Module 6: Neurodegeneration

Introduction – Studying Neurodegeneration

NOT an infectious disease – **no SINGLE aetiology** causing the disease

Have **multiple risk factors** → disease onset → active disease → organ failure

When investigating degenerative disorders – look at the **end** and **work backwards**

NOTE: 'Risk factor' stage and end stage 'Organ failure' can **look very different** (e.g. smoking → Heart disease)

e.g. **Heart Failure:**

- Risk Factors
  - Hypertension
  - Diabetes
  - Smoking
  - Lipid disorders
  - Genetics
- Disease Onset
  - Atheroma
  - Clotting disorder
  - Embolus
  - Infection
- Active Disease
  - Heart attach
  - Muscle disease
  - Hypertension
  - Valve disease
- Failed Organ = heart failure

Apply this to **Parkinson's Disease –**
In order of discovery:

- Failed organ = Parkinsonian Tremor
- Active disease = Loss of midbrain neurons (**50-70%** substantia nigra neurons lost) → loss of dopamine transmission
- Disease onset = **Lewy bodies (α-synuclein accumulation)** found in substantia nigra cells
- Risk factors = Not sure (genetic involvement)

What constitutes as 'Parkinson's' is always **changing**

Importance of Clinical Signs (Phenotype)

Clinical signs indicate the **damaged parts** of brain – tells you **anatomical pathology**

Regions of brain encode different functions because of unique **cell types + circuitry**

Different cell types are due to different **gene expression (biochemistry, cell morphology, energy demands)**

Example: Motor Neuron Disease (Amyotrophic Sclerosis)

Can affect:

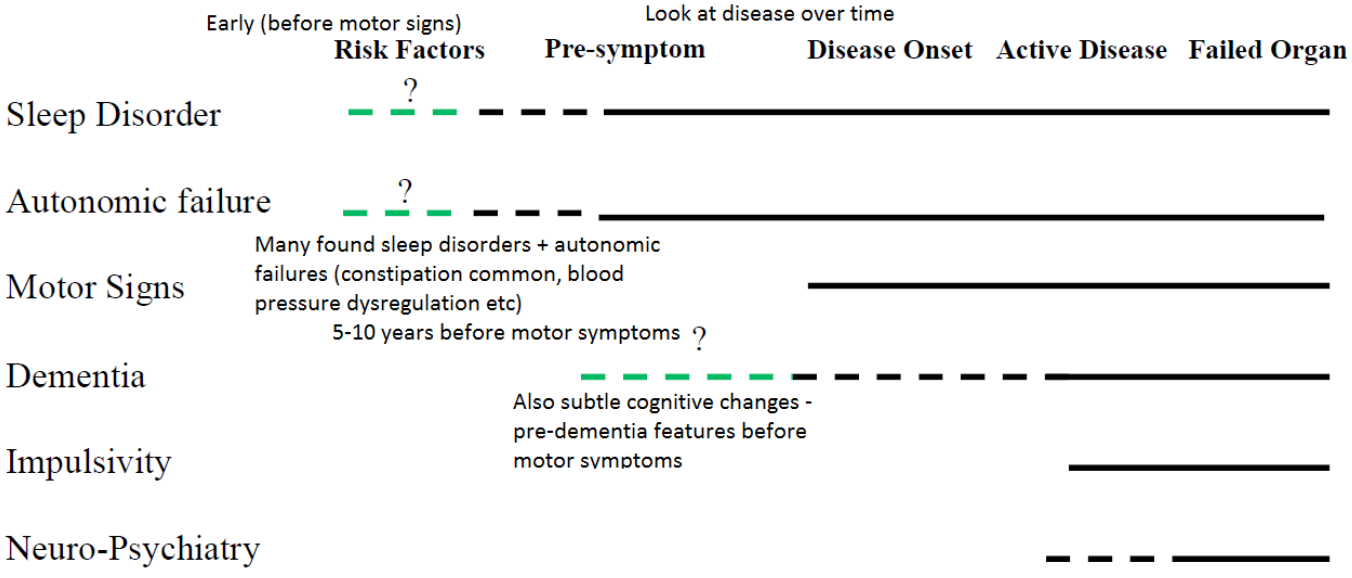
- **Upper motor neuron** (in brain) phenotypes
    - INCREASED reflexes
    - Muscle weakness/paralysis
- **Lower motor neuron** (in spine) phenotypes
    - LOSS of reflexes
    - Fasciculation
    - Wasting
- NO sensory features

Through identifying phenotypes – can pinpoint neurons involved and look at their similarities/morphologies:

- Common embryology
- Long axons (high energy needs)
- Same transmitters
- Similar morphology
- Similar gene expression
    - Mutations in **SOD1** associated with familial MND
        - BUT Chesapeake Retriever (dog) has mutation and has **sensory spinal neuron pathology** – NOT motor neurons
        - Something about pathology in dogs is similar to that in motor neurons of humans
        - Can look at differences in gene expression between human/dog sensory neurons to locate key permitting/inhibiting mechanisms

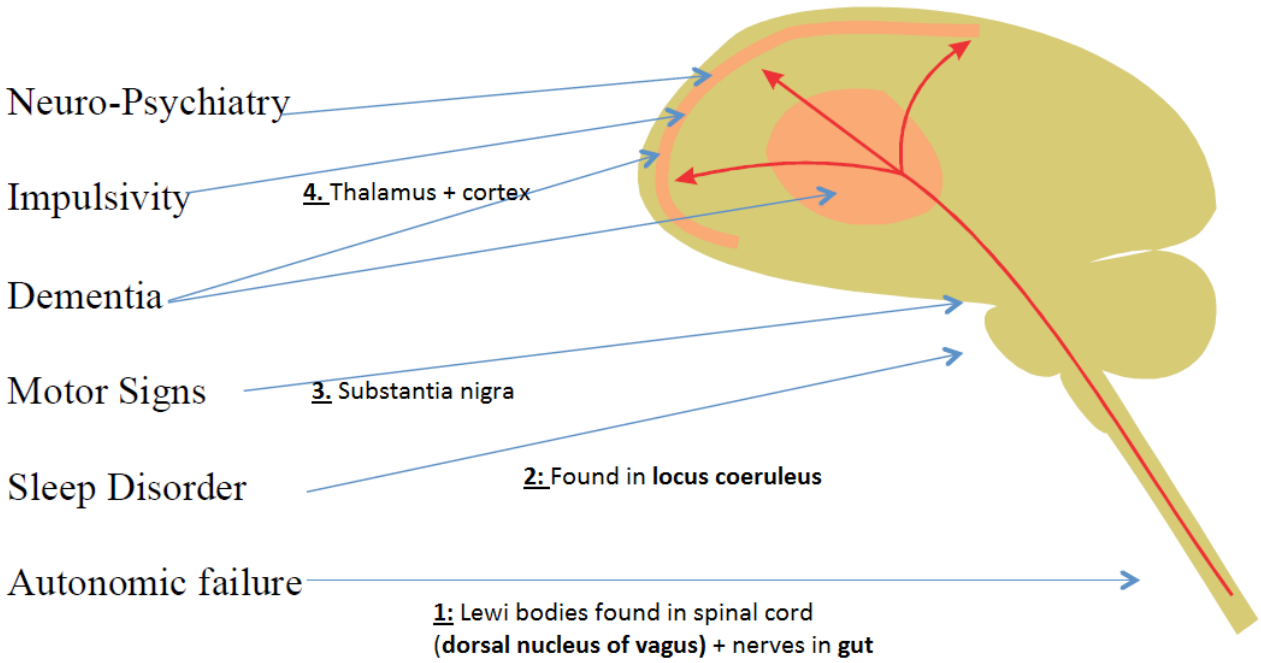
Similar cells have **similar disease susceptibility**

Example: Parkinson's Disease



Based on these symptoms, relate **parts of the brain** to phenotype to uncover which parts of brain are damaged + in what **order**

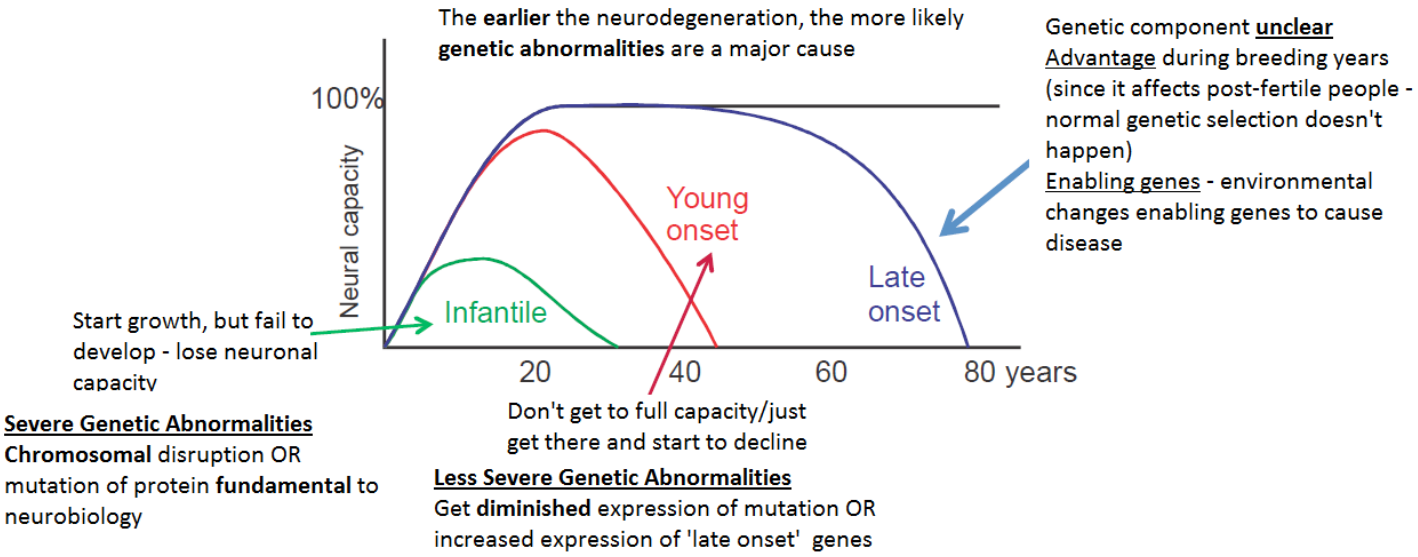
e.g. Neurons controlling sleep damaged first → Movements → Psychiatry



Reveals that:

- Parkinson's is **more** than just substantia nigra affected
    - Not sure if there are **similar neuron types** that are affected
    - **System** of cells affected
- Disease tends to **spread** (correlated by progression of phenotypes observed)
    - But not sure why it spreads
- Other neurodegenerative diseases cause the **same phenotype** but through **different pathologies** (but damage them in the same way, producing same disease phenotype)
  These are **NOT** Parkinson's Disease (symptoms are called '**parkinsonism'**)
    - Can be differentiated by different **marker proteins**
    - Suspect that particular proteins misbehave in each of the different types
    - E.g. SOD1 = motor neuron disease
    - E.g. A-β = Alzheimer's
    - E.g. α-synuclein = Parkinson's + Dementia with Lewy Bodies

Types of Neurodegenerative Disorders



Common feature in pathology of **age-related neurodegenerative disease**
= **CELL LOSS + PROTEIN AGGREGATES**

- Alzheimer's Disease = Tau + Aβ
- Parkinson's Disease = α-synuclein
- Huntington's Disease = Huntingtin

Classification

Phenotypic Classification

Late onset neurodegenerations share **common features:**
Suggests **common mechanisms**

- All **spread** to neighbouring neurons
- Seem to have **energetics** component
- All have **inclusion formations** (autophagy, mis-folding, lysosome disturbances etc)
- All have **axon transport problems**

Examples: Parkinson's Disease + Alzheimer's Disease
Both are **late onset** and have symptom **overlap**

Both have **dementia**, BUT dementia is NOT a single entity – is dysfunction of **association cortex**
Despite overlap, the two diseases exhibit **different features** of dementia

Symptoms:

- Memory: hippocampus + all cortex
- Attention: frontal lobes + all cortex
- Language (temporal lobe): throughout parietal + frontal lobe (fluency of speech)
- Executive function (ability to plan ahead + problem solve): frontal cortex
- Impulsivity: frontal cortex

Parkinson's Disease Dementia/ Alzheimer's Disease Dementia

i.e. in summary:

Parkinson's Disease Dementia: **Frontal cortex/executive dementia**

Alzheimer's Disease Dementia: **Posterior cortex/amnestic dementia + language**

BUT some Parkinson's patients…

- Have **amnestic dementia**
- Increased levels of **A-β**

Not sure if this person **has BOTH diseases** or something to do with **A-β** that causes Alzheimer's symptoms

Conclusion: Perhaps you cannot accurately define diseases based on phenotype since different diseases can have **overlapping phenotypes**