

DEMENTIA AND RELATED NEUROLOGICAL DISORDERS



LECTURE OVERVIEW

- Dementia
- Alzheimer's Disease
- Psychological symptoms
- Biological changes
- Proposed causes
- Diagnosis
- Medical treatments
- Psychosocial treatments
- Other neurological diseases that can cause dementia

850,000

people are estimated to be living with dementia in the UK.

1 in 3

people born in the UK this year will develop dementia in their lifetime.



24% of men and 35% of women born in 2015 will develop dementia in their lifetime.

24.6 million

people in the UK – 38% of the population – know a family member or close friend living with dementia.

5.2%

of people over the age of 60 are living with dementia globally.

209,600

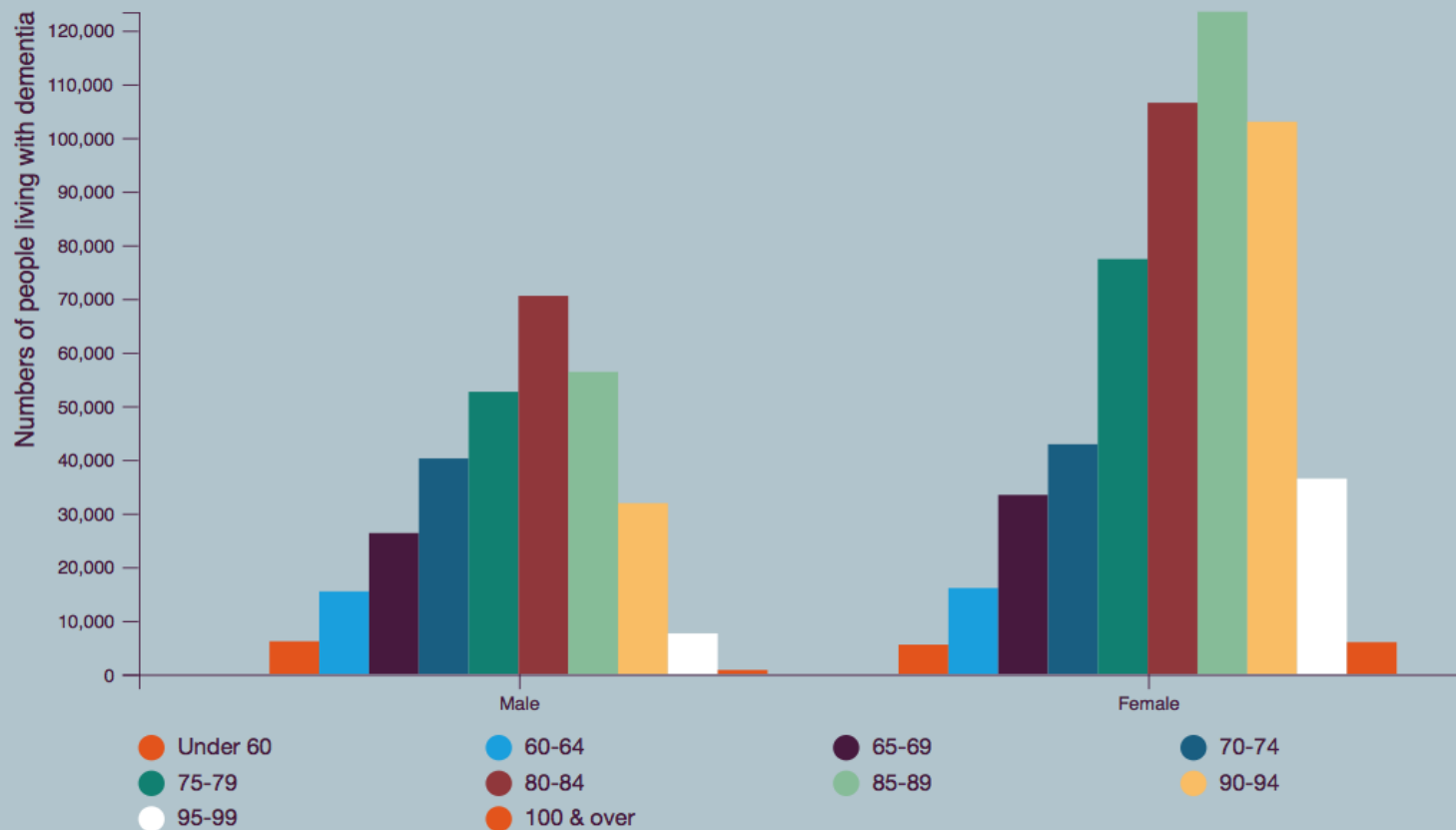
The number of new cases of dementia a year in the UK.



One in 14

people over 65 have dementia in the UK and one in 79 of the whole population.





The majority of dementia costs per year are due to **informal care at £11.6bn (44.2%)**, with social care costing £10.3bn (39.0%) and healthcare costs £4.3bn (16.4%). **The total cost is over £26bn.**

1/4

of hospital beds are occupied by people living with dementia who are over 65.



Lifestyle changes to improve cardiovascular health can reduce the risk of dementia.



Around a third of a person's risk of developing Alzheimer's disease may be due to **modifiable lifestyle factors.**

ATTITUDES TO DEMENTIA



39% of people under 60 years and **52%** of people 60 years and above said that **Alzheimer's is the disease they are most concerned about**. It is the most feared disease for people 60 years and above.

24.6 million

people in the UK – **38% of the population** – know a family member or close friend living with dementia.

49%

of people are worried that they would be seen as mad after a diagnosis of dementia and **56% of people put off seeking a diagnosis** for up to a year or more.

1.5 million people

in the UK, including **both people living with dementia and their carers**, would benefit from new dementia treatments.

3/4

of people are **unaware** that they can affect their risk of developing dementia.



46% of people think dementia mostly affects older people, 15% think dementia affects only old people and 9% of people think dementia can also affect younger people.



23% of people identified dementia as caused by brain disease or degeneration and 46% identified it as loss of memory.



40% of people would adopt a healthier lifestyle to reduce their risk of developing dementia.

3/4

of people didn't think that giving up smoking could reduce your risk of developing dementia.

42%

of people believe that once a person living with dementia stops recognising loved ones, they don't benefit from spending time with them.



85% of people want to stay at home as long as possible after a diagnosis of dementia, 47% think they would be able to.



68% of people feel isolated following a diagnosis of dementia.

IMPACT OF DEMENTIA IN UK

Two thirds of the cost of dementia is paid by people with dementia and their families.

850,000 people in the UK, with numbers set to rise to over 1 million by 2025. This will soar to 2 million by 2051.

225,000 will develop dementia this year, that's one every three minutes.

1 in 6 people over the age of 80 have dementia.

70 per cent of people in care homes have dementia or severe memory problems.

There are over 40,000 people under 65 with dementia in the UK.

Dementia is one of the main causes of disability later in life, ahead of cancer, cardiovascular disease and stroke.

Unpaid carers supporting someone with dementia save the economy £11 billion a year.

There are an estimated 46.8 million people living with dementia and the numbers affected will double every 20 years, rising to 115.4 million in 2050.

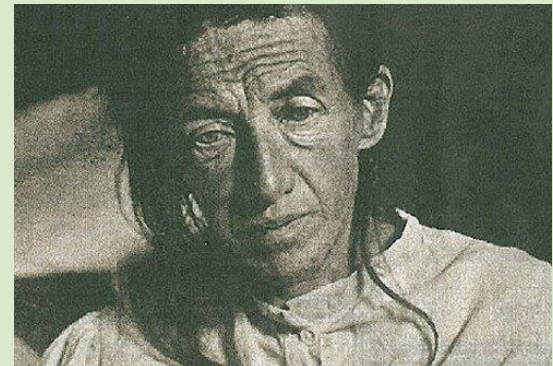
Another 7.7 million people will develop dementia around the world every year.

DEMENTIA

- Loss of cognitive function severe enough to interfere with normal daily activities and social relationships
- Can be caused by diseases that affect the nervous system
 - e.g.
 - Cardiovascular disorders
 - Neurologically-based disorders
 - Abnormalities in other bodily systems

ALZHEIMER'S DISEASE

- Most common cause of dementia
- Alois Alzheimer (1864-1915) First to link changes in brain tissue with observable symptoms
- Alzheimer (1907): Study from 1901–1906
 - Auguste D. Female, late 50s
 - Progressive mental deterioration marked by increasing confusion and memory loss
 - Found an odd disorganisation of the nerve cells in the cerebral cortex
 - Speculated that these microscopic changes responsible for the symptoms
- Slides of brain later confirmed as Alzheimer's disease (Enserink, 1998)



TYPICAL EARLY SYMPTOMS OF ALZHEIMER'S MAY INCLUDE:

Memory

Regularly forgetting recent events, names and faces.

Repetition

Becoming increasingly repetitive, e.g. repeating questions after a very short interval.

Misplacing things: Regularly misplacing items or putting them in odd places.

Confusion

Uncertainty about the date or time of day.

Disorientation

People may be unsure of their whereabouts or get lost, particularly in unfamiliar places.

Language: Problems finding the right words.

Mood and behaviour: Some people become low in mood, anxious or irritable. Others may lose self-confidence or show less interest in what's happening around them.

As the disease develops Alzheimer's develops over time, but the speed of change varies between people.

- **Memory and thinking skills:** People will find that their ability to remember, think and make decisions worsens.
- **Communication and language** become more difficult.
- **Recognition:** People may have difficulty recognising household objects or familiar faces.
- **Day-to-day tasks** become harder, for example using a TV remote control, phone or kitchen appliance. People may also have difficulty locating objects in front of them.
- **Changes in sleep patterns** often occur.
- **Behaviour:** Some people become sad, depressed or frustrated about the challenges they face. Anxieties are also common and people may seek extra reassurance or become fearful or suspicious.
- **Physical changes:** People may have problems walking, be unsteady on their feet, find swallowing food more difficult or have seizures.
- **Hallucinations and delusions:** People may experience hallucinations, where: they see or hear things that aren't there. Others may believe things to be true that haven't actually happened, known as 'delusions'.
- **Care:** People gradually require more help with daily activities like dressing, eating and using the toilet.

PSYCHOLOGICAL SYMPTOMS

- Earliest signs are usually cognitive - occasional loss of memory recent events or familiar tasks
- Changes in personality and behaviour also become evident
- Final stage – loss of ability to perform the simplest and most basic of everyday functions
- Rate of progression varies but there is a fairly regular pattern of loss over time
- Survival time - 7 to 10 years after diagnosis when diagnosed in 60s or 70s
- 3 years if diagnosed in 90s (Brookmeyer et al, 2002)

PROGRESSION



STAGES OF ALZHEIMER'S

- **Stage 1:** Normal
- **Stage 2:** Normal aged forgetfulness
- **Stage 3:** Mild cognitive impairment
- **Stage 4:** Mild Alzheimer's
- **Stage 5:** Moderate Alzheimer's disease
- **Stage 6:** Moderately severe Alzheimer's disease
- **Stage 7:** Severe Alzheimer's disease

AFFECTED BRAIN STRUCTURES

Mild Cognitive Impairment



Duration: 7 years

Disease begins in
Medial Temporal Lobe

Symptoms:
Short-term
memory loss

Mild Alzheimer's



Duration: 2 years

Disease spreads to
Lateral Temporal &
Parietal Lobes

Symptoms include:
Reading problems
Poor object recognition
Poor direction sense

Moderate Alzheimer's



Duration: 2 years

Disease spreads to
Frontal Lobe

Symptoms include:
Poor judgment
Impulsivity
Short attention

Severe Alzheimer's



Duration: 3 years

Disease spreads to
Occipital Lobe

Symptoms include:
Visual problems

BIOLOGICAL CHANGES

Amyloid plaques

- Protein fragments that collect together in a specific way and form insoluble deposits
 - Most closely linked – **beta-amyloid 42** (string of 42 amino acids)
- Initially described as the accumulated waste products of collections of dead neurons
- Formed from a larger protein found in the normal brain – **amyloid precursor protein (APP)**
- Can develop 10-20 years before behavioural symptoms become noticeable
- One of the first events in the pathology of Alzheimer's disease

AMYLOID PRECURSOR PROTEIN

- As APP is manufactured – embeds itself in neuron's membrane
- A small piece is lodged inside the neuron – larger part remains outside
- Normal ageing – outer part trimmed by secretases (enzymes) until it is level with the outer membrane of the neuron
- Alzheimer's brain
 - Erroneous process – APP trimmed in wrong place, causing beta-amyloid 42 to form
 - The trimmed fragments clump together to form beta-amyloid plaques
 - Insoluble, so cannot be removed or recycled

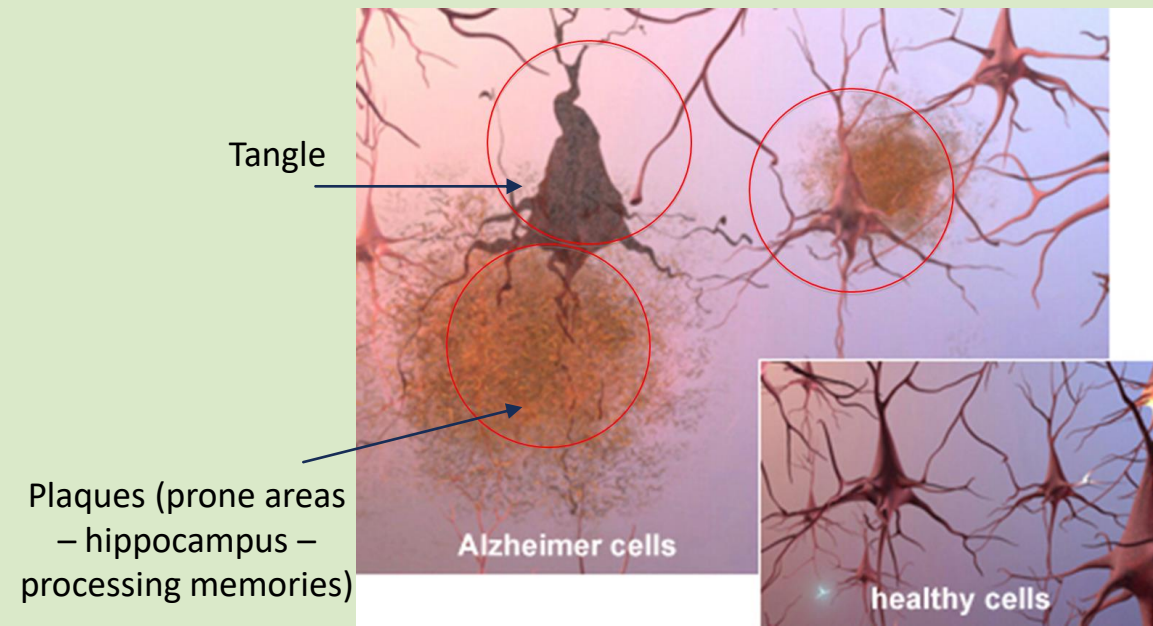
BIOLOGICAL CHANGES

- Caspase theory - proposes that beta-amyloid stimulate production of **caspases** – enzymes that are lethal to neurons
 - This destruction (apoptosis) responsible for the loss of cognitive function seen on Alzheimer's disease

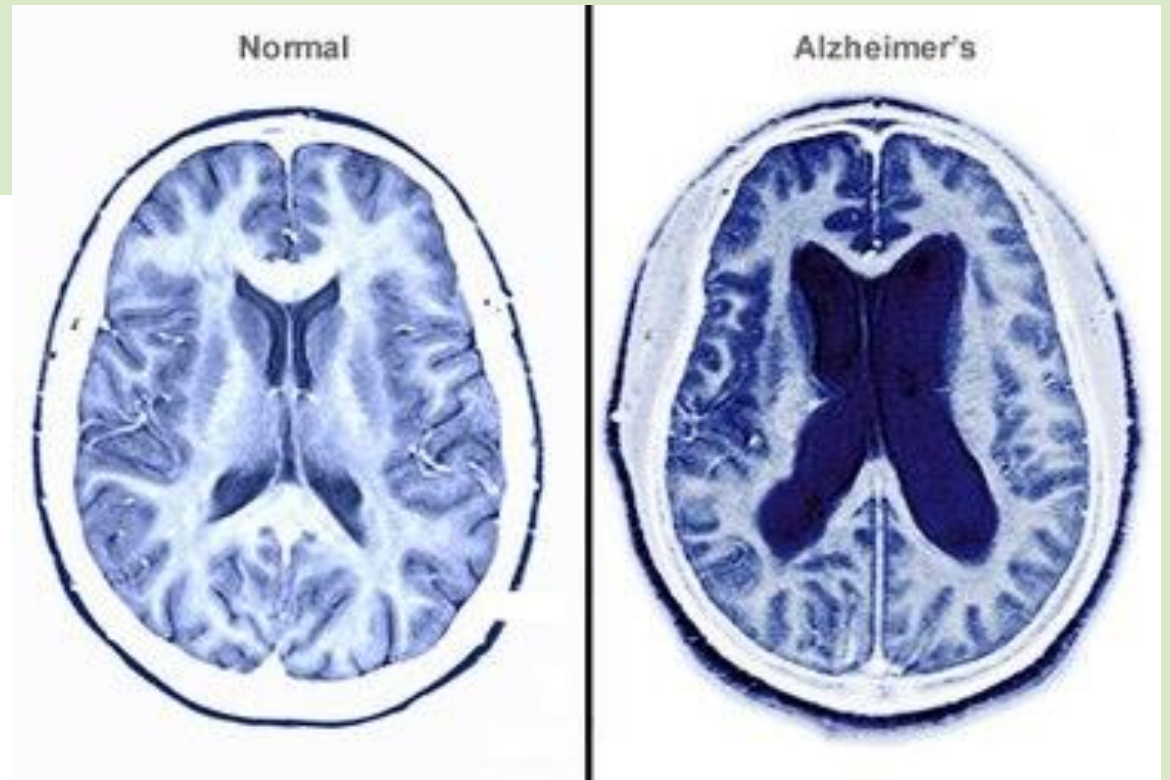
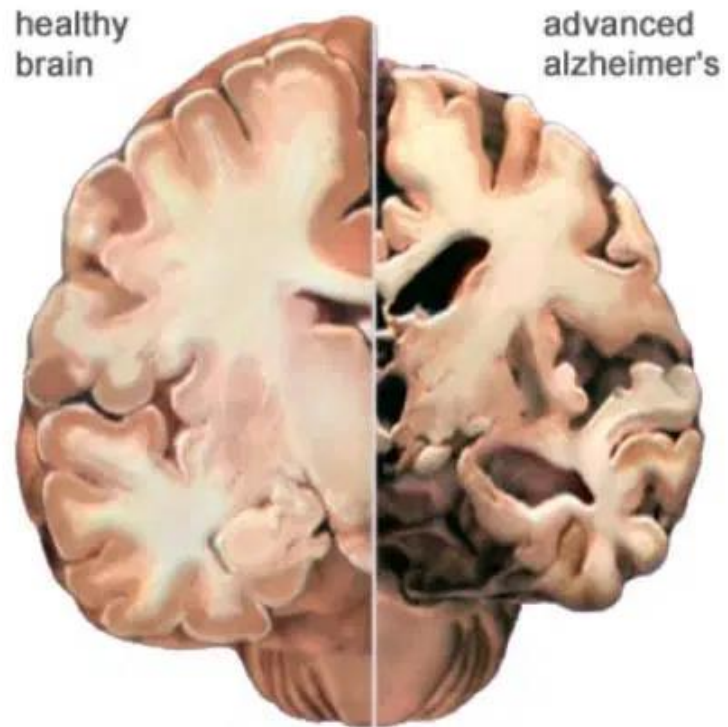
(Galvan et al, 2006)

- Also found in brain of Auguste D.: a profusion of abnormally twisted fibres within the neurons themselves - **neurofibrillary tangles**

- Made up of a protein – tau – which maintains stability of the microtubules in the axons of the neurons.
- Chemical changes in tau prevents this from occurring.
- Unstable microtubules twist around each other.
- Occur early in the disease, particularly in the hippocampus.



DESTRUCTION OF THE BRAIN



PROPOSED CAUSES OF ALZHEIMER'S DISEASE

- Agreed that plaques and tangles are associated with AD, but uncertainty remains with regard to the cause of development of these
 - Do plaques and tangles directly cause neuronal death?
 - Are these a side-product - the result of underlying processes that cause the neurons to die?
- Cognitive symptoms do not always result from these changes
 - Argued that AD is affected by environmental factors as well as biological factors (Styczynska et al, 2008)
 - Variability in both physical and cognitive symptoms (Burton et al, 2006)

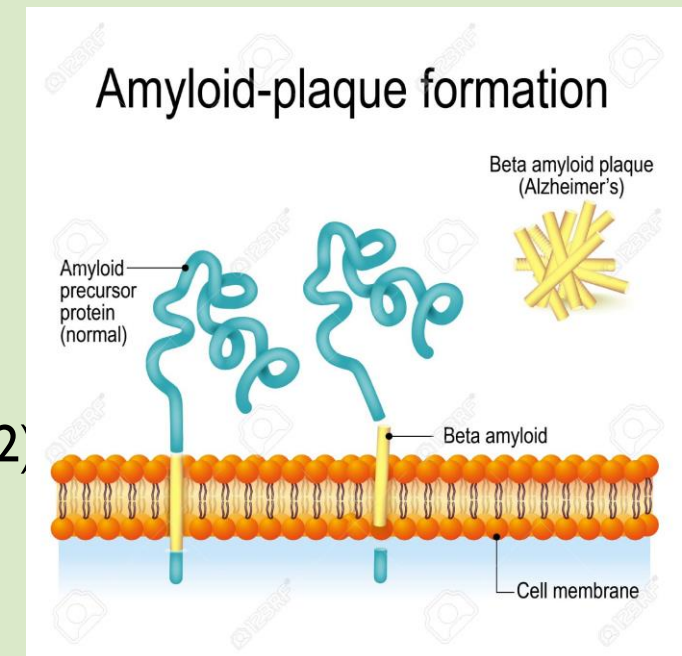
GENETIC ABNORMALITY

- Theory followed by most researchers
- Genetic abnormalities responsible for neuronal death (Tanzi and Bertram, 2008)
- Evidence: high prevalence in certain families – now called **early-onset familial AD**
 - Four genes discovered so far – believed to account for half of early-onset familial cases
 - All are linked to excess amounts of beta-amyloid protein
 - A further gene implicated has been linked to **late-onset familial AD**
 - Onset age 60-65
 - However
 - only approximately 5% of all AD cases are familial
 - the rest show no inherited pattern

GENETIC ABNORMALITY



- One of the main genes involved in late-onset familial AD is the **apolipoprotein E (ApoE) gene**
 - Located on chromosome 19
 - Carries cholesterol throughout the body
 - Binds to beta-amyloid – perhaps playing a role in plaque formation
- APP gene
 - On chromosome 21
 - Controls production of **Amyloid Precursor Protein** that generates beta-amyloid
- Most early-onset cases linked to defects in the **presenilin genes (PS1 and PS2)**
 - Speculated that PS1 and PS2 cause APP to increase production of beta-amyloid
 - This then causes neurofibrillary tangles and amyloid plaques



PREVENTION: MENTAL ACTIVITY

- Higher education and other mental activity – environmental factors that can protect from the development of Alzheimer's
- Evidence: longitudinal study
 - Nuns agreed to donate their brains after death
 - Tested for cognitive performance while alive to compare with brain upon autopsy
 - One key finding: Presence of plaques and tangles, but many nuns showed no symptomatic deficits in cognitive performance while alive
 - Later research found that higher mental activity protected the nun's from symptoms of cognitive decline, despite presence of the brain changes (lacono et al, 2009)

Further research?

PREVENTION: SOCIAL AND ENVIRONMENTAL

- Extensive social networks: reduces risk, even when person has high level of brain pathology (Bennett et al, 2006)
- Physical exercise (Geda et al, 2010)
- Limited alcohol intake in earlier years can protect against dementia in later life (Peters et al, 2008)
- Exercise with stimulation multiple sensory channels (Briones, 2006)
- Mediterranean diet (Lopez-Miranda et al, 2009)



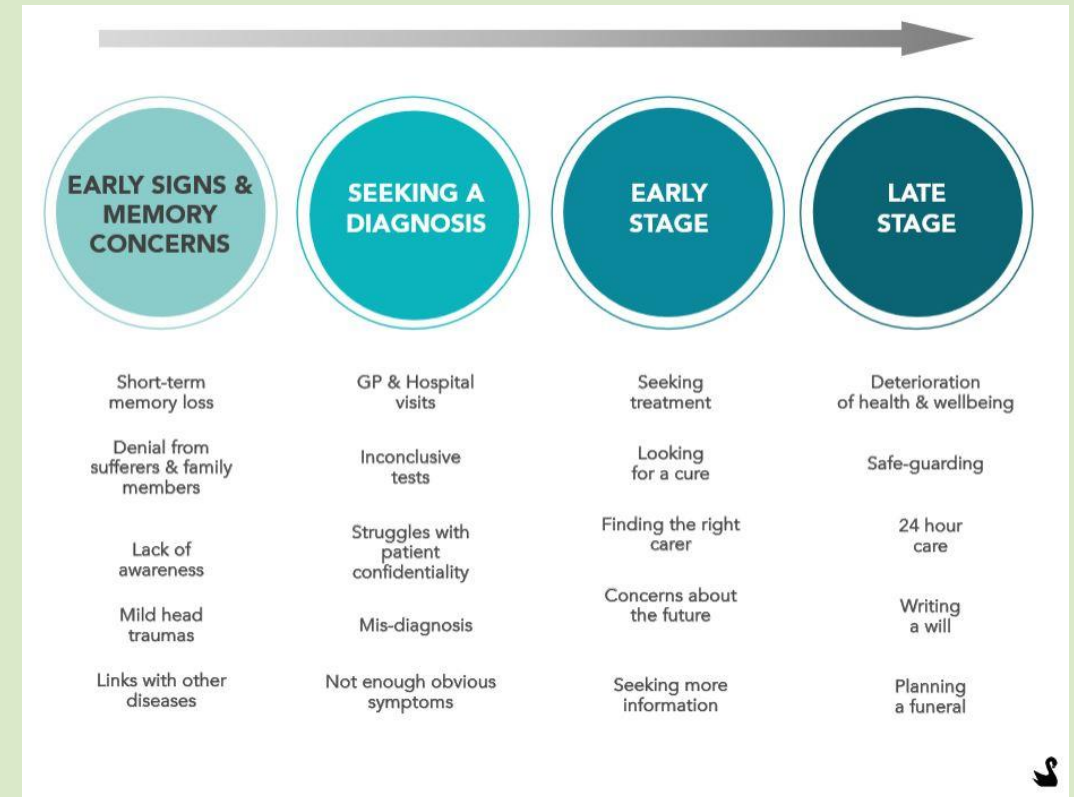
DIAGNOSIS

- Psychiatrists and clinical psychologists

DSM-V : 'Dementia' replaced with
'major neurocognitive disorder'
'mild neurocognitive disorder'

Signs include:

- Progressive memory loss
 - Aphasia (language losses)
 - Apraxia (loss of coordination)
 - Agnosia (recognition)
 - Disturbance in executive functioning (planning and organization)
- Diagnosis involves the process of exclusion – what is not the cause

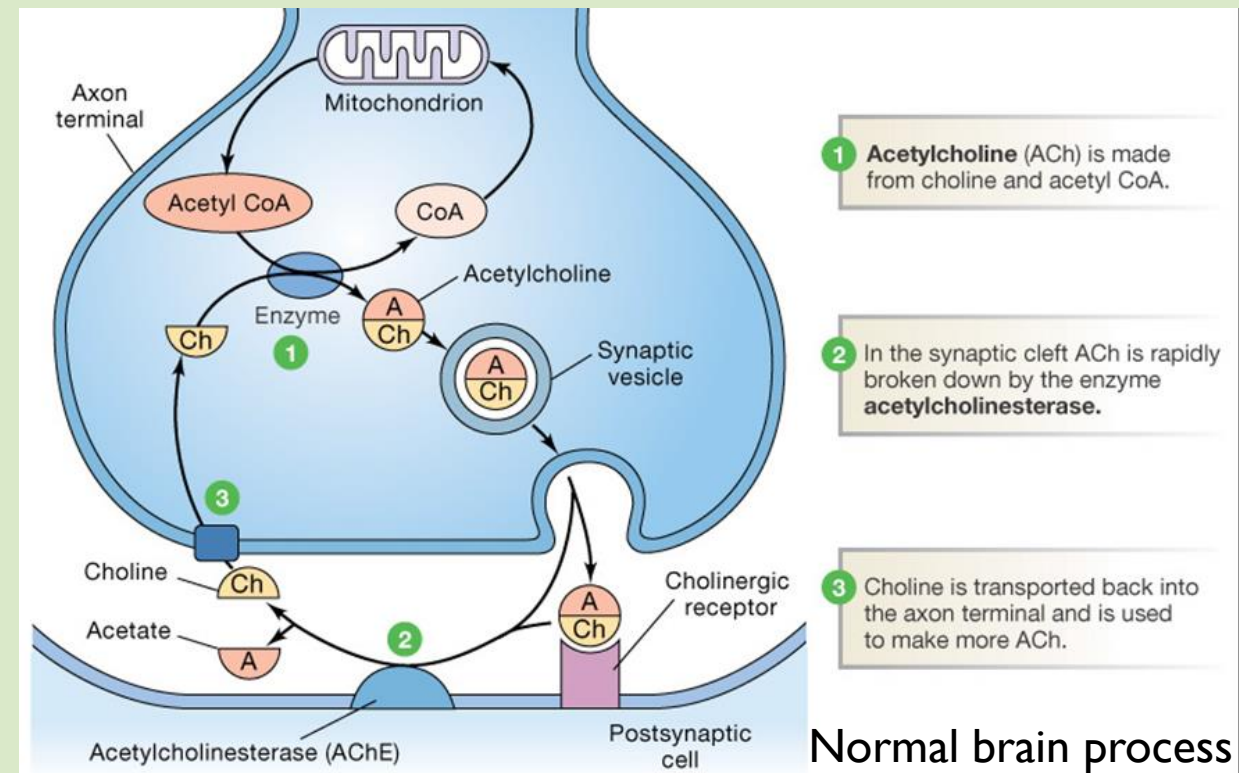


DIAGNOSIS

- Currently only an autopsy can definitively identify Alzheimer's
- Advances in brain scanning – increased accuracy in reliable diagnosis in early to moderate stages
(Xiong et al, 2010)
- One focus – differentiation between moderate memory of Alzheimer's and 'mild cognitive impairment' (a subtle loss of memory and learning abilities)
(Levy et al, 2006)

MEDICAL TREATMENTS

- Current medications can only temporarily alleviate symptoms – they cannot halt progression of dementia
- Memory loss in Alzheimer's: anticholinesterase treatments - acetylcholine (neurotransmitter)
 - Inhibits the action of acetylcholinesterase (enzyme that normally destroys acetylcholine after it's release into the synaptic cleft)
- Prevents deficit in acetylcholine



MEDICAL TREATMENTS

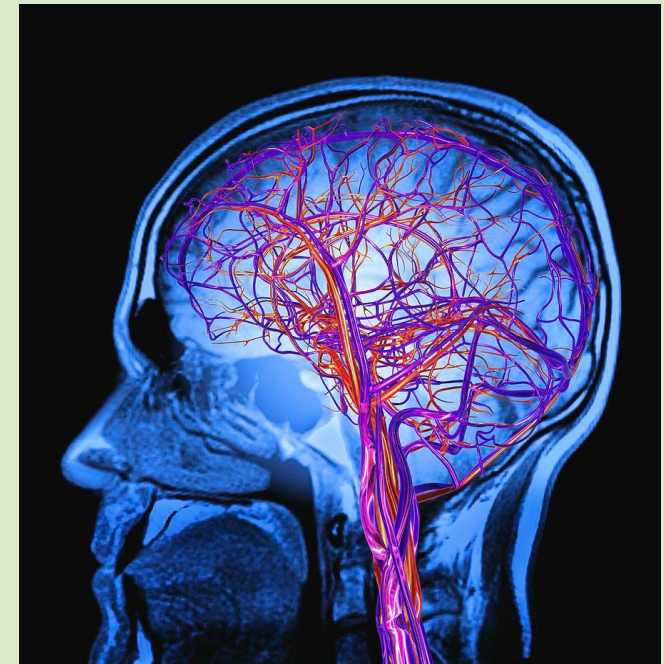
- 'Memantine' operates the glutamate system
 - Glutamate: an excitatory neurotransmitter found widely across the brain
 - Overexcites neurons – results in harmful chemical changes that cause neuronal death
 - Memantine is believed to exert a protective effect against this damage (Lipton, 2006)
 - But – its effects remain limited (Clerici et al, 2009)
 - Current research looks to interfere with disease progression, not just relieving symptoms
 - Targeting beta-amyloids
 - Agents that could protect neurons from cell death
 - Specific at-risk individuals: genetic vulnerability, medical history and exposure to environmental toxins

PSYCHOSOCIAL TREATMENTS

- Emphasis on caregivers to help maintain independence as long as possible
 - Prompts, cues, guidance
 - Modelling – allows for imitation
 - Positive reinforcement
 - Strict daily schedule
 - Management of social situations that may cause confusion or distress

VASCULAR DEMENTIA

- Damage to arteries supplying the brain e.g. result of a stroke – ‘acute onset dementia’
- Most common form of vascular dementia – multi-infarct dementia (MID)
 - Result of transient ischemic attacks (minor strokes – ‘infarcts’) too small to be noticed
 - Blocked or burst artery
 - Progressive damage – loss of cognitive abilities
- Development of MID more rapid than Alzheimer’s
- Personality changes less pronounced – so can go unnoticed for some time
- Related to risk factors similar to those for cardiovascular disease



FRONTOTEMPORAL DEMENTIA

- FTD specifically targets the frontal lobes of the brain
- Personality changes e.g.
 - Apathy
 - Lack of inhibition
 - Obsessiveness
 - Addictive behaviours
 - Loss of judgement Caycedo et al, 2009)
- Eventually
 - Neglectful of personal habits
 - Loss of ability to communicate

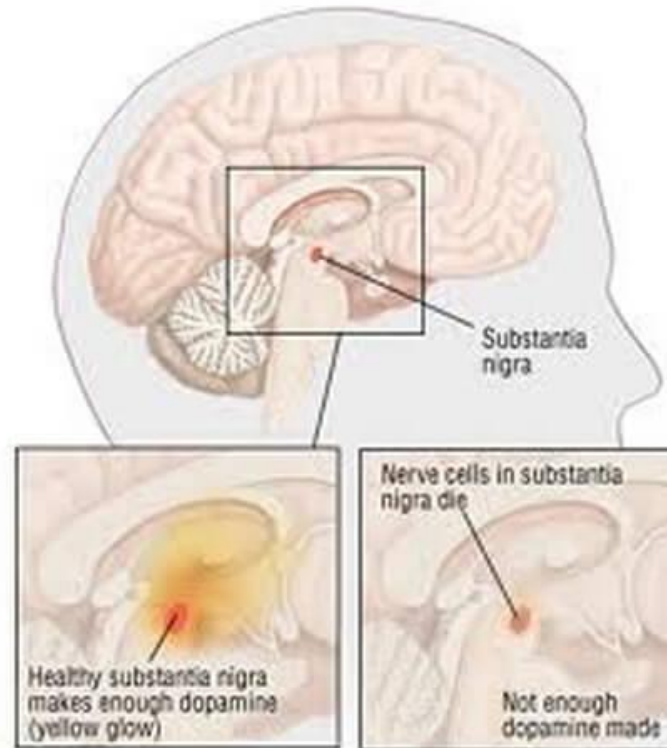
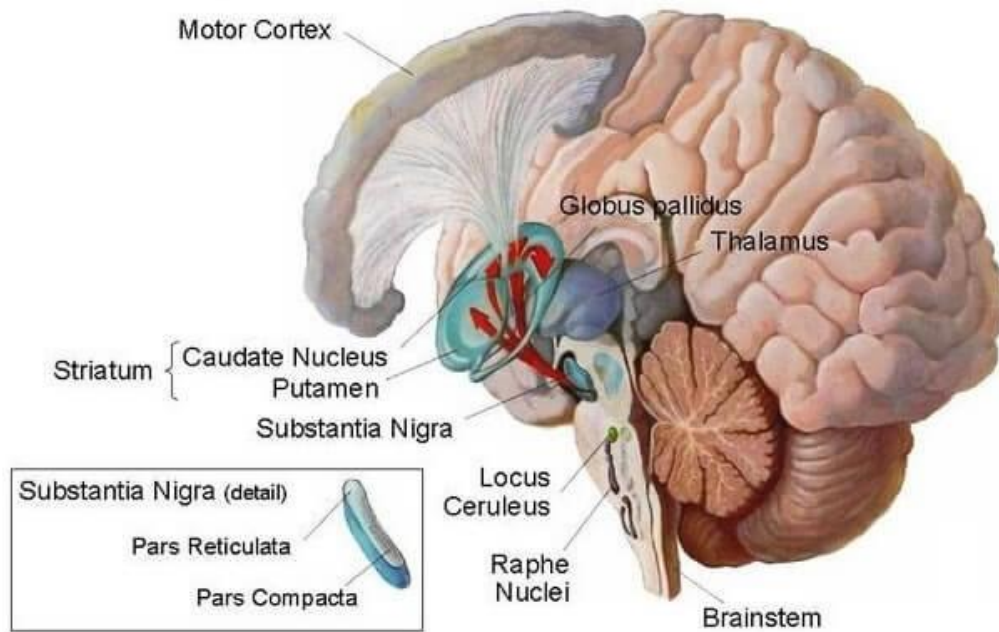


PARKINSON'S DISEASE

- Variety of motor disturbances e.g.
 - Tremors (shaking even when resting)
 - Speech impediments
 - Slowing of movement
 - Muscular rigidity
 - Shuffling gait
 - Postural instability
 - Inability to maintain balance
- Dementia – possible at later stages of Parkinson's
- Survival: 10 to 15 years after symptoms appear
- No cure, but medications can treat symptoms
- Primary drug: Levodopa (L-dopa) increases dopamine
- Loses its effect over time and can become toxic
- Neurological treatment e.g. deep brain stimulation of subcortical movement area of the brain
(Espay et al, 2006)
- Previously surgical removal of areas in the brain
- Also – activating the brain with flashes of light
(Gravinaru et al, 2009)

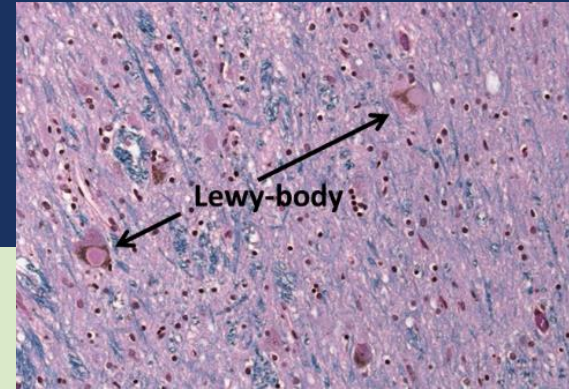
PARKINSON'S DISEASE

Brain Regions Affected by Parkinson's Disease



LEWY BODY DEMENTIA

- Approximately 10 to 15% of dementia cases (McKeith, 2006)
- Lewy bodies: tiny spherical structures consisting of deposits of protein
 - Found in dying nerve cells in damaged regions deep within the brains of people with Parkinson's
- Identified 1961 - Similar to Alzheimer's
 - Progressive loss of memory, language, calculation, reasoning among other higher mental functions
- Fluctuates in severity early in the disease
- Episodes of confusion and hallucinations
- Pure Lewy Body dementia – impairments of motor skills and specific skills involving concentrated attention, problem solving, spatial abilities



PICK'S DISEASE

- Relatively rare form of dementia
- Severe atrophy of the frontal and temporal lobes
- Differs from Frontotemporal dementia
 - Both involve deterioration in these regions
 - Pick's Disease: accumulation of unusual protein deposits (Pick's bodies)
- Symptoms include:
 - Early stages: Disorientation and memory loss
 - Progression: Pronounced personality changes and loss of social constraints
 - Later stages: Mute, immobile, incontinent



Fig 3. Brain lateral view showing frontotemporal atrophy of the left hemisphere.

REVERSIBLE DEMENTIAS

- Presence of a medical condition – effects brain tissue, but does not destroy it
- If not treated – permanent damage to the central nervous system
- If misdiagnosed as Alzheimer's – will be re-graded as untreatable and will not receive necessary treatment in time
- **Normal pressure hydrocephalus:** obstruction in the flow of cerebrospinal fluid
Accumulates in the brain – needs to be diverted
- **Subdural haematoma:** blood clot applies pressure to the brain. Requires surgical removal
- **Brain tumour:** potential for surgical removal

REVERSIBLE DEMENTIAS

- Delirium: temporary, but acute confusion
 - Diseases of heart and lung, infection, malnutrition
 - Sudden onset – requires immediate attention
- Prescribed medication: too strong a dose or in harmful combinations
 - Excretion of medications is slower in older adults due to changes in kidney function
 - More vulnerable to toxic effects
- Wernicke's disease: acute condition – alcohol abuse
 - Delirium, disturbances in eye movements, balance problems, movement difficulties
 - Deterioration of nerves in hands and feet
 - Treatment - Vitamin B (thiamine) - If left untreated – chronic dementia – Korsakoff Syndrome

DSM-5

Delirium

Diagnostic Criteria

- A. A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
- B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
- C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
- D. The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
- E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

QUESTIONS?

