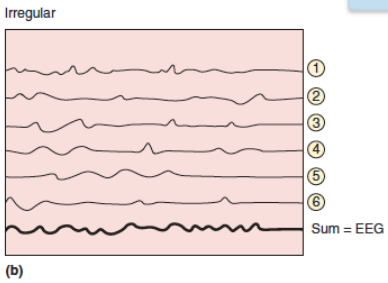
Partial seizures: small area of cortex (1 hemisphere)

- **Simple**: no loss of consciousness
- **Complex**: impairment of consciousness
- **Symptoms**:
  - **Frontal lobe**: behavioural disturbance
  - **Temporal lobe**: abnormal olfactory/gustatory sensation
    - fear
    - déjà vu
  - **Occipital lobe**: flashing lights

Secondarily generalised: spreads from 1 hemisphere to other

Provoked vs. unprovoked seizures

- **Provoked**: known cause
- **Unprovoked**: unknown cause



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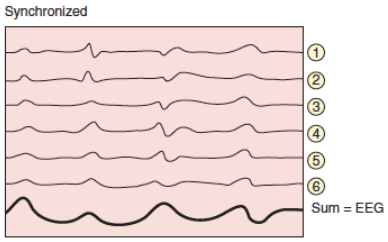


(c)

Causes

- Alterations in ion distribution across neuronal cell membrane
  - e.g. due to mutation in genes for Na^+ channel proteins
- Decreased inhibition of cortical neural activity
- Neurotransmitter imbalances
  - ACh
  - GABA

SLEEP AND EPILEPSY

- 10% of patients have only night-time seizures
- Happens during slow-wave sleep
- Does not happen during REM sleep (no synchronisation)

Types of nocturnal epilepsy

- **Autosomal dominant nocturnal frontal lobe epilepsy**
  - linked to chromosome 8
- **Juvenile mycolonic epilepsy**
  - seizures occur while falling asleep and waking up
- **Nocturnal paroxysmal dystonia (NPD)**
  - seizures occur during non-REM sleep

Treatment

- Anticonvulsant drugs (*benzos*)
  - enhance GABA-mediated inhibition
- Surgery to remove parts of brain
- Surgery to implant vagus nerve stimulator

THE CHEMICAL SENSES - TASTE

TASTE

- Humans have sensitive taste system
- Distinguishes between food and toxins
- Inborn preference for sweetness
  - satisfied by mother's milk
- Bitter substances instinctively rejected
  - many poisons are bitter
  - tolerance can lead to enjoyment (e.g. coffee)

Sense of taste decreases with

- **Age** (but less affected than olfaction)
- **Drugs**
- **Disease**

THE ORGANS OF TASTE

- We taste with tongue
- Other areas of mouth involved:
  - palate
  - pharynx
  - epiglottis
- Odors from food pass via pharynx into nasal cavity

Papillae

- Small projections on surface of tongue
- Shaped like:
  - ridges (**foliate** papillae)
  - pimples (**vallate** papillae)
  - mushrooms (**fungiform** papillae)
- Each papilla has hundreds of **tastebuds**

Taste buds

- Each taste bud has 50-150 **taste receptor cells**
- Taste receptor cells only 1% of tongue epithelium
- Person has 2000-5000 taste buds
- Cells of taste bud constantly replaced
  - lifespan: 2 weeks

Threshold concentration

- Conc. of taste stimuli that evokes perception of taste
- At threshold, papillae sensitive to 1 basic taste
- Above threshold conc., papilla less selective

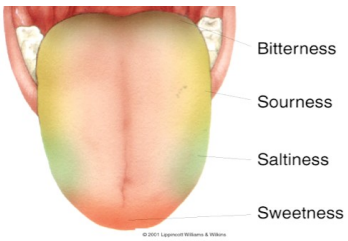
GUSTATORY DISCRIMINATION

Basic taste types

1) Sweet
2) Salty
3) Sour
4) Bitter
5) Unami ('delicious'): detected by receptors for amino acids

Gustatory discrimination

- **Taste regions**: parts of tongue more sensitive to taste type
- Centre of tongue insensitive to taste stimuli



Perception of taste

- Foods are different combinations of the basic types
- Taste and smell sensation work together
  - otherwise onion could be mistaken for apple

TASTE RECEPTORS

- Chemically sensitive part of receptor: **apical end**: membrane
- Apical ends have thin extensions: **microvilli**
- Microvilli project into **taste pore** (opening on tongue)
- Taste receptors form synapses with:
  - gustatory afferent axons near bottom of taste bud
  - basal cells

Activation of taste receptors

1) Chemical stimuli causes membrane depolarisation
2) Voltage-gated Ca^{2+} channels open
3) Ca^{2+} enters cytoplasm
4) Transmitters released
   - we don't know what transmitter is

TASTE TRANSDUCTION

- **Transduction**: process by which stimulus causes electrical response in sensory receptor cell
- Taste transduction involves several processes
- Taste stimuli may:
  1) directly **pass through ion channels** (salt, sour)
  2) bind to and **block ion channels** (sour)
  3) **bind to G-protein-coupled receptors** in membrane that **open ion channels** (bitter, sweet, umani)

Saltiness

- Taste of salt is taste of Na^+
- Salt-sensitive taste cells have Na^+-selective channel
- Transduction:
  1) eat chicken soup
  2) Na^+ conc. rises outside cell
  3) Na^+ passes into cell through Na^+ channel
  4) Membrane depolarises

Sourness

- Foods taste sour because of high acidity
  - **Protons** cause acidity and sourness
- Transduction – **method 1 (Na^+ channel)**:
  1) eat warhead
  2) H^+ conc. rises outside cell
  3) H^+ passes into cell through Na^+ channel
  4) membrane depolarises
- Transduction – **method 2 (K^+ channel)**:
  1) eat warhead
  2) H^+ conc. rises outside cell
  3) H^+ binds to and blocks K^+ channels
  4) membrane depolarises

Bitter, sweet & umami

- **Bitter**: calcium, quinine & poisons
- **Sweet**: sugars (carbs)
- **Umami**: amino acids - glutamate, aspartate (broths, cheese)
- Receptors are G-protein-coupled receptors
- Formed by proteins: T1R & T2R
  - Bitter receptor
    - 30 types
    - formed by T2R
  - Sweet receptor: TIR2 & TIR3
    - 1 type
    - formed by T1R2 & T1R3 bound together
  - Umami receptor:

- Transduction:
  1) eat bitter/sweet/umami food
  2) taste stimuli binds to G-protein-coupled-receptor
  3) activates phospholipase C
  4) increases synthesis of IP_3
  5) IP_3:
    - opens taste cell ion channel ⇨ Na^+ enters cell
    - opens voltage-gated Ca^{2+} channel ⇨ Ca^{2+} enters cell
  6) membrane depolarises

CENTRAL TASTE PATHWAYS

- Flow of taste information is from:
  1) taste buds
  2) **gustatory axons** of cranial nerves
     - VII (facial): innervates anterior 2/3 of tongue
     - IX (glossopharyngeal): innervates posterior 1/3 of tongue
     - X (vagus): innervates throat
  3) medulla
     - **gustatory nucleus**
  4) thalamus
     - ventral posterior medial **(VPM) nucleus**
  5) cerebral cortex
     - **primary gustatory cortex**
     - in Brodmann's area 36
- Lesions on VPM nucleus or primary gustatory cortex cause **ageusia** (loss of taste perception)

NEURAL CODING OF TASTE

- **Population coding**
- Large number of broadly-tuned taste cells used to distinguish between tastes

- 1 type
- formed by T1R1 & T1R3 bound together

THE CHEMICAL SENSES - SMELL

SMELL

- Combines with taste to help identify foods
- Can warn of harmful substances (e.g. spoiled meat)
- Mode of communication
  - e.g. **pheromones** released by body
    - important for reproductive behaviour
    - mark territory
    - identify individuals

Sense of smell decreases with age due to

- Atrophy (wasting) of olfactory bulb
- Loss of olfactory neurons

ORGANS OF SMELL

- We do not smell with our nose!
- Smell with **olfactory epithelium**

Cell types of olfactory epithelium

1) **Olfactory receptor cells**: site of transduction
   - one of few types of neurons that gets replaced
2) **Supporting cells**: help produce mucus
3) **Basal cells**: source of new receptor cells

Olfactory epithelium covered with mucus

- Mucus replaced every 10 mins
- Odorants dissolve in mucus before reaching receptor cells
- Mucus contains antibodies and binding proteins
  - prevent viruses and bacteria entering brain

OLFACTORY RECEPTOR NEURONS

Dendrite

- Have single, thin **dendrite**
- Dendrite ends with **knob** at surface of epithelium
- Waving from the knob (within mucus) are long, thin **cilia**
  - Odorants dissolved in mucus bind to cilia
  - Activates transduction process

Axon

- Have thin, **unmyelinated axon**
- All the olfactory axons constitute the **olfactory nerve** (cranial nerve I)
  - the olfactory axons do not come together as nerve bundle
  - they penetrate thin sheet of bone: **cribriform plate**
  - then course into **olfactory bulb**
- Olfactory axons are fragile
  - can be damaged by blow to head or the flu
  - result: **anosmia** – inability to smell

OLFACTORY TRANSDUCTION

- Transduction molecules located in cilia

Transduction pathway

1) Odorants bind to receptor proteins
2) G-protein stimulated
3) adenylyl cyclase activated
4) cAMP formed
5) cAMP binds to specific cation channel
6) cation channels open ▭ influx of Na^+ and Ca^{2+}
7) Ca^{2+}-activated Cl^- channels open ▭ efflux of Cl^-
8) membrane depolarisation

Termination of olfactory response

- Response may terminate for several reasons:
  1) odorants diffuse away
  2) scavenger enzymes in mucus break odorants down
  3) cAMP ends transduction process
- Even if odorant still there, strength of smell fades
  - receptor cells **adapts** to odorant within 1 min

CENTRAL OLFACTORY PATHWAYS

- Axons of receptor cells:
  1) penetrate **cribriform plate**
  2) enter **olfactory bulb**
  3) synapse on 2nd-order neurons in **glomerulus**
     - receptors expressing particular gene all send axons to same glomeruli
- Second-order neurons go through olfactory tract to brain
  - **olfactory cortex**
  - neighbouring structures in **temporal lobes**

- **Unique -** all other sensory systems pass through thalamus before projecting to cerebral cortex

SPATIAL AND TEMPORAL REPRESENTATIONS OF OLFACTORY INFORMATION

Olfactory population cloning

- Each odor represented by large population of neurons

Olfactory maps

- The neurons responsive to particular odors may be organised into spatial maps

Temporal coding in olfactory system

- The timing of APs may be essential code for particular odors

THE VOMERONASAL ORGAN: PHEROMONES

- **Accessory olfactory system** used to detect pheromones
  - mediates variety of social behaviours
  - mothering, mating, marking territory
- Runs parallel to primary olfactory system
- Consists of **vomeronasal organ** in nasal cavity
  - projects to **accessory olfactory bulb**

○ provides input to **hypothalamus**	

CHEMICAL CONTROL OF BRAIN AND BEHAVIOUR

PATTERNS OF COMMUNICATION IN NERVOUS SYSTEM

- Most systems we look at are point-to-point – require:
  - synaptic activation of target cells
  - signals of brief duration
- These act over great distances for long periods of time time:
  1) Neurons of **secretory hypothalamus**
     - affect many targets by releasing hormones into blood
  2) Neurons of **ANS**
     - work together to activate tissues all over body
  3) **Diffuse modulatory systems**
     - extend reach with divergent axonal projections

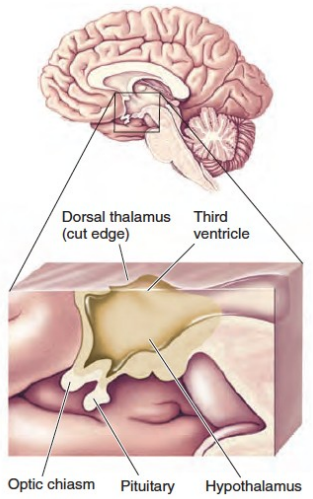
HYPOTHALAMUS

Damage to..

- **thalamus** = discrete sensory/motor deficit
  - e.g. blind spot
- **hypothalamus** = dramatic disruptions of body functions

Location of hypothalamus

- Forms wall of third ventricle
- Sits below thalamus
- Connected to pituitary by stalk ('infundibulum')



2b) control anterior pituitary (gland)

- Controlled by **parvocellular neurosecretary cells**
- These cells secrete **hypophysiotropic hormones** into blood of portal circulation
  - travel to anterior pituitary
  - bind to receptors on pituitary cells
  - cause pituitary cells to secrete/stop secreting hormones
- Regulates the **stress response**
  - hypothalamus secretes **CRH** into portal circulation
  - triggers release of **ACTH** into general circulation
  - ACTH stimulates release of **cortisol** from adrenal gland

ANS

- Periventricular zone of hypothalamus controls ANS
- ANS is network of interconnected neurons
- Somatic motor system + ANS = total neural output of CNS
  - somatic motor system: commands skeletal muscle fibres
  - ANS: commands every other tissue/organ

Sympathetic and parasympathetic divisions

- **Sympathetic** division active during crisis
  - increased HR & BP
  - decreased digestion
  - mobilised glucose reserves

Hypothalamus is part of limbic system

- Involved in processing emotions

Functional zones of hypothalamus

1) lateral
2) medial
3) periventricular

Periventricular zone

- Receives inputs from:
  - the other zones
  - the brain stem
  - the telencephalon
- Has mix of neurons
  - **suprachiasmatic nucleus**
    - synchronises circadian rhythms with light/dark
  - **neuroscecretory cells**
    - secrete hormones into blood
  - other cells that control ANS

Functions of hypothalamus

1) homeostasis

- Maintains body's internal environment within narrow range
- Regulates blood volume/pressure
  1) drop in blood volume/pressure
  2) **kidney** secretes **renin** into blood
  3) renin promotes synthesis of **angiotensin II**
  4) angiotensin II excites **subfornical neurons**
  5) subfornical neurons stimulate hypothalamus
  6) leads to increased **ADH** production & feeling of **thirst**

2) control pituitary

- Pituitary dangles down below base of brain
- Protected by bone
- 'Mouthpiece' from which hypothalamus 'speaks' to body

2a) control posterior pituitary (part of brain)

- **Magnocellular neurosecretory cells** extend down pituitary
- These cells release 2 neurohormones:
  - **oxytocin** – causes uterus to contract, ejection of milk
  - **vasopression** (**ADH**) – regulates blood volume

Neurotransmitters

- **Preganglionic neurotransmitter**: ACh
  - binds to nicotinic ACh receptors
    - evokes fast EPSP
    - usually triggers AP in postganglionic cell
  - binds to muscarinic ACh receptors
    - evokes slow EPSP and IPSPs
- **Postganglionic neurotransmitter:**
  - **sympathetic**: norepinephrine (NE)
    - spreads far, even into blood
  - **parasympathetic**: ACh
    - local effect on targets

Drugs that promote…

- **NE** are **sympathomimetic**
  - effects mimic activation of SNS
- muscarinic actions of **ACh** are **parasympathomimetic**
  - effects mimic activation of PNS

DIFFUSE MODULATORY SYSTEMS

- Neurons with widespread pattern of axons
- Perform regulatory functions
- Modulate numerous postsynaptic neurons

- **Parasympathetic** division active at other times
  - decreased HR & BP
  - increased digestion
- Act in parallel but use distinct pathways
  - different structure
  - different neurotransmitters

Enteric division
- 'little brain'
- Neural system embedded in:
  - oesophagus
  - stomach
  - intestines
  - pancreas
  - gallbladder
- Consists of 2 networks:
  1) **myenteric (Auerbach's) plexus**
  2) **submucus (Meissner's) plexus**
- Controls transport and digestion of food
- Receives input from of SNS and PNS

Neurotransmitters and the systems
- Systems use NE, 5-HT, DA, ACh
- These activate G-protein coupled receptors

Functions of systems depends on…
- How electrically active they are
- How much neurotransmitter is available for release

Noradrenergic locus coeruleus
- Locus coeruleus is a tiny 'blue spot' in the pons
- We have 2 of them – each has 12,000 neurons
- Axons fan out to every part of brain – innervate:
  - spinal cord
  - cerebellum
  - thalamus
  - cerebral cortex
- Involved in regulation of:
  - arousal
  - sleep-wake cycles
  - mood

Serotonergic raphe nuclei
- Serotin-containing neurons clustered in raphe nuclei
- *Raphe* = ridge
  - raphe nuclei lie to either side of midline of brain stem
- Each nucleus projects to different regions of brain
- Innervate same areas & regulate same things as noradrenergic system

Dopaminergic substantia nigra and ventral tegmental area
- Substantia nigra and ventral tegmental area are in **midbrain**
- Substantia nigra projects to stratium
  - facilitates initiation of movement
- Ventral tegmental area projects to limbic and frontal cortex
  - involved in reward system

Cholinergic basal forebrain
- **Basal forebrain complex**
  - cholinergic neurons scattered among several related nuclei at core of telencephalon
    - **medial septal nuclei:** innervate hippocampus
    - **basal nucleus of Meynert**: innervates neocortex
  - function of cells unknown
    - death might cause Alzheimer's?
  - make them more or less excitable
- Essential for aspects of:
  - motor control
  - memory
  - mood
  - motivation

Common principles
1) core has small set of neurons
2) neurons arise from brain stem
3) each neuron can influence many others
4) synapses release neurotransmitters into extracellular fluid
  - diffuse to many neurons (not just 1)

The four systems
1) noradrenergic locus coeruleus
2) serotonergic raphe nuclei
3) dopaminergic substantia nigra and ventral tegmental area
4) cholinergic basal forebrain and bran stem complexes

- **Pontomesencephalotegmental complex**
  - ACh-utilising cells
  - acts on dorsal thalamus
  - regulates excitability of sensory relay nuclei

Drugs and the diffuse modulatory systems
- **Psychoactive drugs** act on CNS by interfering with chemical synaptic transmission
  - **Hallucinogens**: LSD
  - **Stimulants**: blocks reuptake of neurotransmitters
    - cocaine blocks DA reuptake
    - amphetamine blocks NE & DA reuptake

MENTAL ILLNESS

INTRODUCTION

Neurology
- Study of nervous system disorders
- Neurological disorders help us understand normal brain function

Psychiatry
- Study of disorders that affect the mind e.g. –
  - anxiety disorders
  - affective disorders
  - schizophrenia

Mental illness
- Disorder of through, mood or behaviour
- Causes distress or impaired functioning

PSYCHOSOCIAL APPROACHES TO MENTAL ILLNESS

Freud
- Mental illness results when **unconscious and conscious elements of psyche** come into **conflict**

Skinner
- Mental illness is **learned maladaptive behaviour**

BIOLOGICAL CAUSES OF MENTAL ILLNESS

***Treponema pallidum* infection**
- Causes **general paresis of the insane** (and syphilis)
- Symptoms: mania, cognitive deterioration, paralysis
- Treatments:
  - Paul **Ehrlich**: arsphenamine
  - Alexander **Flemming**: penicillin

Dietary deficiency in niacin (VitB)
- Causes agitation, impaired reasoning & depression

HIV infection
- Causes cognitive and behavioural impairments

Hypothalamic-pituitary-adrenal (HPA) axis
- Secretion of cortisol from adrenal gland in response to stress
- Steps:
  1) **CRH** released from hypothalamus
     - corticotropin-releasing hormone
  2) **ACTH** released from anterior pituitary
     - adrenocorticotropin hormone
  3) **Cortisol** released from adrenal cortex

Regulation of HPA axis by amygdala and hippocampus
- **Amygdala** activation stimulates HPA system (and stress)
- **Hippocampus** activation suppresses HPA system
  - has glucocorticoid receptors – sensitive to cortisol
  - important in feedback regulation of HPA axis
  - prevents excessive cortisol release

ANXIETY DISORDERS

Fear
- Adaptive response to threatening situations
- Expressed by autonomic fight-or-flight response
- Many fears are innate
  - Mouse knows to fear cat
- Fear also learned
  - Horse learns to fear electric fence

Anxiety disorders
- Inappropriate expression of fear
- More common in women

Common anxiety disorders
- **Panic disorder** (2% of pop.)
  - frequent panic attacks
- **Agoraphobia** (5% of pop.)
  - anxiety about situations where escape is difficult
  - e.g. in a crowd of people, on a bridge, in a lift
- **Obsessive-compulsive disorder** (2% of pop.)
  - obsessions cause anxiety
  - compulsions neutralise anxiety

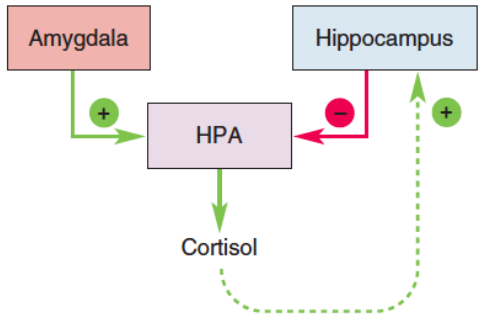
BIOLOGICAL BASES OF ANXIETY DISORDERS
- Fear is evoked by threatening stimulus ('**stressor'**)
- **Stress response**: reaction to stressor
- In anxiety disorders, stress response occurs when:
  - stressor not present
  - stressor not threatening

Stress response
- Characterised by:
  1) avoidance behaviour
  2) increased vigilance and arousal
  3) activation of sympathetic division of ANS
  4) release of cortisol from adrenal glands

Anxiolytic medications
- Mediations that reduce anxiety
- Alter chemical synaptic transmission in brain
- **Benzos:** make $GABA_A$ receptors more responsive to GABA
  - e.g. *valium*
- **SSRIs**: prolong action of serotonin at receptors
  - inhibit reuptake of serotonin
  - e.g. *fluoxetine*
- **CRH receptor antagonists**

AFFECTIVE (MOOD) DISORDERS (7% of pop.)
- Characterised by disordered emotions

Major depression (5% of pop)
- Most common mood disorder
- Symptoms:
  - lowered mood
  - decreased interest/pleasure in activities
  - loss of appetite
  - insomnia
  - fatigue
  - feelings of worthlessness and guilt



Continuous exposure to cortisol causes hippocampal damage

- Continuous exposure to cortisol (during chronic stress) causes hippocampal neurons to wither and die
- Sets off vicious cycle:
  1) stress response more pronounced
  2) more cortisol released
  3) more hippocampal damage

TREATMENTS FOR ANXIETY DISORDERS

Psychotherapy

- Therapist increases exposure to anxiety-producing stimuli
- Reinforces notion that stimuli are not dangerous

Cyclothymia

- Cycles of hypomania and depression

BIOLOGICAL BASES OF AFFECTIVE DISORDERS

The monoamine hypothesis

- Mood tied to levels of monoamine neurotransmitters
  - NE and 5-HT
- **Depression due to deficit**
- Evidence:
  - **reserpine and MAO** (¬¬ 5-HT) cause depression
  - **imipramine** (¬¬ 5-HT) prevents depression

The diathesis-stress hypothesis

- Mood disorders caused by:
  1) genetics
  2) environmental factors
- In depressed patients, HPA function is hyperactive
  - due to decreased feedback inhibition
  - due to diminished hippocampal response to cortisol
  - due to deceased no. of glucocorticoid receptors
  - due to abuse, neglect etc.

TREATMENTS FOR AFFECTIVE DISORDERS

Electroconvulsive therapy

- Induces seizure activity in **temporal lobes**
  - affects hippocampus– regulates HPA axis
- Anaesthetics & muscle relaxants prevent violent movements
- Advantage: quick relief
- Disadvantage: memory loss

Psychotherapy

- Help depressed patients overcome negative views
- Used to treat mild to moderate depression

Antidepressants (<u>all increase NE & 5-HT</u>)

1) **tricyclic compounds**: block reuptake of NE & 5-HT
  - e.g. *imipramine*
  - reduce HPA axis activity
  - diminished concentration

Dysthymia (2% of pop)

- Mild form of depression

Bipolar disorder

- Episodes of mania (elevated or irritable mood)
- Symptoms:
  - inflated self esteem
  - decreased need for sleep
  - increased talkativeness
  - racing thoughts
  - distractibility
  - increased goal-directed activity
- **Type I** (1% of pop): **mania**
- **Type II** (0.6% of pop): **hypomania**
  - mild form of mania
  - can increase efficiency and creativity
  - episodes of depression

2) **SSRIs**: block reuptake of 5-HT
  - e.g. *fluoxetine*
  - increase neurogenesis (neuron synthesis) in hippocampus

3) **NE-selective reuptake inhibitors**: block reuptake of NE
  - e.g. *reboxetine*

4) **MAO inhibitors**: reduce degradation of NE & 5-HT
  - e.g. *phenelzine*

Lithium

- Stabilizes mood of bipolar patients
- Prevents mania and depression

o increase no. of glucocorticoid receptors in hippocampus	

AUDITORY SYSTEM: HEARING

THE NATURE OF SOUND

- Sounds are audible variations in air pressure

Frequency

- No. of compressed patches of air that pass by ears per second
- Units: Hertz (Hz)
- Range: 20 - 20,000 Hz
- High frequency waves have high **pitch**

Intensity

- High intensity waves are **loud**

STRUCTURE OF THE AUDITORY SYSTEM

Basic auditory pathway (TOOCS)

1) sound waves move **tympanic membrane**
2) moves **ossicles**
3) move membrane at **oval window**
4) moves fluid in **cochlea**
5) causes response in **sensory neurons**

THE MIDDLE EAR

Tympanic membrane

Ossicles

- Types:
  1) **malleus**
  2) **incus**
  3) **stapes**
- Amplify sound

Muscles that attach to ossicles

- Types:
  1) **tensor tympani**
  2) **stapedius**
- Important in attenuation reflex
  - loud sound causes muscles to contract
  - ossicles become more rigid
  - sound conduction to inner ear is diminished

Eustachian tube

- Connects middle ear to nasal cavities
- Important in pressure equalisation

THE INNER EAR

- Consists of:
  1) **cochlea** (auditory)
  2) **labrinyth** (vestibular)

ANATOMY OF COCHLEA

Cochlea

- Spiral shape
- Similar to drinking straw rapped 2.5x around pencil
- Central pillar of cochlea (pencil): **modiolus**

At base of cochlea are 2 membrane-covered holes

1) **oval window**
2) **round window**

Tube divided into 3 fluid-filled chambers (*scala* = staircase)

1) **scala vestibuli**
   - meets oval window
   - fluid: **perilymph**
2) **scala media**
   - fluid: **endolymph**
3) **scala tympani**
   - meets round window
   - fluid: **perilymph**

separated by **basilar membrane** *(basilar at BASE of cochlea)*
organ of Corti is on membrane (contains auditory receptors)

Perilymph vs endolymph

- Perilymph: low K^+ and high Na^+
- Endolymph: high K^+ and low Na^+
  - similar to intracellular fluid
- **Endolymph** has **more +ve electrical potential**
  - called **endocochlear potential**
  - enhances auditory transduction

PHYSIOLOGY OF COCHLEA

Organ of corti and associated structures

- Auditory receptors (**hair cells**) located here
- **Each receptor has** 100 hairy-looking **sterocilia**
- Bending of cilia critical to transduction of sound

Transduction by hair cells

1) motion at stapes
2) basilar membrane moves upward
3) hair cell bends outward
4) mechanically-gated cation channels open
   - **TRPA1** (transient receptor potential) **channels**
5) K^+ enters
6) depolarises hair cell
7) voltage-gated Ca^{2+} channels open
8) Ca^{2+} enters
9) neurotransmitter released onto **spiral ganglion cells**
   - make up **auditory nerve**

Innervation of hair cells

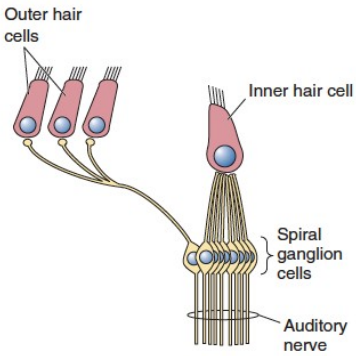
- inner hair cells feeds 10 spiral ganglion cells
- 3 outer hair cells feed 1 spiral ganglion cell
- Weird that:

CENTRAL AUDITORY PROCESSES

- Signals travel from **spiral ganglion** to **auditory cortex**
- Primary pathway (SVSIMA):
  1) spiral ganglion
  2) ventral cochlear nucleus
     - monoaural neurons: receive input from one ear
  3) superior olive
     - binaural neurons: receive input from both ears
  4) inferior colliculus
  5) MGN
  6) auditory cortex

SVSIMA: some **v**ery **s**mart Indian maths academic

- more outer hair cells than inner hair cells
- BUT 95% of cochlear output is from inner hair cells



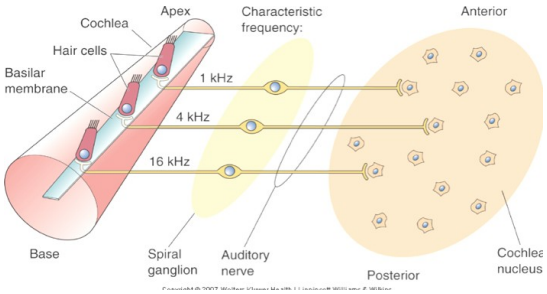
Amplification by outer hair cells

- Outer hair cells amplify sound
- By increasing movement of basilar membrane
  - Motor proteins (**prestin**) change length of outer hair cells

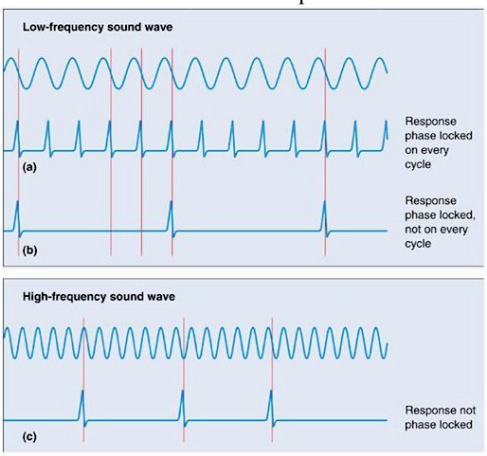
Stimulus frequency

- Sources of information about sound frequency:
  1) tonotopic maps
     - used for **high** and intermediate frequencies
  2) timing of neural firing (phase locking)
     - used for **low** and intermediate freq.

- **Tonotopic maps on basilar membrane**
  - **base** of cochlear: membrane resonates w/ **high** freq.
  - **apex** of cochlear: membrane resonates w/ **low** freq. (*think opposites!*)

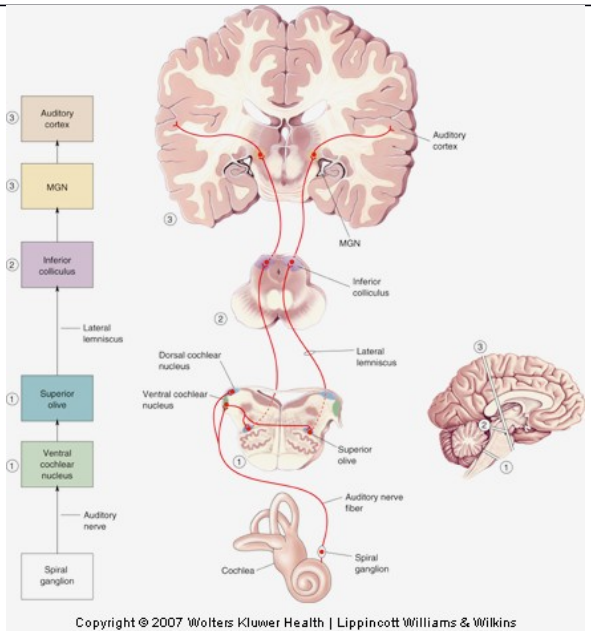


- **Phase locking**
  - Cell fires at same phase of sound waves
    - frequency of sound same as frequency of APs
  - Occurs with sound waves up to 4 kHz



AUDITORY CORTEX

- **Primary auditory cortex (A1)** on superior temporal lobe
- Has tonotopic organisation
  - strips of neurons for processing similar frequencies



ENCODING SOUND INTENSITY & FREQUENCY

Stimulus intensity

- Coded by:
  1) firing rates of neurons
  2) no. of active neurons

MECHANISMS OF SOUND LOCALISATION

- Different techniques for locating sources in:
  - horizontal plane (left-right)
  - vertical plane (up-down)

Localisation of sound in horizontal plane

- Sources of information about sound location:
  1) interaural time delay
     - used for **low** freq. (20 – 2,000 Hz)
  2) interaural intensity difference
     - used for **high** freq. (2,000 – 20,000 Hz)

- **Interaural time delay**
  - sound coming from right reaches right ear first

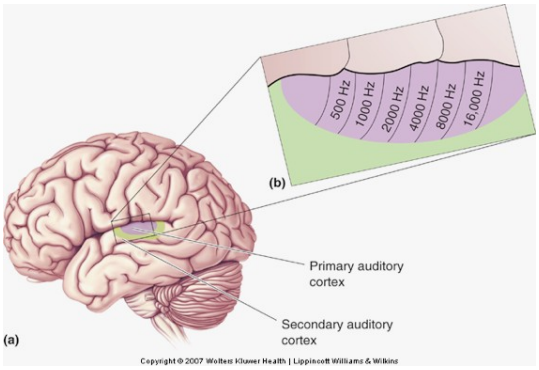
- **Interaural intensity difference**
  - sound comes from right ⊏ left ear hears lower intensity
    - sound shadow on left
  - sound comes straight on ⊏ both ears hear same intensity
    - sound shadow behind head

Sensitivity of binaural neurons to sound location

- Binaural neurons play role in sound localisation
- First structure where present: **superior olive**

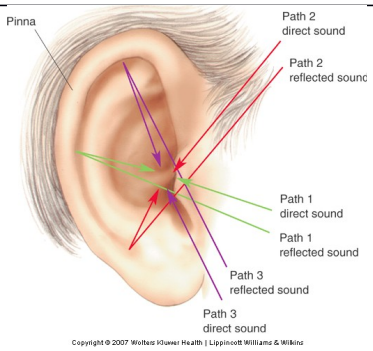
Localisation of sound in vertical plane

- Based on reflections from the pinna



Effects of lesions and ablation

- Bilateral ablation: deafness
- Unilateral lesion: normal auditory function
  - different effect in visual cortex: blindness in 1 hemifield



VESTIBULAR SYSTEM: BALANCE

FUNCTIONS

- Functions:
  - **monitors** position and movement of head
  - **gives sense** of balance and equilibrium
  - **coordinates** movements of head and eyes
  - **adjusts** body posture
- When function disrupted: **motion sickness**

VESTIBULAR LABYRINTH

- Interconnected chambers containing hair cells
- Made up of 2 structures:
  1) **otolith organs**
     - detect head tilt + acceleration
  2) **semicircular canals**
     - detect head rotation + acceleration
- Transmit mechanical energy (head movement) to hair cells

THE OTOLITH ORGANS

- Pair of large chambers
  1) **saccule**
  2) **utricle**
- Each otolith has sensory epithelium: **macula**
  - contains hair cells
    - cilia project into **gelatinous cap**
- When head straight ▭ macula is level
  - cilia from hair cells straight
- When head tilted ▭ macula tilted
  - gravity pulls the otoliths
  - deform gelatinous cap
  - cilia bend

Transduction

- Each hair cell has one tall cilia: **kinocilium**
- **Bending** of hairs **towards** kinocilium results in **depolarising** receptor potential
- Transduction then same as auditory hair cells

THE SEMICIRCULAR CANALS

- Bulge along canal: **ampulla**
  - contains sheet of cells**: crista**
    - contains hair cells
      - cilia project into **gelatinous cupula**
        - ➢ bathed in **endolymph** that fills canals
- When head rotates ▭ canal rotates
  - endolymh lags behind
  - endolymph applies force to cupula
  - cilia bend
  - excites/inhibits neurotransmitter release from hair cells

Push-pull activation of semicircular canals

- 3 semicircular canals
- Each canal paired with another on opposite side of head
- Rotation:
  - excites hair cells of one canal
  - inhibits hair cells of partner canal

CENTRAL VESTIBULAR PATHWAYS

- Integrate info. about head/body movement
- Use it to control output of motor neurons
- Pathway:
  1) **Vestibular axons** from cranial nerve VIII
  2) **Vestibular nucleus**
  3) Ventral posterior (VP) nucleus of **thalamus**
  4) **Neocortex**

VESTIBULO-OCULAR REFLEX (VOR)

- Keep your eyes in particular direction when dancing
- Works by sensing rotations of head
- Commands compensatory movement of eyes

MEMORY SYSTEMS & LEARNING 1

TYPES OF MEMORY

- **Learning**: acquisition of new information
- **Memory**: retention of learned information

Declarative and non-declarative memory

- **Declarative (explicit)**: for facts and events
  - results from conscious effort
  - can be accessed for conscious recollection
  - easy to form, easily forgotten
- **Non-declarative (implicit)**:
  - **Procedural**: for skills, habits, behaviour
  - results from direct experience
  - can't be accessed for conscious recollection
  - hard to form, hard to forget

Long-term, short-term and working memory

- **Long-term**: last days, months or years
- **Short-term**: last seconds or hours
- **Working**:
  - temporary form of information storage
  - limited in capacity
  - requires rehearsal
  - studied by measuring person's **digit span** (max no. of random numbers person can remember)

Memory consolidation

1) Memories stored in short-term memory
2) Memories selectively converted into permanent form

- BUT consolidation can occur without short-term memory

AMNESIA

- Loss of memory and/or ability to learn
- Causes:
  - concussion
  - chronic alcoholism
  - encephalitis
  - brain tumour
  - stroke

Types of amnesia

- **Limited**: most common after trauma
- **Dissociated amnesia**: no other cognitive deficit
- **Retrograde**: loss of old memories (discrete period)
- **Anterograde**: inability to form new memories

Electrical stimulation of human temporal lobes

- Causes flashbacks
- Suggests temporal lobe important for learning & memory

THE TEMPORAL LOBES AND DECLARATIVE MEMORY

Effects of temporal lobectomy

- Expect it to have profound effect on learning & memory
- **Human study: H.M.**
  - medial temporal lobe removed to alleviate seizures
  - no effect on perception, intelligence, personality
  - BUT severe amnesia
    - **partial retrograde amnesia** - years before operation
    - **extreme anterograde amnesia**
      - can't form new declarative memories (facts)

Medial temporal lobes and memory processing

- Important for declarative memory consolidation
- Structures:
  - **hippocampus**
  - **cortical areas** ventral to (in front of) hippocampus

- **Transient global**:
  - retrograde amnesia – for recent events
  - anterograde amnesia – lasts minutes to days
  - person appears disoriented, asks same questions
  - causes:
    - cerebral ischemia (reduced blood flow to brain)
    - concussion from trauma *rugby*

SEARCH FOR THE ENGRAM

- **Engram**: location of a memory

Lashley's studies of maze learning in rats

- Studied effects of brain lesions on learning in rats
- Severity of learning deficits linked to **size of lesions**
  - not location of lesions!

Hebb and the cell assembly

- How is external stimulus represented in brain activity?
- Theory:
  1) external stimulus activates cortical cells (**cell assembly**)
     - cells are interconnected
  2) object held in memory while activity in cell assembly
  3) if activation persists, consolidation occurs by 'growth process' - makes connections more effective
  4) later: fraction of cells of assembly activated by stimulus
  5) connections cause whole assembly to become activated
- Suggested engram could:
  - be widely distributed among cell assembly connections
  - involve neurons involved in sensation/perception

Localisation of declarative memories in neocortex

- **Hebb**: if engram relies on visual info, will be in visual cortex
  - **cortex processes sensory info and stores memories**
- Studies of visual discrimination consistent with this

Macaque monkeys: lesion study

- **Macaque monkeys** trained to visually discriminate
- After training, lesion made in visual cortex
- Animal can no longer visually discriminate

Humans: fMRI study

- Responses are specific to different objects
- Visual cortex in bird experts more activated by bird images
- Visual cortex in car experts more activated by car images

Medial temporal lobes and amnesia

- Macaque monkey brain similar to human brain
- Trained in delayed non-match to sample (**DNMS**) task
  1) Monkey displaces sample object to get food
  2) After delay – 2 objects shown
  3) Monkey displaces non-matching object to get food
- Task requires **recognition memory**
- Effect of bilateral medial temporal lesions on task:
  - short delay: normal performance
  - long delay: errors made (forgot sample object)
- Conclusion – lesions cause:
  - anterograde amnesia

DIENCEPHALON AND MEMORY

- Diencephalon is outside temporal lobe
- It is associated w/ memory and amnesia

Regions of diencephalon involved in recognition memory

1) anterior thalamus
2) dorsomedial thalamus
3) mammillary bodies in hypothalamus

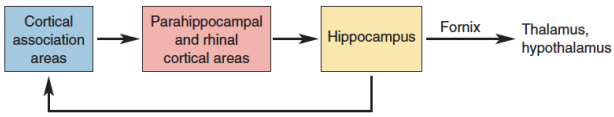
- entorhinal cortex
- perirhinal cortex

} **rhinal cortex**

- **parahippocampal cortex**
  - pathways that connect structures with other parts of brain

Information flow through medial temporal lobe

1) cortical association areas
2) parahippocampal and rhinal cortical areas
3) hippocampus
4) fornix
5) thalamus, hypothalamus

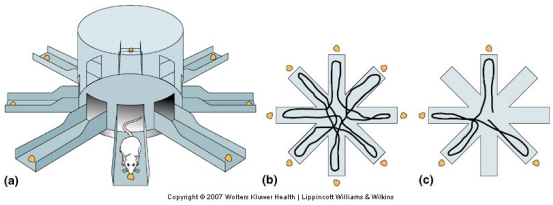


MEMORY FUNCTIONS OF HIPPOCAMPUS

- Involved in diverse memory functions
  - declarative memory
  - recognition memory
  - working memory
  - relational memory (e.g. spatial relationships)

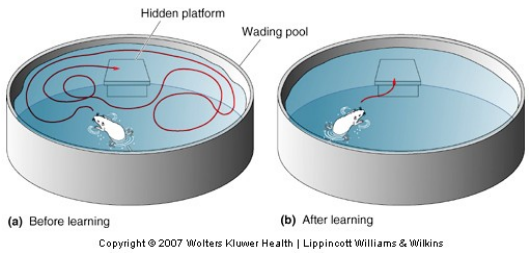
Effects of hippocampal lesions in rats: radial arm maze

- Rat placed in 8 arm radial maze
- If all arms contain food, rat goes down each arm once
- If rat learns 4/8 arms never contain food, it will ignore these
- Rat w/ hippocampal lesion:
  - goes down same arms more than once
  - leave arms containing food unexplored
    - **lesion disrupts working memory**



Effects of hippocampal lesions in rats: morris water maze

- Rat placed in pool filled w/ water
- Hidden platform below surface
- Naïve rat swims around until it bumps into platform
- Normal rats learn the location of platform – swim to it
- Rat w/ hippocampal lesion:
  - don't remember location of platform
    - **lesion disrupts spatial memory**



Pre-frontal cortex and working memory

- Monkey**: delayed-response task**

Damage to diencephalon and amnesia

- Fencing foil went into N.A.'s brain
- Lesion in left dorsomedial thalamus
- Caused:
  - retrograde amnesia – 2 years
  - severe anterograde amnesia
    - can't form new declarative memories
- Very similar to what happened to H.M.
- Medial temporal lobes and diencephalon both involved in memory consolidation

Korsakoff's syndrome

- Results from **chronic alcoholism**
- Characterised by:
  - confusion
  - memory impairment
  - apathy
- Thiamin deficiency causes lesions to:
  - dorsomedial thalamus
  - mammillary bodies in hypothalamus

STRIATUM AND PROCEDURAL MEMORY

- Basal ganglia control voluntary movements
- Two elements:
  1) caudate nucleus
  2) putamen

  } **striatum**
- Striatum:
  - receives input from frontal & parietal cortexes
  - sends output to
    - thalamus
    - cortical areas involved in movement

Lesion studies: 'light' radial arm maze task

- Small lights above arms containing food
- Rat doesn't have to remember which arms it has explored
- Has to form habit based on association between food & light
- Lesion in striatum impaired performance in light maze
  - **lesion disrupts procedural memory**

Habit learning in humans and non-human primates

- **Parkinson's** due to degeneration of inputs to striatum
- **Amnesia** due to damage to temporal lobe
- **Memory task 1: cards (procedural memory)**
  - 4 cards presented in combinations
  - icons indicate sun or rain
  - patients had to learn to predict sun or rain
  - amnesic patients improved
  - Parkinson's patients didn't
- **Memory task 2: MCQ (declarative memory)**
  - series of MCQ asked
  - Parkinson's patients were fine
  - amnesia patients were impaired

THE NEOCORTEX AND WORKING MEMORY

- **Working memory**: info held in mind for immediate need
  - e.g. remembering phone number
  - e.g. remembering arms of maze already explored
- **Hippocampus** involved in working memory
- BUT so is **pre-frontal cortex**

○ monkey sees food placed in well below cover ○ after delay, monkey chooses well ○ gets reward if correct one ○ lesion in pre-frontal cortex degrades performance • Human: **Wisconsin card-sorting test** ○ person asked to sort deck of cards ○ first by colour, then by shape ○ lesion in pre-frontal cortex degrades performance - difficulty when sorting category changes - continue to sort according to old rule	

MEMORY SYSTEMS & LEARNING 2

INTRODUCTION

- **Hebb** was right: memories can reside in synaptic alterations

PROCEDURAL LEARNING

- Amendable to investigation
- Involves learning motor response in reaction to sensory input
- Types:
  1) non-associative learning
  2) associative learning

Non-associative learning

- Change in behavioural response to stimulus over time
- Types:
  1) **habituation**
     - learn to ignore stimulus that lacks meaning
     - e.g. dog barking
  2) **sensitisation**:
     - strong stimulus
     - learn to intensify response to all stimuli
     - e.g. in black out – footsteps, headlights make you jump

Associative learning

- Form associations between events
- Types:
  1) **classical conditioning**
     - associate stimulus that evokes response (unconditional stimulus) with second stimulus that doesn't evoke response (conditional stimulus)
     - Pavlov: US = meat response = salivation CS = bell
  2) **instrumental conditioning**
     - associate a response (motor act) w/ reward
     - e.g. rat pressing lever for food

SIMPLE SYSTEMS: INVERTEBRAE MODELS OF LEARNING

- Invertebrate nervous systems have experimental advantages:
  - small nervous system
  - large neurons
  - identifiable neurons
  - identifiable circuits
  - simple genetics

Non-associative learning in Aplysia

Habituation of gill-withdrawal reflex

- If water squirted onto *Aplysia*, the gill will retract
- Eventually, it habituates
- Repeated stimulation of sensory nerve causes:
  - **reduced neurotransmitter release**
  - due to ineffective voltage-gated Ca^{2+} channels
  - Ca^{2+} doesn't enter ⎵ no AP

Sensitisation of gill-withdrawal reflex

- Apply shock to head of *Aplysia*
- Exaggerated gill withdrawal in response to siphon stimulation
- Strong stimulation of sensory nerve causes:
  - **increased neurotransmitter release**
  - due to closure of K^+ channels
  - more Ca^{2+} enters during AP

Associative learning in Aplysia

Classical conditioning

- US = strong shock to tail
- Response = gill withdrawal
- CS = stimulation of siphon
- Pairing causes greater activation of adenylyl cyclase
  - stimulates production of cAMP
  - closes K^+ channels
  - **increases neurotransmitter release**

VERTEBRATE MODELS OF LEARNING

ATTENTION

- **Attention**: selectively processing sources of info
- Benefits performance of behavioural tasks
- ADHD demonstrates how important attention is

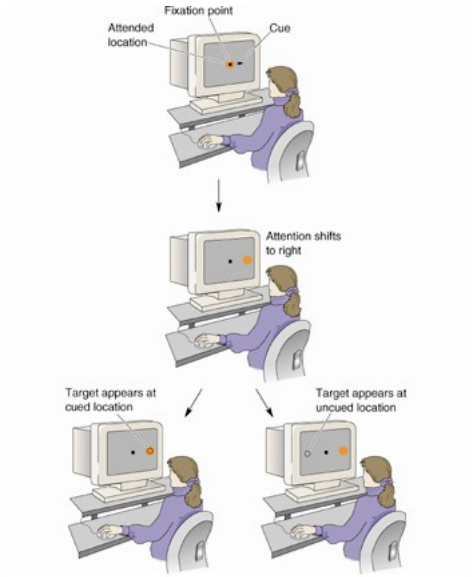
What is happening in brain when paying attention?

- Imaging studies show cortical activity is altered

BEHAVIOURAL CONSEQUENCES OF ATTENTION

Enhanced detection

- Observer maintains steady fixation
- Cue directs her to shift attention to one side of screen
- Observer asked which side of screen circular target seen on
- Detection more likely when cue on correct side (valid)



Faster reaction times

- Reaction time faster when cue on correct side

Neglect syndrome as an attentional disorder

- Person ignores objects and people to one side of gaze
  - as if half of universe doesn't exist
- Associated w/ damage to right cerebral cortex
  - neglect objects to left side
- Patients in denial

PHYSIOLOGICAL EFFECTS OF ATTENTION

- Effects in numerous sensory areas from:
  - area V1 in parietal lobe
  - visual cortical areas in temporal lobes

fMRI imaging of attention to location (spotlight of attention)

- **Task:**
  - Subjects view stimulus
  - Stimulus = line sectors radiating out from central point
  - Orientation & colour of sectors changed ever 2 secs
- **Results:**
  - Enhanced activity in visual cortex
  - Patch of enhanced activity associated w/ attended sector

PET imaging of attention to features

- **Task:**
  - Observer sees 2 frames
  - Contain moving elements - change shape, colour, speed

- Observer indicates whether stimuli are same or different
- **Results:**
  - Different areas of cortex active when different attributes discriminated
    - **colour & shape (blue & orange)**:
      - occipital lobe (V4 & IT)
      - temporal lobe
    - **speed (green)**: MT – middle temporal lobe

Enhanced neuronal responses in parietal cortex

- Assumption: attention changes location before eyes move
- Experiment by **Wurtz, Goldberg, Robinson**
- **Task:**
  - recordings made from parietal cortex of brain
    - area involved in directing eye movements
  - monkey fixates on point on computer
  - when target appears (in receptive field), animal makes saccade to target
- **Results**:
  - parietal cortex had:
    - activity when target flashed in receptive field
    - enhanced activity when saccade to target occurred
  - activity before saccade consequence of attention shift ?

Receptive field changes in area V4

HOW IS ATTENTION DIRECTED?

Pulvinar nucleus

- In posterior thalamus
- Role in guiding attention
- Sends efferents to visual cortical areas of:
  - occipital lobe
  - parietal lobe
  - temporal lobe

Attention and eye movements

- Parts of brain that direct eyes play role in guiding attention
- **Frontal eye fields (FEF) – cortical area**
  - FEF connected to areas influenced by attention in:
    - occipital lobe
    - parietal lobe
    - temporal lobe
  - neurons in FEF have motor fields (areas in visual field)
  - if current passed into FEF, eyes move to motor field of stimulated neurons
- **Moore's experiment**
  - current passed into FEF
  - activity of neuron in V4 recorded
  - stimulus presented ⎵ FEF stimulation occurs after delay
  - V4 response greater on trials with FEF stimulation
  - **Therefore** FEF mimics effects of attention

SCHIZOPHRENIA

INTRODUCTION

- Severe mental disorder
- Major public health problem – 1% of pop.

Description of schizophrenia

- Characterised by:
  - loss of contact w/ reality
  - disruption of thought, perception, mood, movement
- Name means 'divided mind'
  - patients oscillate between normal and abnormal

Positive symptoms: abnormal thoughts/behaviours

- Delusions
- Hallucinations
- Disorganised speech
- Disorganised behaviour

Negative symptoms: absence of normal responses

- Reduced emotion
- Poverty of speech
- Difficulty in initiating goal-directed behaviour
- Memory impairment

Types of schizophrenia

- **Paranoid**: themed delusions
- **Disorganised**: disorganised speech/behaviour
- **Catatonic**: disruption of movement

BIOLOGICAL BASES OF SCHIZOPHRENIA

Genes

- Schizophrenia runs in families
- Chance declines as no. of genes you share w/ affected family member decreases
- Several genes found to increase susceptibility
  - all have role in synaptic transmission/growth of synapses

Environment

- If identical twin has it, 50% chance you will have it
- Suggests genes make people vulnerable to enviro. factors:
  - viral infections during development
  - poor maternal nutrition
  - stresses throughout life

Large changes in brain

- Enlarged lateral ventricles
- Indicates loss of brain tissue

Microscopic changes in brain

- Defects in myelin sheaths around axons in cerebral cortex
- Clusters of neurons in cortex
- Changes in synapses and neurotransmitter systems

Dopamine hypothesis – symptoms caused by:

- Increased activation of DA receptors
  - DA is inhibitory
- Evidence:
  - amphetamines cause dopamine release
  - overdose leads to psychotic episodes

Glutamate hypothesis – symptoms caused by:

- Decreased activation of NMDA receptors (for glutamate)
  - glutamate is excitatory
- Evidence:
  - phencyclidine (PCP) inhibits NMDA receptors
  - causes positive and negative symptoms of schizophrenia

TREATMENTS FOR SCHIZOPHRENIA

- Drug therapy
  - **conventional drugs (*-azine, -idol*)**
    - act at D_2 receptors
    - **reduce +ve** symptoms
  - **atypical drugs (*-apine, -idone*)**
    - don't act at DA receptors in striatum
    - **reduce +ve and –ve** symptoms
- Psychosocial support
- Transcranial magnetic stimulation
  - stimulation of **frontal cortex** reduces symptoms