# Neurodegenerative Diseases

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- What are the some hallmarks of most neurodegenerative diseases?

  (Write your list, then discuss with your tablemates.)

Hallmarks of neurodegenerative diseases:

- Neurons die.
- Dysfunction is progressive.
- Specific systems
- Typically an accumulation of an abnormal protein is the cause of cell death.
- Common causes: aging, genetics, environmental factors

# Other commonalities to take note of...

- NO cures
- By the time symptoms are apparent, the disease typically has progressed quite a bit.
- Late onset is often considered “sporadic”- aging or the environment.
- Early onset is often caused by genetics.
- Even in motor disorders, some kind of cognitive decline often occurs.

# With tablemates, match the disease to the brain area

- Huntington's
- Alzheimer's
- Frontotemporal lobar degeneration
- Parkinson's
- Cerebellar ataxia
- Amyotrophic Lateral Sclerosis

- Caudate nucleus
- Striatum
- Frontal cortex
- Hippocampus
- Cerebellum
- Substantia nigra
- Motor neurons
- Entorhinal cortex
- Temporal cortex

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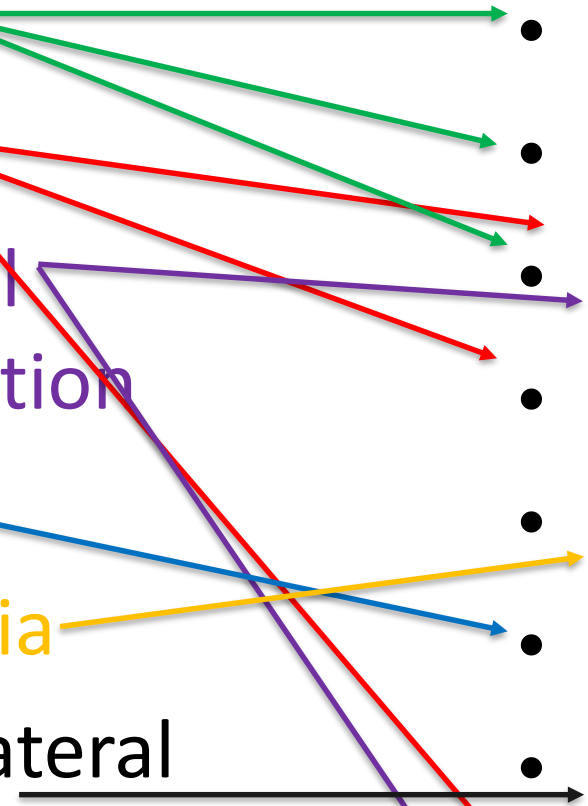

- Caudate nucleus
- Striatum
- Frontal cortex
- Hippocampus
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- Substantia nigra
- Motor neurons
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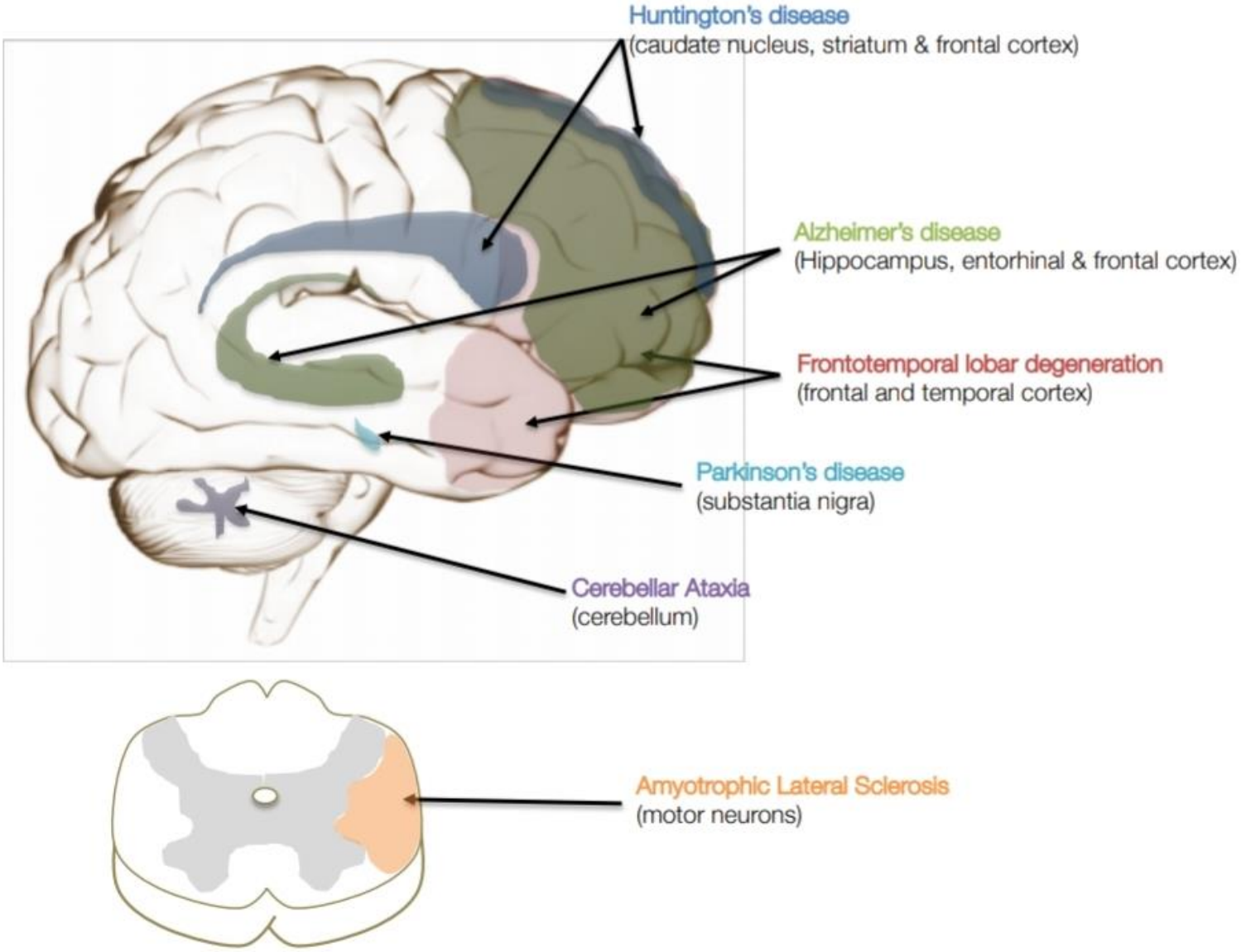
# Neurodegenerative diseases target specific areas, the knowledge of which is integral for diagnosis!



# Neurodegenerative Diseases: A Table

| Disease | Location | Risk Factors | Symptoms | Treatment |
|---|---|---|---|---|
| Alzheimer's | Frontal cortex, hippocampus, entorhinal cortex | | | |
| Frontotemporal lobar degeneration | Frontal and temporal cortices | | | |
| ALS | Motor neurons | | | |
| Huntington's | Caudate nucleus, striatum, frontal cortex | | | |
| Parkinson's | Substantia nigra | | | |

# Motor Disorders

With tablemates, discuss a possible diagnosis and treatment plan for the following example:

A patient goes to a clinic with the following symptoms:

- Trouble initating movement
- Tremors
- Face lacks expression or animation
- Doesn’t move an arm or leg normally
- Depression
- Trouble sleeping

With tablemates, discuss a possible diagnosis and treatment plan for the following example:

A 75 year old patient goes to a clinic with the following symptoms:

- Trouble initating movement
- Tremors
- Face lacks expression or animation
- Doesn't move an arm or leg normally
- Depression
- Trouble sleeping

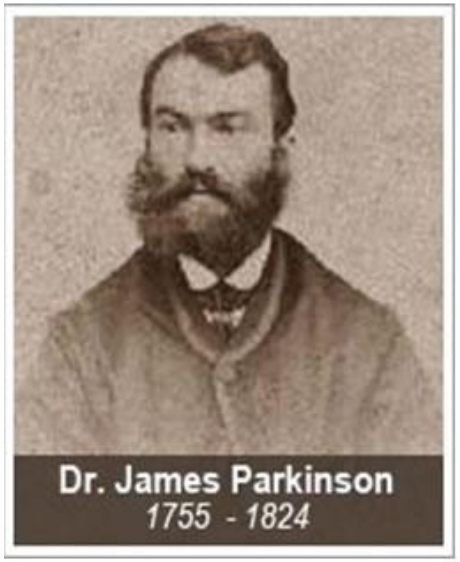
Diagnosis: Parkinson's
Treatment: L-DOPA, Deep brain stimulation

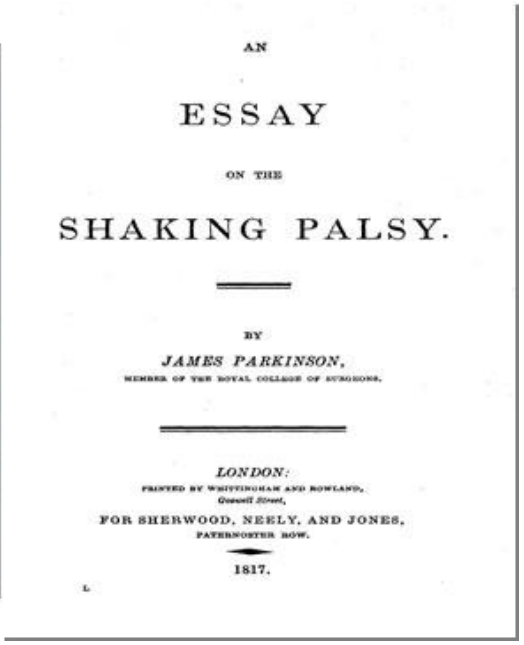
# Parkinson’s Disease

# Parkinson’s disease (PD):

**Parkinson's disease (PD)** belongs to a group of conditions called *motor system disorders*, which are the result of the **loss of dopamine-producing brain cells in the substantia nigra (>50-70%)**.

Named after the English physician **James Parkinson**, who described the disorder in “An Essay on the Shaking Palsy” in **1817**.





AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

**Parkinson's disease (PD):**

95% Sporadic PD

Late Onset PD

5% Familial (Genetics)

Early Onset PD

**Sporadic** PD:

- associated with risk factors, notably **aging (>50 yrs)** and **exposure to pesticides (***e.g.* **rotenone) or herbicides (***e.g.* **Agent Orange)**

# Symptoms of PD:

**The four primary motor symptoms of PD referred as *Parkinsonism* are:**

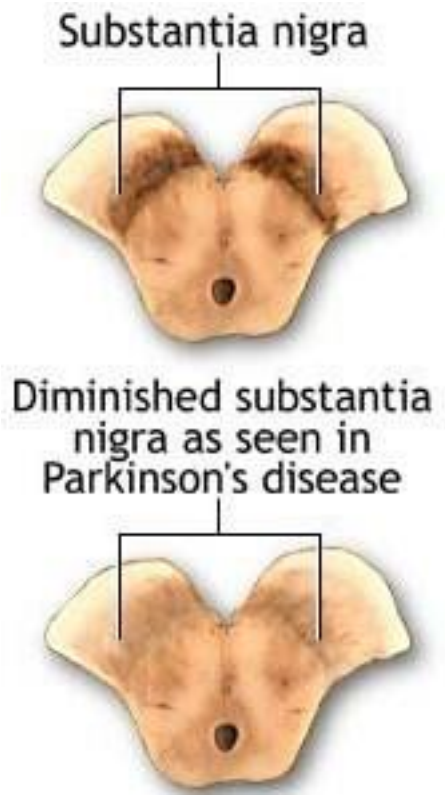
- *tremor* (trembling in hands, arms, legs, jaw, and face)
- *rigidity* (stiffness of the limbs and trunk)
- *bradykinesia* (slowness of movement)
- *postural instability* (impaired balance and coordination).

**In the advanced stages of the disease, cognitive and behavioral problems may arise, with dementia commonly occurring (in 30-80% of subjects with PD).**

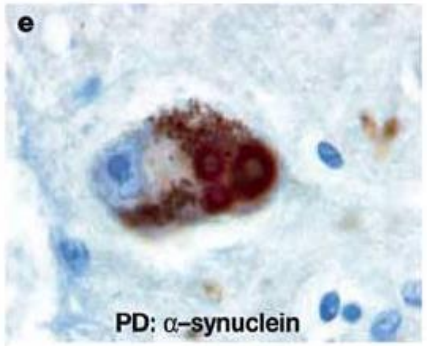
*Note:*
*There is increasing evidence that olfactory dysfunction, sleep abnormalities, cardiac sympathetic denervation, constipation, depression and pain may preceed the onset of motor signs of Parkinson's disease.*

# Histopathological features of PD:

## Macroscopic




## Microscopic





**Lewy bodies and Lewy neurites** *(intracellular aggregates of* ***α-Synuclein*** *in the soma and neurites respectively). The role of* ***α-Synuclein*** *is the healthy brain is unknown.*

nature medicine

Ross & Poirier (2004) Nat Med, **10 Suppl**:S10-7.

# Treatment of PD

There is currently **no cure but treatments exist to drastically relieve motor symptoms:**

- **L-DOPA**
- **dopamine receptor agonists**
- **Deep Brain stimulation (DBS)**

# Neurodegenerative Diseases: A Table

| Disease | Location | Risk Factors | Symptoms | Treatment |
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| Alzheimer's | Frontal cortex, hippocampus, entorhinal cortex | | | |
| Frontotemporal lobar degeneration | Frontal and temporal cortices | | | |
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| Huntington's | Caudate nucleus, striatum, frontal cortex | | | |
| Parkinson's | Substantia nigra | Genetics, aging, pesticide/herbicide exposure, head injury | Tremors, bradykinesia, rigidity, postural instability, cognitive decline | L-DOPA, dopamine receptor agonists, deep brain stimulation |

# With tablemates, discuss the following:

- If dopaminergic cell death is the cause of symptoms in PD, why not give patients dopamine instead of L-DOPA?
- When patients are prescribed L-DOPA, they tend to have a side effect that is characteristic of another disease mentioned in this lecture. Which is it and theorize why that may be.

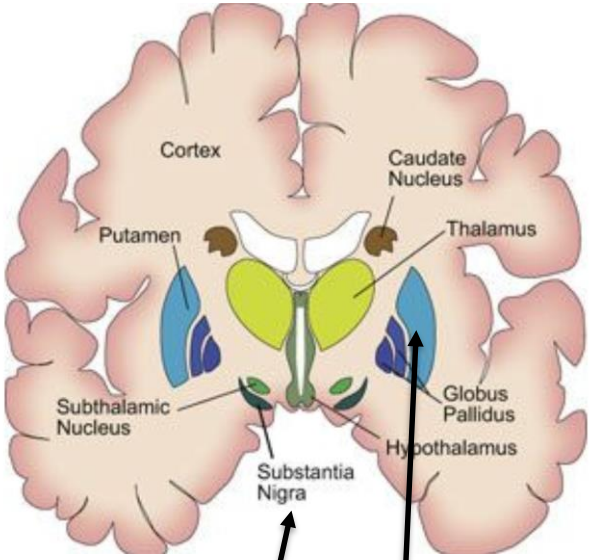
# With tablemates, discuss the following:

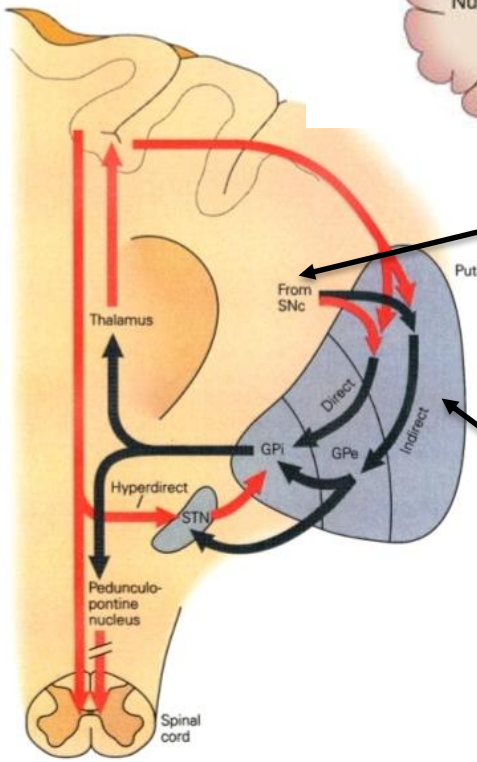
- If dopaminergic cell death is the cause of symptoms in PD, why not give patients dopamine instead of L-DOPA?
  - Dopamine will not cross the blood brain barrier, but L-DOPA will, which is a precursor to dopamine.
- When patients are prescribed L-DOPA, they tend to have a side effect that is characteristic of another disease mentioned in this lecture. Which is it and theorize why that may be.
  - Some patients will have chorea or hyperkinesia, which are uncontrolled, dance-like movements, a symptom of Huntington's. Huntington's involves death of neurons that inhibit movement, which results in increased movement. Increased dopamine signaling promotes increased movement.

# Parkinson's and Huntington's pathology share common pathways in the Basal Ganglia Circuitry

- Parkinson's involves degeneration of dopaminergic neurons in the substantia nigra
  - Dopaminergic neurons **promote** movement by activating the "direct" movement pathway in the basal ganglia.
  - Death of these neurons hinder movement.

- Early Huntington's involves degeneration of GABAergic inhibitory neurons in the putamen.
  - These neurons **suppress** movement by activating the "indirect" pathway.
  - Death of these neurons promote **too much** movement (hyperkinetic movement).




Parkinson's

Huntington's

# Huntington’s Disease

# Huntington’s disease (HD):

*VI. A. 1. Definition:*

**Huntington's disease (HD)** is a **neurodegenerative genetic disorder** that affects **muscle coordination and leads to cognitive decline** and psychiatric problems.

In HD, **medium spiny neurons** of the *striatum* are particularly vulnerable to cell death, and also leads to the dysfunction and death of neurons in other brain regions, including the substantia nigra, cortex, hippocampus, thalamus and cerebellum.

The disease is caused by an *autosomal dominant* mutation in the **Huntingtin** (*HTT*) gene, which consists in an **expansion of a trinucleotide (CAG) repeat stretch** (polyglutamine) within the Huntingtin gene.

# Huntington's disease (HD):

Genetic

- due to "mutations" in ***Htt (Huntingtin)***
- Aberrant CAG expansion can reach **250 trinucleotide repeats**
- **Direct relationship between length of the expansion and disease onset**
  (Subjects with >60 CAG will develop a severe juvenile form of HD)

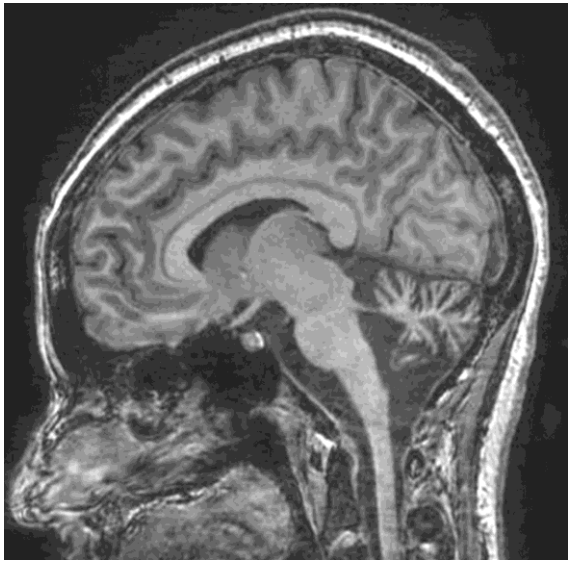
| Repeat length | Classification | Disease status |
|---|---|---|
| <35 | Normal | Unaffected |
| 36-39 | Increased Risk | +/-Symptomatic |
| >40 | Full penetrance | Symptomatic |

**Pathological threshold**

# Trinucleotide repeat neurodegenerative disorders :

## Polyglutamine (polyQ) diseases- (CAG repeats)

| Type | Gene | Pathogenic repeats |
|---|---|---|
| SCA1 | ATXN1 (ataxin-1) | 49-88 |
| SCA2 | ATXN2 | 33-77 |
| SCA3 | ATXN3 | 55-86 |
| SCA6 | CACNA1A (P/Q calcium channel 2.1) | 21-30 |
| SCA7 | ATXN7 | 38-120 |
| SCA17 | TBP (TATA-binding protein) | 47-63 |
| SBMA | AR (androgen receptor) | 38-62 |
| DRPLA | ATN1 (atrophin) | 49-88 |



Tazen et al., 2012; *Movement Disorders*

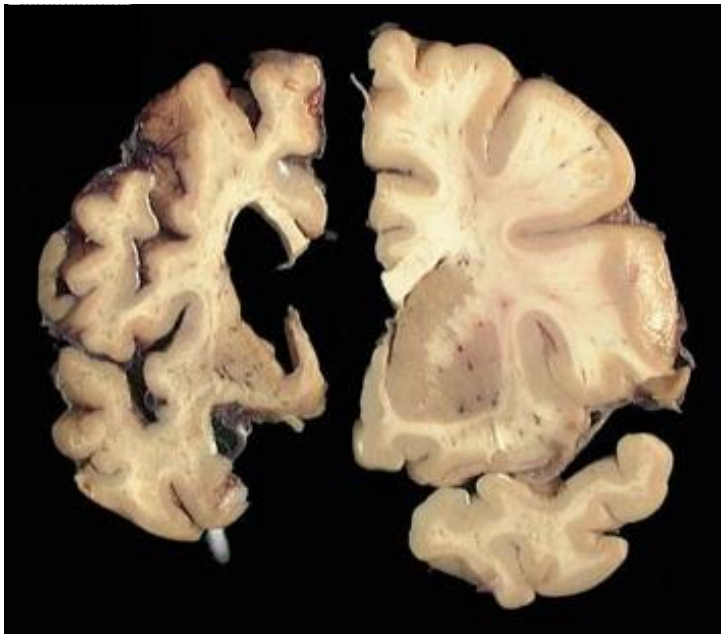
## Non-polyglutamine diseases- (not CAG repeats)

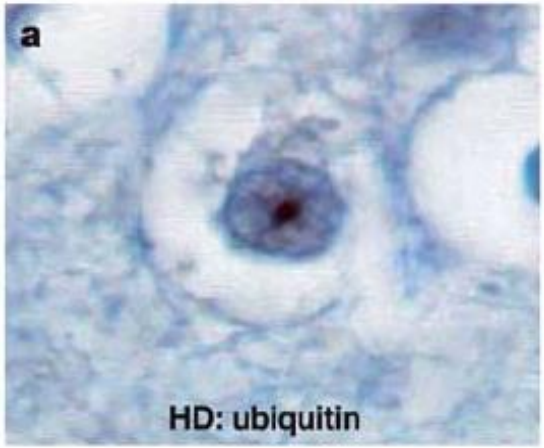
| Type | Gene | Repeat | Pathogenic repeats |
|---|---|---|---|
| FRDA (Friedreich's ataxia) | FXN (frataxin) | GAA | >100 |
| SCA8 | SCA8 | CTG | 110-250 |
| SCA12 | SCA12 | CAG-5'UTR | 66-78 |

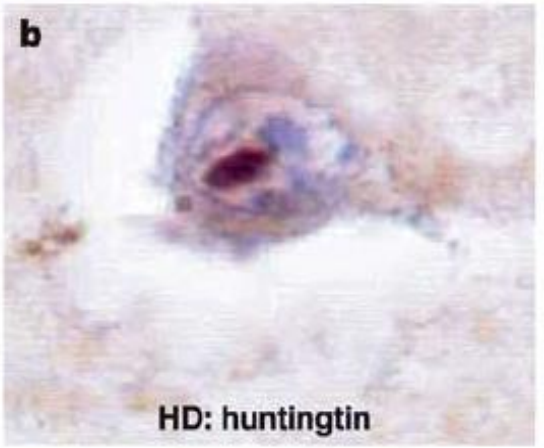
*Histopathological features of HD:*

**Huntington's disease** is neuropathologically characterized by the appearance of **nuclear and cytoplasmic inclusions** that contain **mutant huntingtin protein with a polyglutamine insert**.

| Macroscopic | Microscopic |
| --- | --- |






nature medicine

Ross & Poirier (2004) Nat Med, **10 Suppl**:S10-7.

*Symptoms of HD:*

**The most characteristic symptoms are:**

- *Chorea* (random and uncontrollable movements) (**initial**)
- *rigidity, writhing motions or abnormal posturing* (**with disease progression**)
- *Mood and personality changes*
- *Cognitive decline*

Physical symptoms of HD can start at any age from infancy to old age, but often begin between **35-44 years of age**.

*Treatment of HD:*

There is currently **no cure but treatments exist to relieve motor and cognitive symptoms:**

- **monoamine transport inhibitors**
  Tetrabenazine
- **Antipsychotics**
  risperidone (Risperdal®)
- **Physical and speech therapy**

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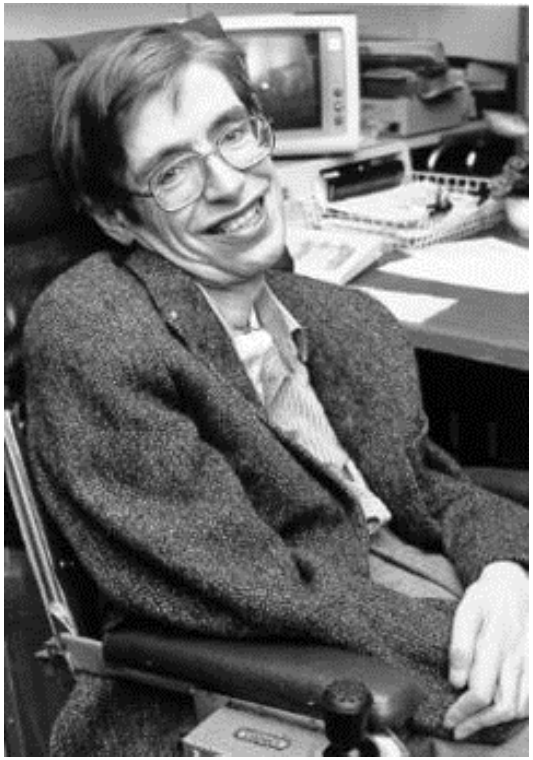
# Amyotrophic Lateral Sclerosis (ALS)

# Amyotrophic Lateral Sclerosis (ALS):

The most common motor neuron disease in human adults is amyotrophic lateral sclerosis (ALS). The primary hallmark of ALS is the **selective killing of motor neurons, which initiates a progressive paralysis in mid-life**.

Lou Gehrig



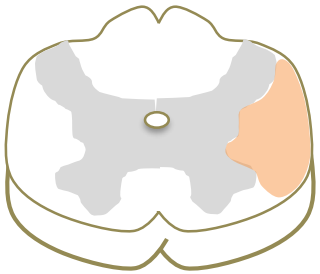
Stephen Hawking

# Symptoms of ALS:

**ALS is the most common of the motor neuron diseases (MNDs)**.

The hallmark of this disease is **the selective death of motor neurons in the brain and spinal cord, leading to paralysis of voluntary muscles.**

**The disease usually progresses to death very quickly.**



**ALS is characterized by:**

- *progressive weakness and atrophy of muscles,*
- *dysarthria* (difficulty speaking),
- *dysphagia* (difficulty swallowing),
- *decline in breathing ability.*

Usually, sensory neurons are spared.

sALS is associated with risk factors, notably **aging (mean onset at ~55 yrs)** and **gender** (*the male:female ratio is 3:2*)

With your tablemates, discuss which cranial nerves would be affected in ALS.

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| | | *general motor* | *parasympathetic* | *general sensory* | *special sensory* |
|---|---|---|---|---|---|
| I | Olfactory | | | | X (olfaction) |
| II | Optic | | | | X (vision) |
| III | Oculomotor | X[a] | X | | |
| IV | Trochlear | X[a] | | | |
| V | Trigeminal | X[b] | | X[c] | |
| VI | Abducens | X[a] | | | |
| VII | Facial | X[b] | X | X | X (taste) |
| VIII | Vestibulocochlear | | | | X (auditory & vestibular) |
| IX | Glossopharyngeal | X[b] | X | X[c] | X (taste) |
| X | Vagus | X[b] | X | X[c] | X (taste) |
| XI | Accessory * | X[a] | | | |
| XII | Hypoglossal | X[a] | | | |

* cervical component; cranial component included with vagus

[a] somatic motor – innervates muscles that develop from somites

[b] branchial motor – innervates muscles that develop from pharyngeal (branchial) arches

[c] includes visceral sensory as well as somatosensory

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# With your tablemates, discuss which cranial nerves would be affected in ALS.

- ALS typically characterized by:
  - dysarthria (difficulty speaking)
  - dysphagia (difficulty swallowing)
  - difficulty breathing
  - Which cranial nerves contribute to those functions?

- Vagus Nerve (X): General motor for the larynx (for speaking), parasympathetic to much of the digestive track, heart, lungs.
- Glossopharyngeal Nerve (IX): General motor for throat muscle, parasympathetic motor for the parotid gland (salivary gland), glands of the throat.
- Hypoglossal (XII): general motor for tongue.
- Generally, any of the cranial nerves involved in motor or parasympathetic function are vulnerable.

# Treatment of ALS

There currently is **no cure but treatment with:**

- **sodium channel blocker**

Riluzole (Rilutek®)

modestly increase survival (~up to 12 months)

# Neurodegenerative Diseases: A Table

| Disease | Location | Risk Factors | Symptoms | Treatment |
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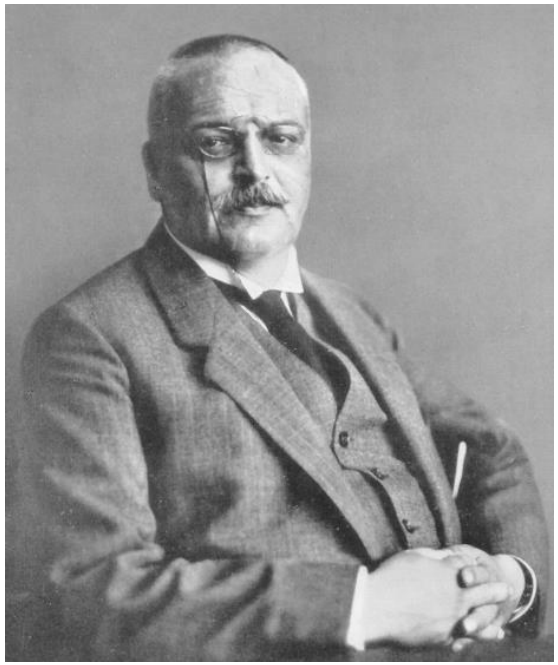
| Alzheimer's | Frontal cortex, hippocampus, entorhinal cortex | | | |
| Frontotemporal lobar degeneration | Frontal and temporal cortices | | | |
| ALS | Motor neurons | Aging, genetics, gender | muscle atrophy, dysarthria, dysphagia, decline in breathing ability | sodium channel blocker |
| Huntington's | Caudate nucleus, striatum, frontal cortex | Genetics | Chorea (early), rigidity, postural instability, mood/personality changes, cognitive decline | Monoamine transporter inhibitors, anti psychotics, speech and physical therapy |
| Parkinson's | Substantia nigra | Genetics, aging, pesticide/herbicide exposure, head injury | Tremors, bradykinesia, rigidity, postural instability, cognitive decline | L-DOPA, dopamine receptor agonists, deep brain stimulation |

# Non-motor/ Diseases of Dementia

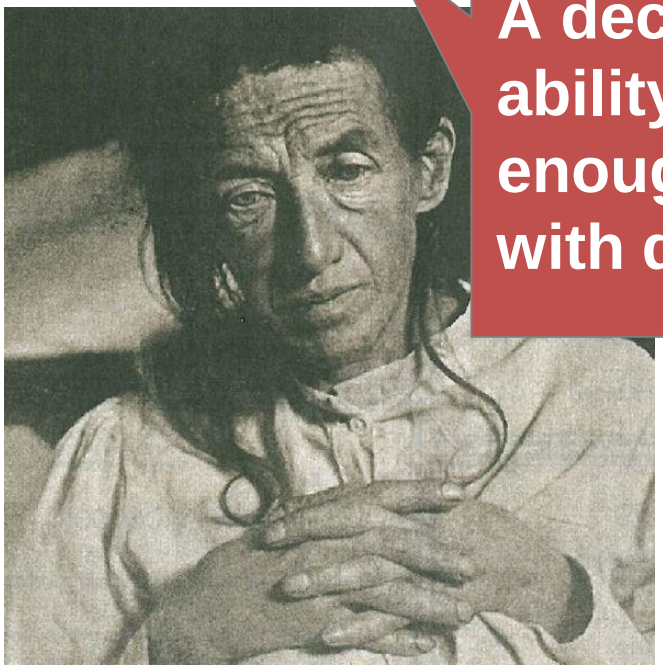
# Alzheimer’s Disease

# Alzheimer's disease:

- progressive neurodegenerative dementia
- most common type of **dementia** in the elderly
- 13% of the population 65 years old and older have AD
- duration of the disease varies from 3 to 20 years (after clinical manifestation).



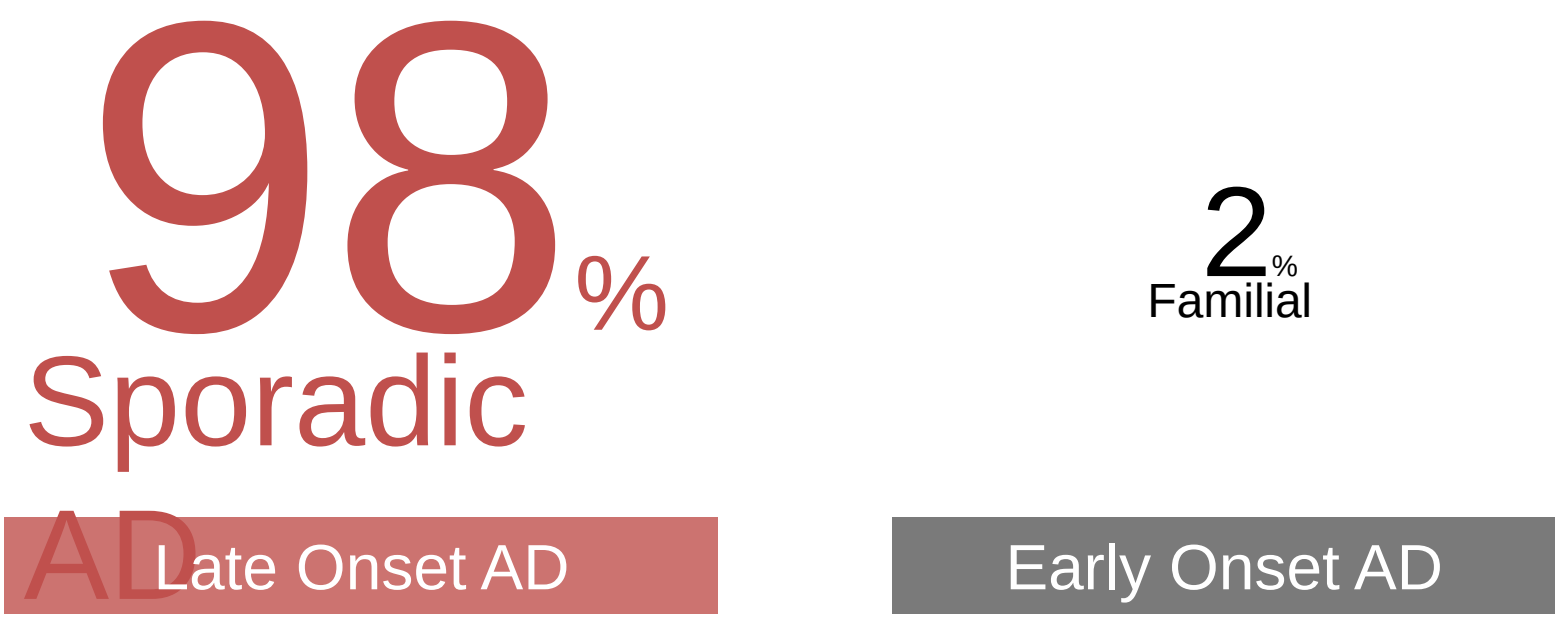
*Alois Alzheimer (1909)*



*Auguste D. (1901)*

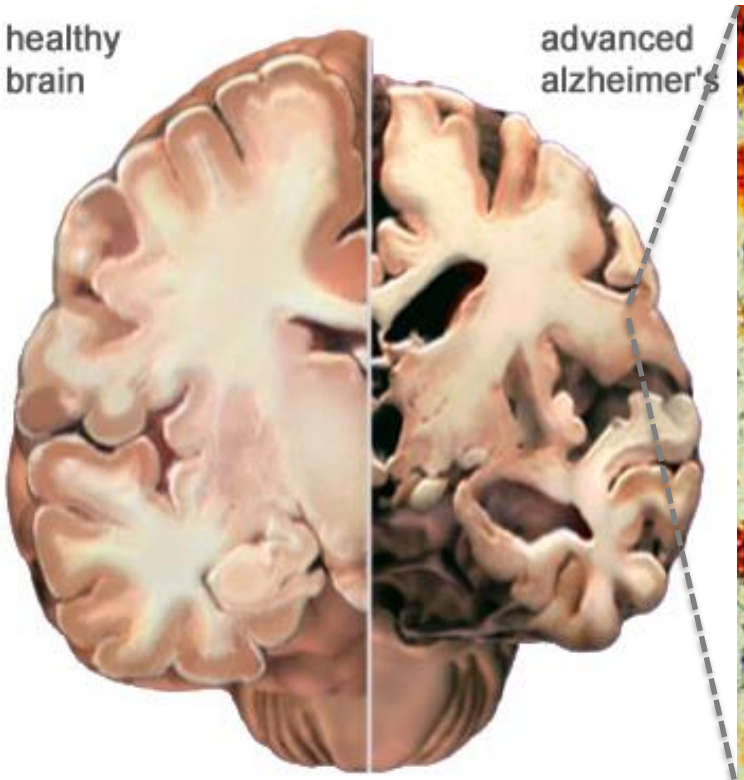
**A decline in mental ability severe enough to interfere with daily life.**

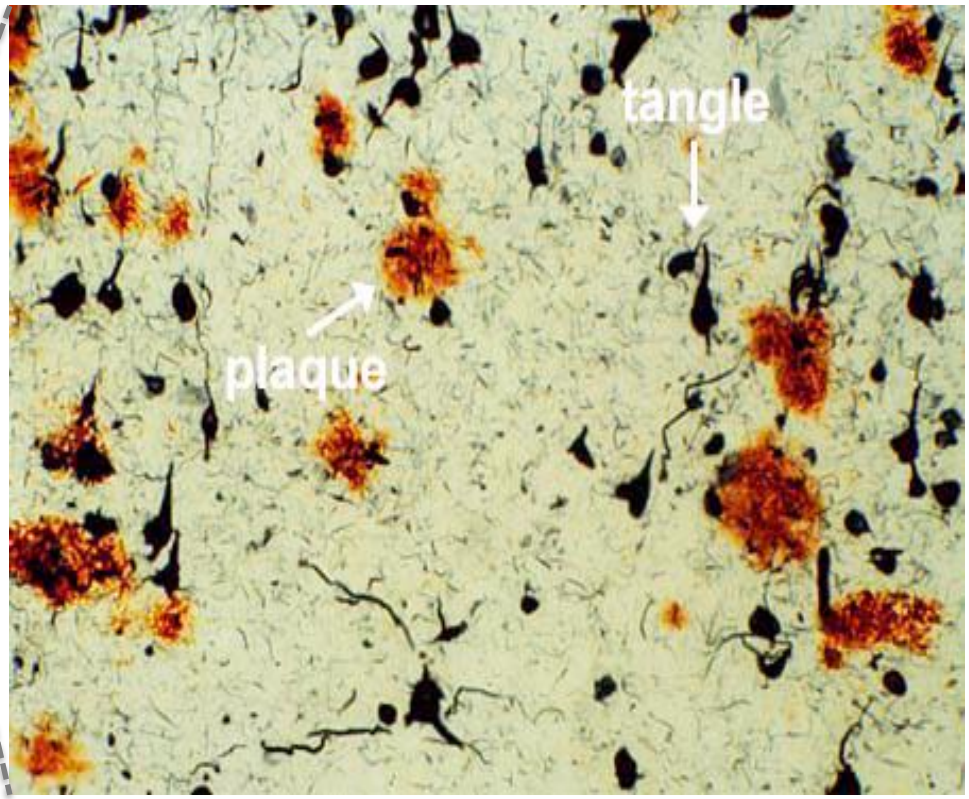
**Alzheimer's disease:**



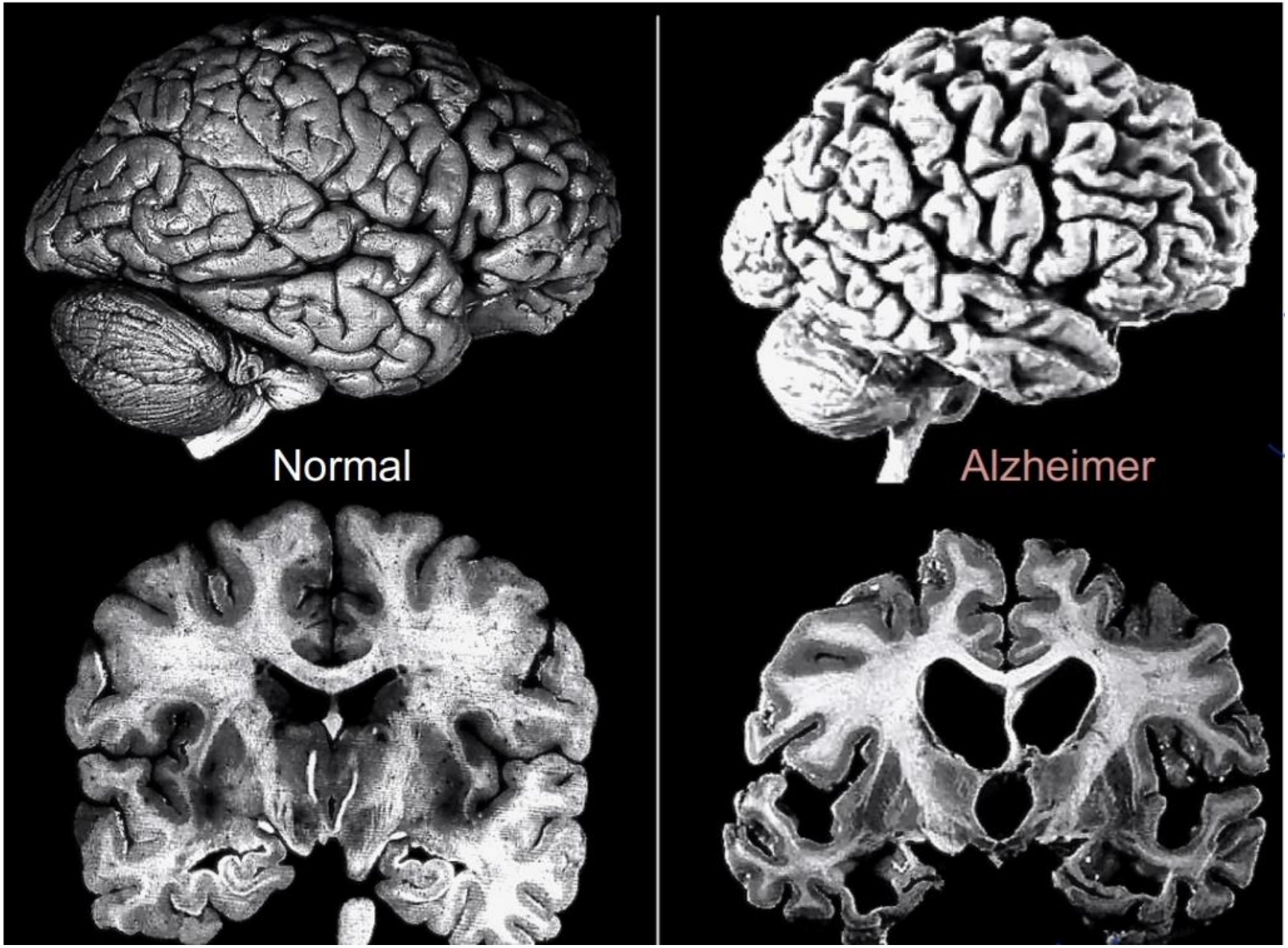
# Histopathological features of Alzheimer's Disease

| Macroscopic | Microscopic |
| --- | --- |

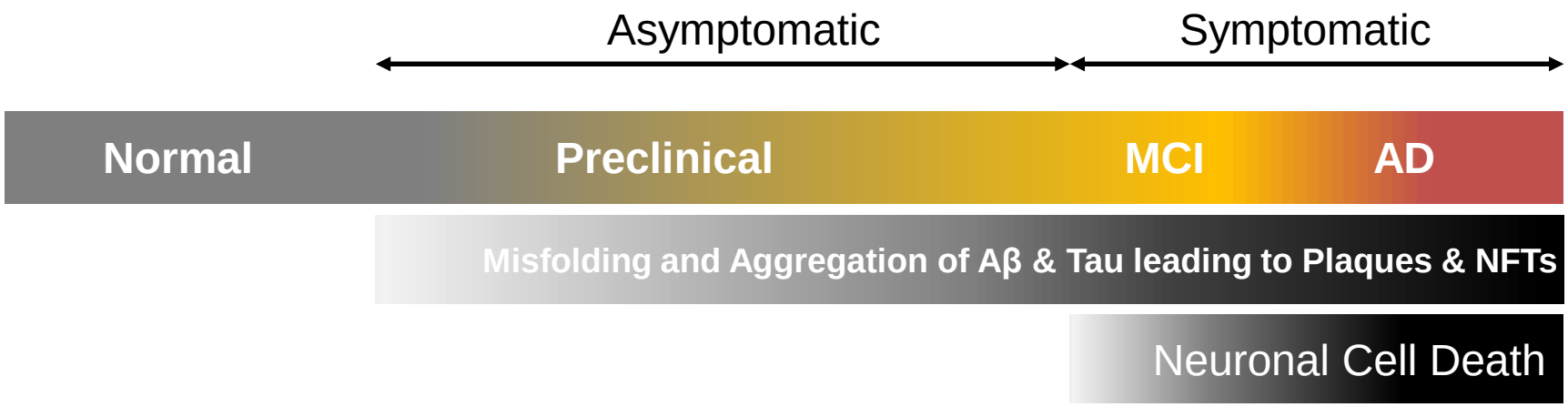


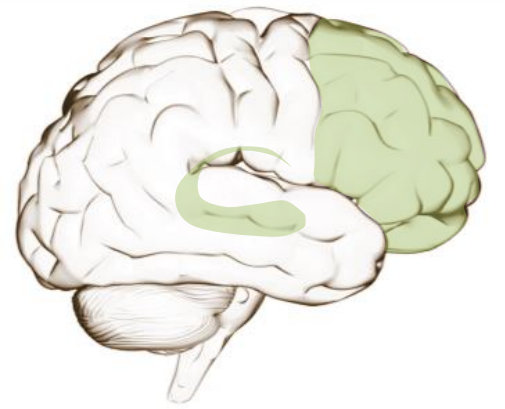




Extracellular accumulation of **amyloid-beta (Aβ)** in ***amyloid plaques*** and intracellular accumulation of **tau inclusions** forming ***neurofibrillary tangles*** constitute invariant pathological hallmarks of Alzheimer's disease.


Normal
Alzheimer

# Symptoms of Alzheimer's Disease:



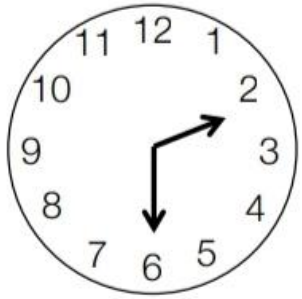



**The clinical presentation varies with the stage of AD**

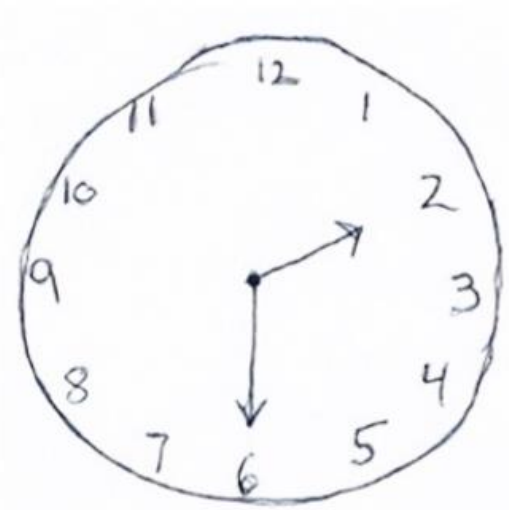
- Memory loss that disrupts daily life
- Challenges in planning or solving problems
- Confusion with time or place
- Trouble with visual and spatial
- New problems with word finding and speaking
- Decreased or poor judgment
- Changes in mood or personality

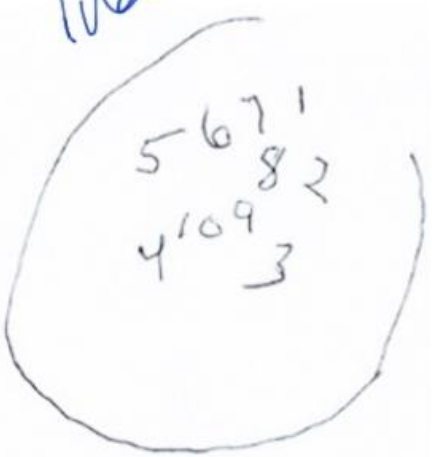
# Test used to assess AD progression

**Mini-Cog**




1. Remember and a few minutes later repeat the names of three common objects
2. Draw a face of a clock showing all 12 numbers in the right places and a time specified by the examiner

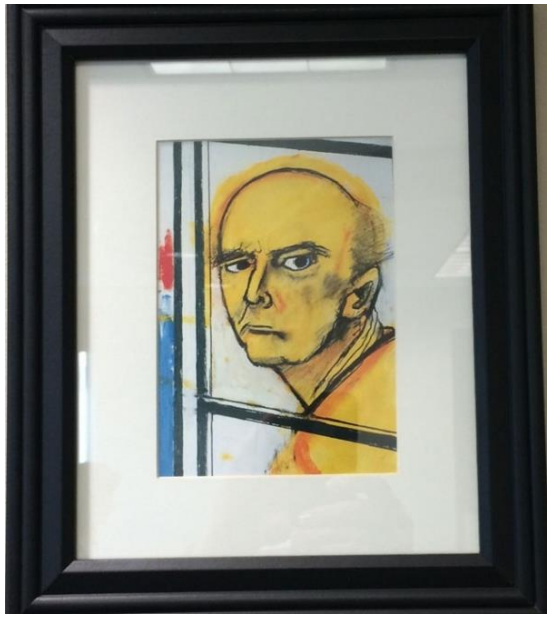


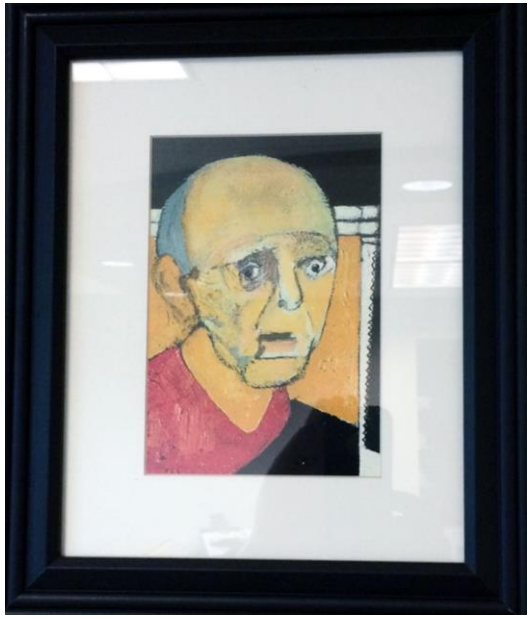



**Normal** | **MCI, early AD** | **Late AD**

Mattson, 2014 (*Front. Neurosci.*)

Artist William Utermohlen drew self portraits for five years after being diagnosed with Alzheimer's:





# AD treatment

- Cholinesterase Inhibitors: Donezepil (Aricept), Rivastigmine (Excelon), Galantamine (Razadyne)
- NMDA receptor antagonists: Memantine (Namenda)

# Neurodegenerative Diseases: A Table

| Disease | Location | Risk Factors | Symptoms | Treatment |
|---|---|---|---|---|
| Alzheimer's | Frontal cortex, hippocampus, entorhinal cortex | Aging, genetics | Memory loss, changes in mood/personality, confusion with time/space, deficits in problem solving, decreased judgement. | Cholinesterase inhibitors, NMDA receptor antagonists |
| Frontotemporal lobar degeneration | Frontal and temporal cortices | | | |
| ALS | Motor neurons | Aging, genetics, gender | muscle atrophy, dysarthria, dysphagia, decline in breathing ability | sodium channel blocker |
| Huntington's | Caudate nucleus, striatum, frontal cortex | Genetics | Chorea (early), rigidity, postural instability, mood/personality changes, cognitive decline | Monoamine transporter inhibitors, anti psychotics, speech and physical therapy |
| Parkinson's | Substantia nigra | Genetics, aging, pesticide/herbicide exposure, head injury | Tremors, bradykinesia, rigidity, postural instability, cognitive decline | L-DOPA, dopamine receptor agonists, deep brain stimulation |

# Frontotemporal Dementia

# Frontotemporal dementia:

**Frontotemporal dementia (FTD)** defines a large group of **clinically, pathologically and genetically heterogeneous disorders associated with atrophy in the frontal lobe and temporal lobe** of the brain.

Because disease onset occurs before 65 years of age in ~75-80% of cases, FTD is considered a **pre-senile dementia**.

- **2nd most common cause of early-onset dementia** after Alzheimer's disease.

The symptoms of FTD and Alzheimer might overlap.

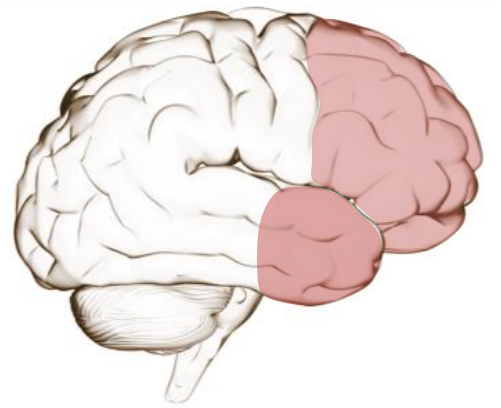
**Frontotemporal dementia:**

75%
Sporadic
PD
Late Onset FTD

25%
Familial
Early Onset FTD

**Sporadic** FTLD is associated with risk factors, notably **aging (>40-65 yrs)**

# Symptoms of FTD:



**The clinical presentation varies with the type of FTD**

- extreme changes in behavior and personality
- impairment or loss of speech and language difficulties
- Movement impairments (rarer)

# FTD Treatment

- According to the Association for Frontotemporal Degeneration website, there is no FDA approved treatment.
- However, patients are given a variety of drugs to try: selective serotonin reuptake inhibitors, antipsychotics, cholinesterase inhibitors, memantine, benzodiazepines, L-DOPA, psychostimulants....
- Seems like physicians are just throwing everything at a wall to see what sticks...

# Neurodegenerative Diseases: A Table

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| Frontotemporal lobar degeneration | Frontal and temporal cortices | Aging | Extreme changes in mood/personality, impairment/loss of speech or language | ???? |
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Consider you have someone's fresh brain tissue and a list of their dementia-related symptoms and medical history. With tablemates, discuss how a diagnosis of Alzheimer's could be differentiated from FTD. Consider symptoms, histology, etc.

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- Does the histology show amyloid beta plaques or neurofibrillary tangles? (AD)
- At what age was the onset of symptoms? FTD symptoms tend to show up pre-senility.
- Identify AD-specific genes and look for the expression of those genes in the brain tissue or in family/medical history.
- Inspect brain for degeneration specific to the entorhinal and frontal cortices and the hippocampus (AD). Caveat- It seems that degeneration spreads in AD, so that could still be kinda confusing to differentiate.
- Did the patient have memory loss? (AD)

# Labs that study neurodegeneration at UMN

ALS
- Gulin Öz

Huntington's
- Rocio Pastor-Gomez

Parkinson's
- Matt Johnson
- Steven Graves
- Colum MacKinnon

Cerebellar Ataxia
- Harry Orr
- Marija Cvetanovic

Alzheimer's
- Sylvain Lesné
- Karen Ashe
- Ling Li
- William H Frey II
- Michael Koob
- Keith Vossel