The brain and its connections

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Suggested reading

- Bennett MR, Hacker PMS. *History of cognitive neuroscience*. Chichester: Wiley-Blackwell, 2008: 199-236
- Cobb M. *The idea of the brain. A history*. London: Profile Books, 2020
- Glickstein M. *Neuroscience: a historical introduction*. Cambridge, Mass: MIT Press, 2014

Outline

- Neuroanatomy – structure: brain, spinal cord, peripheral nerves, muscles
- Neurophysiology – function: movement, sensation, cognitive function
- Clinical neurology
- How does the history of neuroscience inform the understanding and treatment of neurological disease?

Method:

- Chronological account encompassing some significant figures and their work: some clinicians, some scientists.

The Ancients

Aristotle (4th century BCE):

- conceived of the heart as the locus of sensation, perception, imagination, thought

Galen (2nd century CE):

- Located these functions to the brain; linked higher mental function to the ventricles

Nemesius (4th century CE):

- Developed the doctrine of ventricular localization of all mental functions: anterior – sensation, imagination; middle – intellect, reason; posterior – motion, memory.

Physiology

Fernel (1542):

- Involuntary actions: simple behaviours = reflexes

Descartes (1640s-1650s):

- Animal spirits flowing from the ventricles: “hydraulic model”.

Thomas Willis (1621-75)

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- *Cerebri anatome* ...(1664): Willis directed the dissection of brains by Richard Lower, illustrated by Christopher Wren; the circle of Willis.

- Coined the term “neurology” - the doctrine of the nerves.

- Psychological attributes are functionally dependent on the cortex, not on the ventricles.

- Animal spirits circulate in brain and nerves.

- Hughes JT. *Thomas Willis 1621-1675. His life and work*. London: Royal Society of Medicine Services, 1991

Physiology

Robert Whytt (1750s):

- Questioned fluid flow in thin nerves
- Pupillary reflexes – immaterial sentient principle

Luigi Galvani (1790s):

- Nerves conduct electricity like metal wires
- “Animal spirits” rendered obsolete

Sensory and motor nerves

Charles Bell and Francois Magendie (1810-1820s):

- Posterior spinal nerves are sensory
- Anterior spinal nerves are motor
- Anatomical division is functional

Marshall Hall (1830s):

- Spinal cord as a reflex centre, non-sentient, non-volitional: “reflex arc”. Sensory stimulus evokes involuntary motor response.

Sensation

Johannes Müller (1838):

- Sensation is not unitary: orthodoxy of five distinct senses, following Aristotle

Law of specific nerve energy:

- Each modality has characteristic sensory quality.
- Each sensory nerve has a unique responsiveness to a specific (adequate) stimulus.

Electrical nerve impulses

- Emil du Bois-Reymond (1818-1896) discovered the nerve action potential (1848).

- Hermann von Helmholtz (1821-1894) measured nerve conduction velocity (1849): 35-45 m/s.

Movement

- Voluntary:

  Motor cortex: Fritsch & Hitzig (1870), Ferrier (1873)

  Cerebellum: Flourens (1794-1867)

  Basal ganglia

- Clarke E, Jacyna LS. *Nineteenth-century origins of neuroscientific concepts*. Berkeley: University of California Press, 1987

Jean-Martin Charcot (1825-93)

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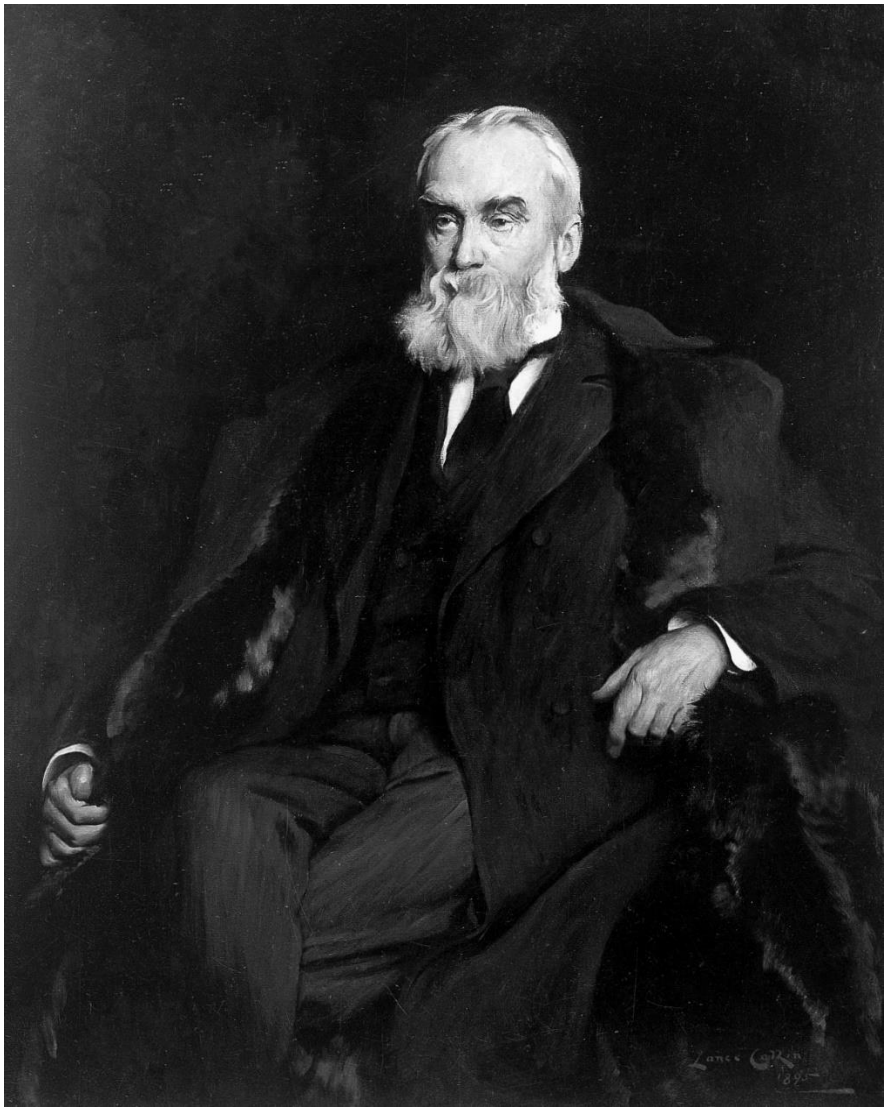
- *Methode anatomo-clinique*.
- Careful clinical examination during life correlated with post mortem findings (Paris medicine tradition of pathological anatomy – Bichat).
- Advanced ideas of multiple sclerosis and motor neurone disease.
- Stimulated usage of the term “Parkinson’s disease”, following Parkinson’s original report of 1817.

- Goetz CG, Bonduelle M, Gelfand T. *Charcot. Constructing neurology*. Oxford: Oxford University Press, 1995

John Hughlings Jackson (1835-1911)

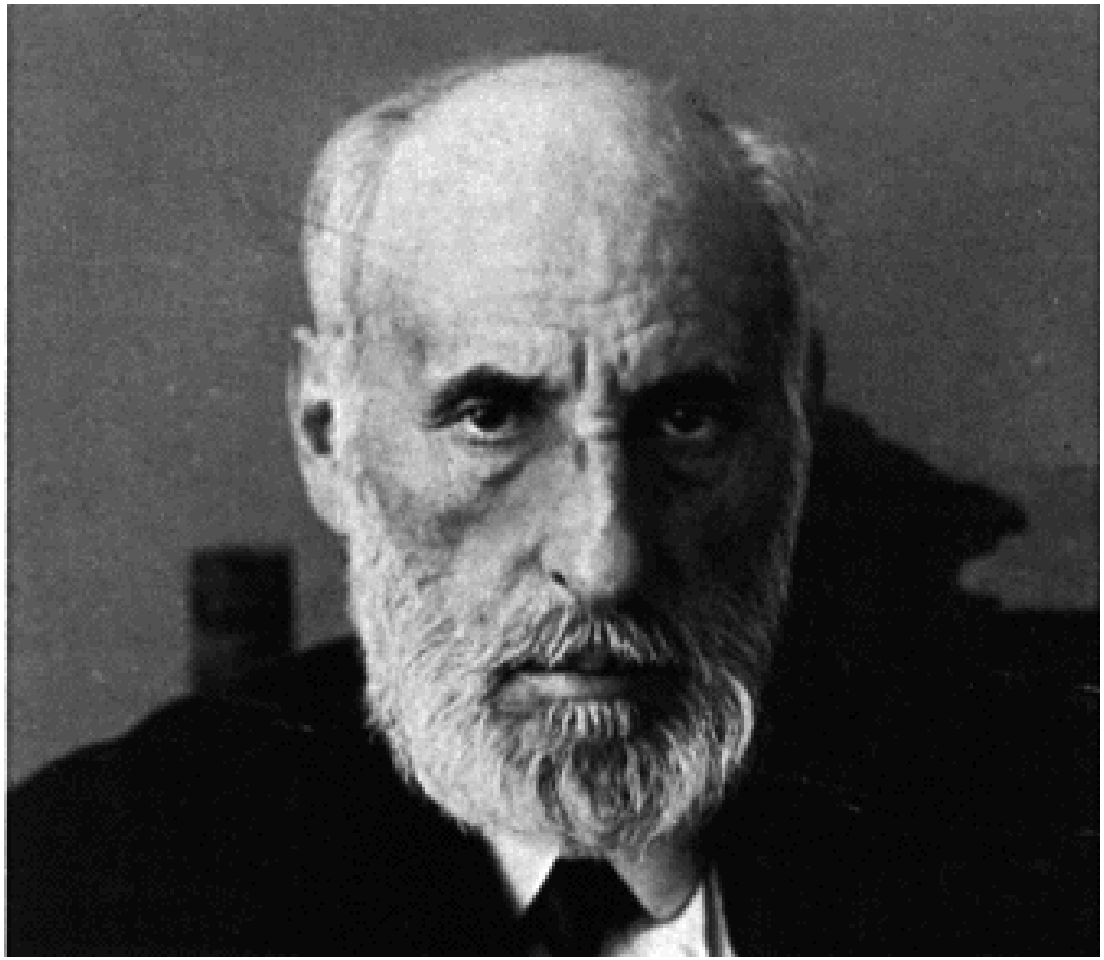


John Hughlings Jackson (1835-1911)

- Based on careful clinical observation, inferred a hierarchy of brain centres; localisation
- Jacksonian epilepsy - clinical spread permitted inferences about brain structure.
- Positive and negative neurological symptoms

- Critchley M, Critchley EA. *John Hughlings Jackson. Father of English neurology*. Oxford: Oxford University Press, 1998

Santiago Ramon y Cajal (1852-1934)



Santiago Ramon y Cajal (1852-1934)

- Used Golgi method to study microscopic anatomy of the brain and retina.

- Refuted Golgi's "reticular theory", in favour of the "neurone doctrine".

CS Sherrington (1857-1952)

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- Named points of contact between neurones “synapses”.
- Reflex contraction and reciprocal inhibition within the spinal cord.
- Spinal reflexes modulated by cortical pathways.
- “Final common pathway”.
- *The integrative action of the nervous system* (1906)

Synaptic transmission

Otto Loewi (1873-1961) + Henry Dale (1874-1968)

- Demonstrated the chemical nature of synaptic transmission:
- in frog heart (Loewi; *Vagus Stoff*)
- in voluntary muscle (Dale; acetylcholine).
- Paved the way for the discovery of other neurotransmitters: noradrenaline, dopamine, glutamate, GABA
- JN Langley: receptors

Electroencephalography (EEG)

- Hans Berger (1873-1941) made the first recording of the human EEG in 1924
- Acknowledged prior work of Richard Caton in Liverpool, who recorded electrical activity in the animal brain in 1875
- Remains an important technique for diagnosis and investigation of neurological disorders such as epilepsy.

- Brazier MAB. *A history of the electrical activity of the brain. The first half-century*. London: Pitman, 1961.

Nature of the action potential

- Recording from squid giant axon, Alan Hodgkin (1914-98) and Andrew Huxley (1917-2012) developed a model of nerve impulse based on changes in membrane permeability to Na^+ and K^+ (1952).
- Hodgkin AL. *The Conduction of the Nervous Impulse*. Liverpool: Liverpool University Press, 1964.

- Specific membrane channels: mutations in which underpin various neurological diseases

Neurophysiology of membranes

- Characterisation of ion channels in excitable membranes (e.g. by patch clamp technique) and of genes which encode specific ion channels and membrane receptors for neurotransmitters.

- Role of long term synaptic potentiation as a possible explanation for learning.

Brain anatomy in vivo

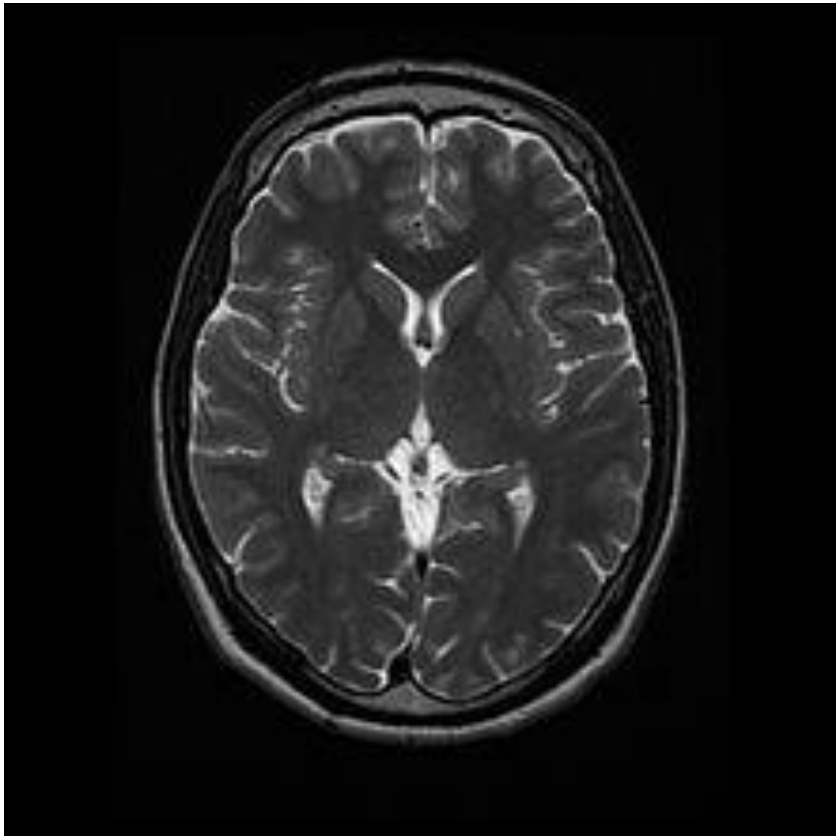
Godfrey Hounsfield (1919-2004):

•Computed tomography of the brain

Brain anatomy in vivo

Peter Mansfield (1933-2017)/Paul Lauterbur:

- Magnetic resonance imaging of the brain



Modern neuroimaging

Enhanced understanding of brain morphology and pathology using increasingly sophisticated imaging techniques:

- Structural: CT, MRI, voxel-based morphometry
- Functional: SPECT, PET, DaTScan, functional MRI

“Equipotentiality”

- “Equipotentiality”: preservation of any region may permit acquisition of a task

Flourens (1820s)

Karl Lashley (1890-1958):

- in rats, brain volume removed rather than its specific location determined spatial learning memory – law of mass action: generalised ability to learn complex tasks

Localisation

Gall (1791):

- “organology”- each psychical and moral faculty possessed its own cortical organ

Spurzheim:

- “phrenology”, analysis by examining the external contours of the skull (“cranioscopy”).

Ferrier (1873)

- “localise phrenologically the organic centres of various mental endowments”

Localisation: Language function

Paul Broca (1824-80), 1861:

- patient M. Leborgne (“Tan”) with non-fluent aphasia with preserved comprehension – focal lesion of third frontal convolution

Carl Wernicke (1848-1904), 1874:

- patients with fluent aphasia with impaired comprehension – lesion of superior temporal lobe

Localisation: Perceptual function (vision)

- Tatsuji Inouye (1881-1976) – Russo-Japanese war 1905
- Gordon Holmes (1876-1965) – World War I
- Mapped visual field defects and correlated with occipital lobe gunshot injuries (X-rays, surgery).
- Macula represented at the occipital pole; sup/inf fields map to inf/sup calcarine fissure.

- McDonald I. *Brain* 2007; 130: 288-98

Localisation: Memory function

- Patient ‘HM’: Henry Molaison (1926-2008)
- Anterior bilateral temporal lobectomy for intractable epilepsy 1953
- Profound anterograde memory impairment – studied by Brenda Milner
- Importance of the hippocampus in memory
- HM was a research subject for > 50 years, shed much light on brain mechanisms of memory

- Corkin S. *Permanent present tense. The man with no memory, and what he taught the world*. London: Allen Lane, 2013
- Dittrich L. *Patient H.M. A story of memory, madness and family secrets*. London: Chatto & Windus, 2016

Wilder Penfield (1891-1976) and Herbert Jasper (1906-99)

- Stimulated brain prior to neurosurgery in awake patients
- Mapped sensory and motor cortices: cortical homunculus
- Jasper H, Penfield W. *Epilepsy and the Functional Anatomy of the Human Brain.* 2nd edition. Little, Brown and Co., 1954.

Neurobiology of disease

Neurobiology of disease

Traumatic brain injury

Epilepsy

Parkinson’s disease

Alzheimer’s disease

Traumatic brain injury

Ramon y Cajal:

- Lack of neuroregeneration in mammalian brain, contrast with potential for regeneration in peripheral nervous system, and in non-mammalian organisms

Current understanding:

- regenerative capacity is present, substrate hostile to regeneration: scar, neuroinhibitory molecules
- Treatment: change the substrate: olfactory ensheathing cells; activate residual connections extrinsically (implantable electrodes)

Epilepsy

Disorder of brain electrical activity:

- Hypersynchronous discharges of brain tissue, focal or generalised, causing paroxysmal motor, sensory, psychic symptoms
- Many causes: brain injury, infection, neurodegeneration
- Treatment: anti-epileptic drugs, many of which act on ions channels to modulate electrical activity

Parkinson's disease

Disorder of movement:

- Imparied brain neurochemistry: deficiency of dopaminergic neurotransmission through the nigrostriatal tract (Hornykiewicz)

- Treatment: repletion of neurotransmitter through provision of pro-drug, levodopa, metabolised in situ to dopamine (Cotzias); and/or drugs which act at dopamine receptors

Alzheimer's disease

Disorder of brain connectivity:

- Proteinopathy: accumulation of proteins, amyloid beta peptide in plaques, tau in hyperphosphorylated state in neurofibrillary tangles. Disordered axonal transport, synaptic failure.
- Secondary disorder of brain neurochemistry: cholinergic neurotransmission through the basal forebrain

Treatment:

- Symptomatic: repletion of neurotransmitter through provision of cholinesterase enzyme inhibition
- Disease modifying: prevention of deposition/synthesis of amyloid beta peptide, hyperphosphorylated tau
- Not yet achieved (*contra* lecanemab)

- Thank you!
- Questions?