- Less structured images are brighter; structured images are darker > why it is good for pathological reasons; detects fluid in the brain which then causes swelling
- 2m resolution; 5 minutes to scan the whole brain
- Forms the basis of BOLD fMRI
- Brain intensity: brightness of image - CSF>GM>WM

ADVANTAGES OF HIGHER TELSA: increased SNR, less scanning time for similar quality, increased spatial resolution, increased technical challenge DISADVANTAGES: more heat, more absorption of radio frequencies

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LO2: Understand what each scan mentioned in the lecture indexes in the brain - i.e., know which measure functional or structural properties, and know which kinds of structural and functional properties each technique measures.

	What does it do?	**Functional v Structural properties**	**What it specifically measures**	**Static (picture) v Dynamic (video/changes over time)**
X Ray	Involves injecting into one part of the body a substance that absorbs x-rays, either less than or more than the surrounding tissue The injected substance then heightens the contrast between the part of the body and the surrounding tissue	Structural	It looks at the contrast between places that have been injected with substance and those that have not	Static
CT	Many X-rays in slices of the body	Structural	""	Static
MRI (structural/basic)	Magnetic energy absorbed by hydrogen (H) atoms in the body, which is then re-released and picked up by transmitter	Structural	All structure of the brain (sulci and gyri) and other things contained within (e.g. blood, bone)	Static
DWI	"" but tuned for water (H_2O)	Structural	"" except: better tuned for water/blood (appears white instead of grey)	Static
DTI	Similar to DWI, modified specifically for water in white matter	Structural	"" except: better tuned for white matter tracts	Static
Functional MRI	Same as above, but tuned for blood	Functional	Same as DWI except tuned for blood, and viewed over time: Can see blood flow to parts of brain during activities to see which parts of brain responsible for action	Dynamic
EEG	Uses electrodes (like metal stickers on your head) which pick up electrical activity in the brain (caused by neurons firing) *Requires "reference" EEG to establish baseline for patient/equipment*	Functional	Brain waves	Dynamic
MEG	Same as MRI *Does not require "reference" MEG to establish baseline*	Functional	Brain waves Useful for epilepsy	Dynamic

Summary: lots of ways to look at the brain – **no method is the best** – MRI: multi-modal, fMRI: superior spatial resolution – EEG/MEG: superior temporal resolution – EEG: superior portability – TMS: superior inference

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Week 3: Dementia and Alzheimer's Disease

LO1: What is Dementia?

Dementia is not a disease – it is a way to describe a set of symptoms including: poor memory and difficulty learning new information; this makes it difficult to function independently

- Considered an unusual loss of function that exceeds what is caused by "normal aging"

Symptoms associated with dementia:

- A reduced sensitivity to the environment
- Tendency to perform repetitive, stereotyped actions
- A deficit that is greater for controlled processing than for automatic processes or responses
- Depression

Epidemiology

A 2% annual increase in the incidence of dementia after that age of 75years;

Above 80 years, around 25% of the population are significantly demented; rising to 40% after 85 years

Diagnosis: DSM-V

DSM-V criteria:

Loss of intellectual ability with resulting social and occupational handicap, and one or more of:

- Impaired judgement
- One of the instrumental disorders including aphasia, apraxia, agnosia, constructional difficulties or
- Personality changes

No single test to unambiguously diagnose dementia however there are some clinical tests that can be used:

Name as many as possible within a minute (quick and dirty) - Folstein mini-mental state exam - Activities of daily living scale

Other screen tests include: blood tests, MRI, scans, lumbar puncture

Causes of dementia

Dementia is associated with ageing, although AGEING IS NOT A CAUSE – usually caused by some sort of damage to brain cells, which would be caused be a variety of diseases

Some causes of dementia include:

- Neurodegenerative disorders – AD, PD, HD; vascular disorders (e.g. multi-infarct dementia or MID – associated with small strokes in the brain); metabolic, endocrine and nutritional disorders (disorders of thyroid, pituitary); infection (e.g. AIDS, meningitis, encephalitis); toxins (e.g. alcohol, drugs, metal poisoning) - list is not exclusive
- Psychiatric disorders – pseudo-dementia – secondary deterioration in cognition; AD (60%) and MID (15%) most commonly associated with dementia

MID: prevalence higher in males (cerebrovascular origins); onset of MID is typically abrupt and progression is step-like; initial symptoms are associated with headaches and dizziness, and tend to be quite focal

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LO2: Alzheimer's Disease: What it is – Inheritance/Genetics Symptoms – Neuropathology – Histological Biomarkers – Treatment

Alzheimer's Disease: the most common cause of dementia – involves a loss of neurons in the brain particular in the cortex – associated with aphasia, agnosia, apraxia; must be paired with general decline in intellect or cognitive function – appearance of symptoms is progressive/gradual

Difference between people with AD and normal aging

Clinical symptoms only appear after a threshold number of plaques have been exceeded – there is a threshold of degeneration that occurs before symptoms start to manifest – hard to test these diseases pre-manifest

Everyone will develop plaques and tangles with age, but do not normally develop aphasia, agnosia and apraxia – qualitative differences exist in regional pattern of neuronal cell loss in the hippocampus of those with AD and normal elderly people – all of these diseases have selective degeneration – cell loss is specific to certain regions in the brain and so is the spread

In studies of AD: regions of the brain with reduced metabolism in patients with AD – compared to controls, the AD group had reduced bilateral activation in prefrontal, parietal, temporal and posterior cingulate regions – makes sense since there is atrophy in those regions

Diagnosis: brain biopsy AFTER DEATH - diagnosis is made by "exclusion" and can only then can we say it may be "probable AD" – NO CURE; treatment in the form of medication but the benefits are small

Inheritance/Genetics of AD

If a person has a first degree relative with AD, then s/he has a 50% chance of developing – Gene on chromosome 19 (coding for ApoE4) also strongly associated with an increased risk of developing AD (as well as heart disease, MID, etc)

- The risk of Alzheimer's disease is higher the more copies of the apoE-4 allele are on chromosome 19 – Nearly all persons born with two copies of the allele die before 80 with AD. Even so, a few individuals more than 90 years old have this genetic risk factor but show no signs of dementia – increases risk by 12-fold
- Higher education appears to protect against dementia in later years –The basis for this strong effect is mysterious.
    - One hypothesis is that higher education builds up reserve synapses and circuits in the brain that are a buffer against the neuron damage during Alzheimer disease – exercise is believed to activate the brains

Symptoms

Early symptoms: forgetfulness, impaired recent memory, transient confusion, anomia, disorientation, confabulation and anosmia

Followed by: deficits in general cognitive functioning (e.g. abstract reasoning, etc) – performance of concurrent tasks also impaired which highlights the frontal component of the brain– find that people need to go into a nursing home because they can no longer do the basic stuff

Later symptoms (very): repetition, apathetic, careless with appearance and hygiene, emotional lability, indifference, restlessness, agitation, impatience, disinhibition, pessimism, aggression

True aphasia, agnosia and apraxia, and the motor disorders come later – do not see huge motor deficits – more of a cognitive disorder

Eventually patient becomes bed-ridden, mute and unresponsive

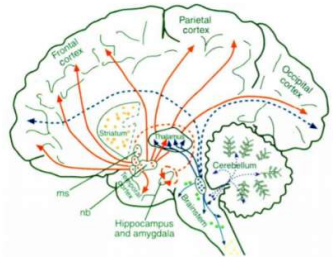
Memory: memory loss is profound and deterioration is rapid (most common symptom) – Episodic memory more at risk – everyday memory impairments – *severe memory acquisition deficit* (more so for newly acquired info) – poor performance in recall memory – implicit and procedural memory are typically preserved (over time these do go as well)

Control processing: Deficit in controlled processing (automatic processing not as effected) – Deliberate, effortful controlled processing requires the use of limited processing resources and attention

- Deficit could be linked to the degeneration of the nucleus basalis of Meynert (a structure known to be an early target of AD – remember AD is a global disease)
  NUCLEUS BASALIS OF MEYNERT (nb)
  - Primary cholinergic innervation of cortex
  - "nb" projects to frontal, parietal and temporal cortices (red);

  Theory: is that the innervation into those cortical regions is abnormal which then triggers this whole neuropathology

  Still do not know what the causes of these diseases are – how the spread occurs
  - Also, projects to hippocampus
  - Controlled and automatic processes – linked to structure ->



Language: lang deficits appear fairly early but follows mem deficits – automatic aspects (syntax) preserved until quite later – progression is sequential (1. unable to recognise name of objects/anomia 2. repetition of speech with little context/transcortical sensory aphasia 3. Wernicke's aphasia 4. Global aphasia)

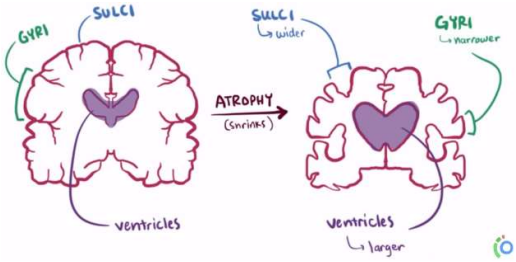
Cognitive: unusual word associations – visuoperceptual deficits (face recog) – spatial deficits (navigation)

Neuropathology

Widespread cortical atrophy and ventricular enlargement in AD – Loss of large neurons of frontal, temporal and parietal lobes (and decreased dendritic branching) – Massive (up to 75%) cell loss in the nucleus basalis of Meynert

Other major neurotransmitter imbalances:

- Noradrenergic system (general arousal)
- Serotonergic system (down regulation of arousal)
- Dopaminergic system (movement control, reward, attention, emotion)



As neurons die, large scale changes start to take place in the brain – the brain atrophies (shrinks): gyri become **narrower** – sulci become **wider;** ventricles become **larger**

Histological Biomarkers

Evidence of things in the brain that indicate the present of AD: Neuritic plaques – Neurofibrillary tangles (flame shaped) found commonly in hippocampus and other parts of the brain – amyloid beta-protein: amyloid accumulation in the brain is believed to start from the blood then it travels up to cause the neuropathology

- *Role of Amyloid Beta Protein in AD:* ABP may be released by neurons, glial cells or the circulatory system and accumulates as diffuse plaques – As it is being released, other proteins become embedded in this plaque mix causing neuronal degeneration – ABP, glial cells and other proteins become embedded in the plague matrix causing nearby neuronal degeneration

Treatment

Treatment for Mild to Moderate Alzheimer's

Cholinesterase inhibitors: may help delay or prevent symptoms from becoming worse for a limited time and may help control some behavioural symptoms – Razadyne® (galantamine), Exelon® (rivastigmine), and Aricept® (donepezil) – on the market

- Do not yet fully understand how cholinesterase inhibitors work, but research indicates that they prevent the breakdown of acetylcholine, a brain chemical believed to be important for memory and thinking
  - As Alzheimer's progresses, the brain produces less and less acetylcholine; therefore, cholinesterase inhibitors may eventually lose their effect

Treatment for Moderate to Severe Alzheimer's

Namenda® (memantine), an N-methyl D-aspartate (NMDA) antagonist

Drug's main effect is to delay progression of some of the symptoms of moderate to severe AD – It may allow patients to maintain certain daily functions a little longer than they would without the medication

- Namenda® may help a patient in the later stages of the disease maintain his or her ability to use the bathroom independently for several more months, a benefit for both patients and caregivers
  - Works by regulating glutamate, which if produced in excessive amounts may lead to brain cell death.

  Because NMDA antagonists work very differently from cholinesterase inhibitors, the two types of drugs can be prescribed in combination

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Summary: • AD is a cortical dementia with no single agreed cause • AD causes plaques and tangles with neuronal loss in various brain regions • Symptoms include profound memory loss with a range of other cognitive features • There may be a genetic predisposition to the development of AD and various drugs may delay progression

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Week 4: Parkinson's Disease

LO1: Parkinson's Disease: Causes – Symptoms – Pathology – Treatment

Movement disorder where the dopamine-producing neurons in the substantia nigra (of the basal ganglia) of the brain, undergo degeneration

One of the most common neurological disorders – progressive – adult onset disease (65yos) – becomes more common with age (affects 1% of people over 60yo) – slowed general motor and cognitive function – no specific test to diagnose Parkinson's