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Understanding the underlying causes of degenerative neural diseases

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Degenerative neural diseases (DND), such as dementia, Parkinson's disease, motor neuron disease or multiple sclerosis, are becoming more prevalent in our ageing society. Here we explain why different DND classes display characteristic disease-specific symptoms, but also why they often share common features that can be triggered by a wide range of very different causes. Explanations are drawn from the complex biology of nerve fibres which are the cable-like processes of nerve cells that tend to be prime lesion sites in DNDs. We hope that our explanations will help GPs to improve their understanding of DNDs, which might then facilitate conversations with affected patients about their condition and also lower the threshold to engage in further reading on the topic.

Clinical Case scenario

John is 61 years old with no relevant past medical history. He has been concerned about his symptoms over the last few months. He works a lot with a computer and is now struggling with typing, especially using his right hand. When dressing himself, he now has great difficulty with buttons and zips. His writing has become very small. Family members have commented on him slowing down in general. His wife reports that he always used to stride ahead on walks, but now he lags behind. Very occasionally he notices a tremor in his right hand, often when he is sitting to relax, such as when watching television.

You suspect a diagnosis of Parkinson's disease and refer him to a specialist who confirms the diagnosis. He is started on levodopa medication which markedly improves his symptoms.

Some weeks later he comes to see you wanting further information about his condition. He wants to understand what has caused his 'brain cells' to degenerate and whether anything can be done about this.

The socio-economic burden of DNDs

Worldwide the number of patients suffering from degenerative neural diseases (DNDs) is on the rise (Steinmetz et al., 2024; for numbers in the UK see Box 1). The estimated health cost caused by dementia patients in the UK alone sums up to about £34.7 billion and is expected to increase since the number of dementia sufferers is projected to increase from 0.9 to 1.6 million by 2050, not least because the number of people over 65 most vulnerable to the condition is predicted to double over the next 30 years (Alzheimer's Society, 2024; Alzheimer's Research UK). These statistics suggest that GPs will be faced with an increasing number of DND patients who may often want to know more about their conditions. A better understanding of DNDs and their underlying causes would facilitate such conversations.

Explaining the different classes of DNDs

There are numerous different classes and types of DNDs, but GPs may most frequently encounter older patients suffering from forms of dementia or Parkinson's disease, younger patients suffering from multiple sclerosis, and occasionally patients suffering from ataxias or motor neuron diseases (Box 1, Tab.1). These different forms of DNDs are usually accompanied by characteristic, disease-specific functional losses, such as the memory and personality loss in dementias, the loss of motor control in Parkinson's disease or ataxias, or paralysis in multiple sclerosis or motor neuron diseases.

Box 1. The number of people suffering from certain DNDs in the UK as reported by bespoke charities in 2023

- 944,000 patients are diagnosed with dementias (two-thirds of which suffer from Alzheimer's disease; AD)
- 153,000 with Parkinson's disease (PD)
- 31,000 with Frontotemporal dementia (FTD)
- 150,000 with multiple sclerosis (MS)
- 10,500 with progressive ataxias
- 5,000 with motor neuron disease (MND)
- 2,000 with hereditary spastic paraplegia (HSP)

These very different neurological manifestations occur because DNDs do not affect the entire nervous system, at least initially. Depending on the disease, different subregions or cell types of the brain, spinal cord or peripheral nervous system become dysfunctional, each causing different neurological symptoms (Tab.1, Fig.1, Box 2). These are used by neurologists for diagnosis, together with other criteria including age at disease onset, speed of progression, or family history. Despite these differences, all DNDs have in common the progressive dysfunction or even loss of neurons, as will be explained in the following.

Table 1. Information about different DND classes.

Disease	Pre-valence (UK)	Median survival (years post diagnosis (YPD)	Affected brain area/cell type	Symptoms	Causes	
					Hereditary (no. of linked genes)	Other
Alzheimer's disease (AD) (65+ YOA)	1 in 14 people	8-10 YPD	Cerebral cortex: language, reasoning, and social areas	Loss of memory, poor decision making, and behavioural problems	~81 genes	Sporadic (>95%) Other: Diet, Aluminium & Viral Infection
Parkinson's disease (PD)	1 in 37 people	9 YPD	Dopaminergic neurons in the substantia nigra and basal ganglia	Tremor, rigidity and slowness of movement	~78 genes	Sporadic (~95%) Other: Heavy Metals, Pesticides & Illicit Drugs
Huntington's disease (HT)	4.1-5.2 in 100,000 people	15-18 YPD	Striatum	Cognitive decline, personality changes and involuntary movements	97% hereditary ~6 genes	Sporadic (3%)

Amyotrophic lateral sclerosis (ALS)	1-2 in 100,000 people	3-4 YPD	Upper motor neurons and Lower motor neurons	Muscle weakness, muscle wasting and speech problems	~15 genes	Sporadic (90-95%) Other: Head Trauma, Smoking, Lead & Pesticides
Frontotemporal dementia (FTD)	15-22 in 100,000 people	3-6 YPD	Frontal and temporal lobes	Changes in social behaviour, loss of empathy and apathy	~2 genes	Sporadic (50-70%) Other: Toxins & Chemicals
Hereditary Spastic Paraplegia (HSP)	7.4 in 100,000 people	Normal life expectancy	Upper motor neurons (complex forms include lower motor neurons)	Weakness, spasticity, and stiffness of the legs	majority hereditary ~72 genes	Sporadic
Multiple Sclerosis (MS)	1 in 500 people	Normal life expectancy	Myelin sheath of neurons in the CNS	Movement issues, fatigue, and vision problems	~3 genes	Sporadic (majority) Autoimmune disease
Spinocerebellar ataxia, autosomal recessive (SCAR) (>50% genetic ataxias)	1.8 in 100,000 people	**Class I:** Friedreich's ataxia – adolescent onset **Class II:** early-onset recessive ataxia – onset before 5 YOA **Class III:** adolescent-onset recessive ataxia **Class IV:** adult-onset recessive ataxia	Cerebellum, proprioceptive and/or vestibular systems	Progressive limb and gait ataxia, dysarthria, dysphagia, and polyneuropathy affecting the posterior columns and corticospinal tract with associated areflexia and sensory loss	**Class I:** ~1 gene **Class II:** ~28 genes **Class III:** ~15 genes **Class IV:** ~7 genes	Sporadic (>2/3 cases Friedreich's ataxia)
Charcot Marie Tooth Disease (CMT)	1 in 2,500 people	Normal life expectancy	Sensory and motor neurons	Muscle weakness and atrophy in the arms, legs, hands, and feet	majority hereditary ~3 genes	Sporadic
Hereditary sensory and autonomic neuropathy (HSAN)	1 in 125 million people	Varied due to severity of type	Sensory and autonomic neurons	Sensory and autonomic dysfunction	~11 genes	Sporadic
Chemotherapy Induced Peripheral Neuropathy (CIPN)	30-6,0% of cancer patients	No effect on survival	Sensory neurons	Numbness and tingling in the hands and feet	~4 genes	Sporadic (majority) Chemotherapy
Lysosomal Storage Disorder (LSD) e.g. Niemann-Pick Disease A/B/C1/C2 (NPD)	1 in 250,000 people (NPD)	10-20 YPD (NPD)	Cerebellum, hippocampus, cortex, thalamus, and caudate nucleus (NPD)	Muscle weakness, cognitive dysfunction, and reduced use of the senses (NPD)	~4 genes (NPD)	Sporadic (late-onset NPD)

Diabetic Neuropathy	**Type 1** Diabetes – 28.7% **Type 2** Diabetes – 50.7%	25-50% mortality rate within 5 to 10 YPD	Peripheral sensory and motor nerves	Numbness, tingling, muscle weakness, extreme sensitivity and foot problems	~8 polymorphisms (increased risk of DN)	Other: Diabetes

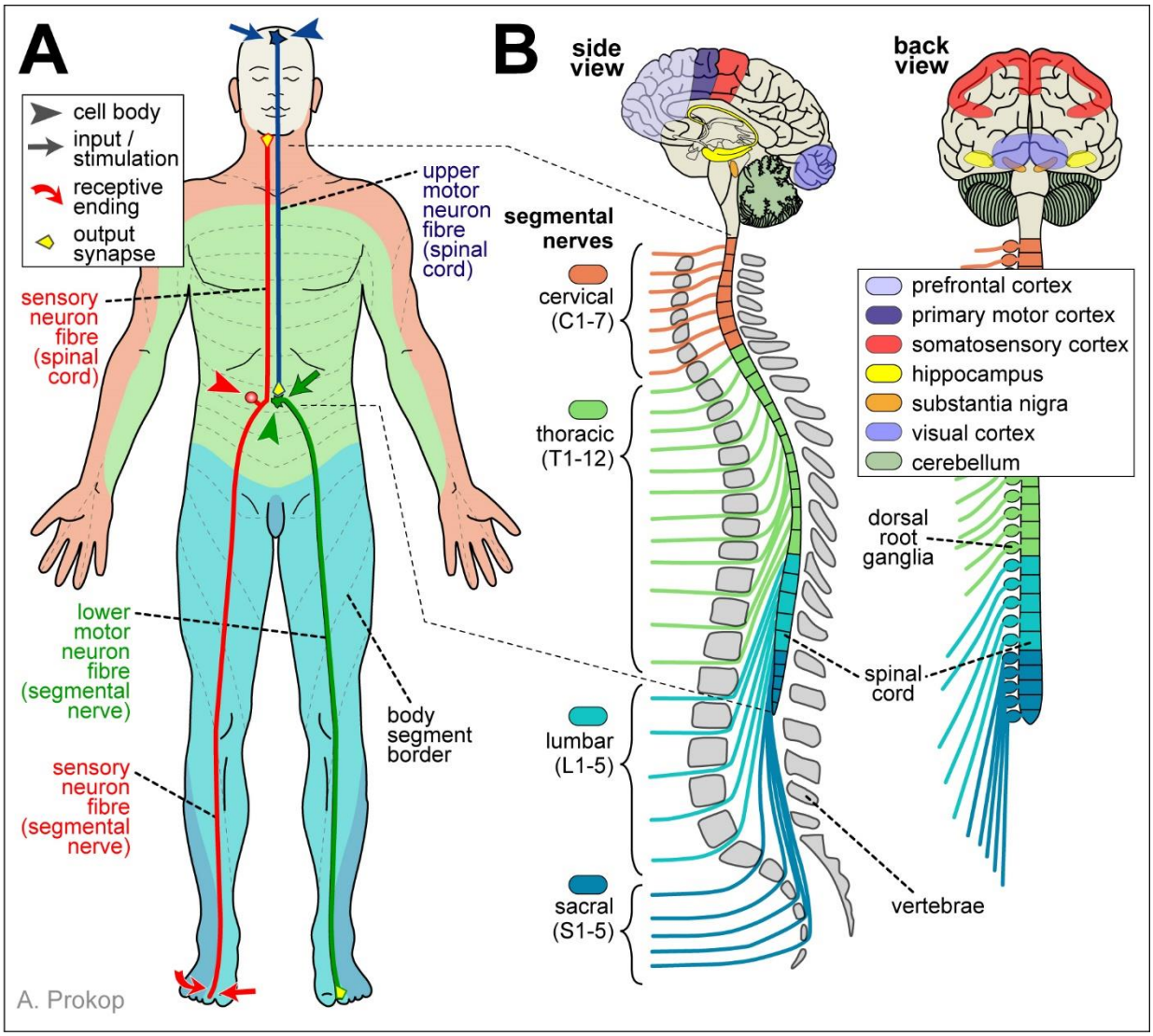

Figure 1. Fundamental organisation of the human nervous system*. All details are explained in the figure and Box 2 (also see Prokop, 2024); colour codes and symbols are consistently used in A and B.*

The importance and vulnerability of nerve fibres in DNDs

It has been known for over a century that neurons take on a polar organisation, receiving information at one end (arrows in Fig.1) and passing it on to further cells at the other (yellow dots in Fig.2A; Prokop, 2020). Neurons in the central nervous system (CNS) typically form branched dendrites on their cell bodies which receive information via input synapses from other neurons (Fig.2A). Sensory neurons of the peripheral nervous system (PNS) have peripheral nerve fibre endings (Fig.2A) specialised to perceive external stimuli, such as stretch, heat, injury or body posture. In both cases, the received information is propagated along nerve fibres, also called axons (Fig.2A).

Box 2. Key functions and associated DNDs of different brain regions, spinal cord and sensory system (compare Fig.1 for illustrations, Box 1 for abbreviations, Tab.1 for further details)

- The **cerebral cortex** is the outermost layer of the brain with its characteristic folds found only in humans and apes. It is subdivided into different regions: for example, the **primary somatosensory cortex** receives and processes sensory information from the skin and musculoskeletal organs, the **visual cortex** from the eyes. Two regions have strong links with DNDs:
  - The **primary motor cortex** contains the upper motor or pyramidal neurons with nerve fibres that reach up to a meter into the spinal cord to instruct voluntary muscle movements; DNDs affecting upper motor neurons include MND, HSP or MS and are associated with body paralysis.
  - The **prefrontal cortex** coordinates highly complex behaviours such as decision-making and personality expression; it explains personality loss in FTD patients.
- The **hippocampus** mediates consciously aware (explicit) learning and memory formation; it is usually the first area affected in AD.
- The **substantia nigra** is a mid-brain area rich in dopaminergic neurons and involved in the regulation of voluntary movement; it is primarily affected in PD patients, explaining the characteristic movement disorder.
- The **cerebellum** is an accessory area to the hindbrain coordinating and fine-tuning motor functions; it is primarily affected in ataxias explaining lost motor control including balance and speech.
- The **spinal cord** is the central nervous system of the body; it forms a long tubular structure extending from the brainstem down the vertebral column. It transmits information between the brain and the rest of the body and controls information flow in each body segment including the reflexes.
  - **Lower motor neurons** have their cell bodies in the spinal cord and form the long nerve fibres in our segmental nerves that innervate the somatic musculature.
  - **Sensory neurons** of the trunk have their cell bodies in dorsal root ganglia lateral to the spinal cord; they form long nerve fibres in our segmental nerves that convey information about stretch, heat, injury or body posture from the periphery to the spinal cord where these fibres often continue up to the mid brain (achieving lengths of up to 2 m in total).

Axons are slender cellular processes of neurons (Prokop, 2020). They form the biological cables that wire our bodies and nervous systems. They measure maximally 15 µm in diameter but can be about a meter long in upper and lower motor neurons, and up to 2 m long in sensory neurons (Fig.1A). They are specialised to propagate information as nerve impulses (action potentials) from the point of reception to other parts of the body or nervous system, where they form output synapses to pass the information on to other neurons, muscles, or gland cells (Fig.2A).

Most axons cannot be replaced. They must survive and be maintained functional for up to a century in humans. Understanding the mechanisms that sustain axons for so long (see next section) might provide important explanations for the causes of their decay during ageing or in disease: a healthy person loses about 40% of axons towards high age (Calkins, 2013; Marner et al., 2003); in DNDs, this loss is accelerated to a degree that can no longer be functionally compensated for, thus causing symptoms (Adalbert and Coleman, 2012).

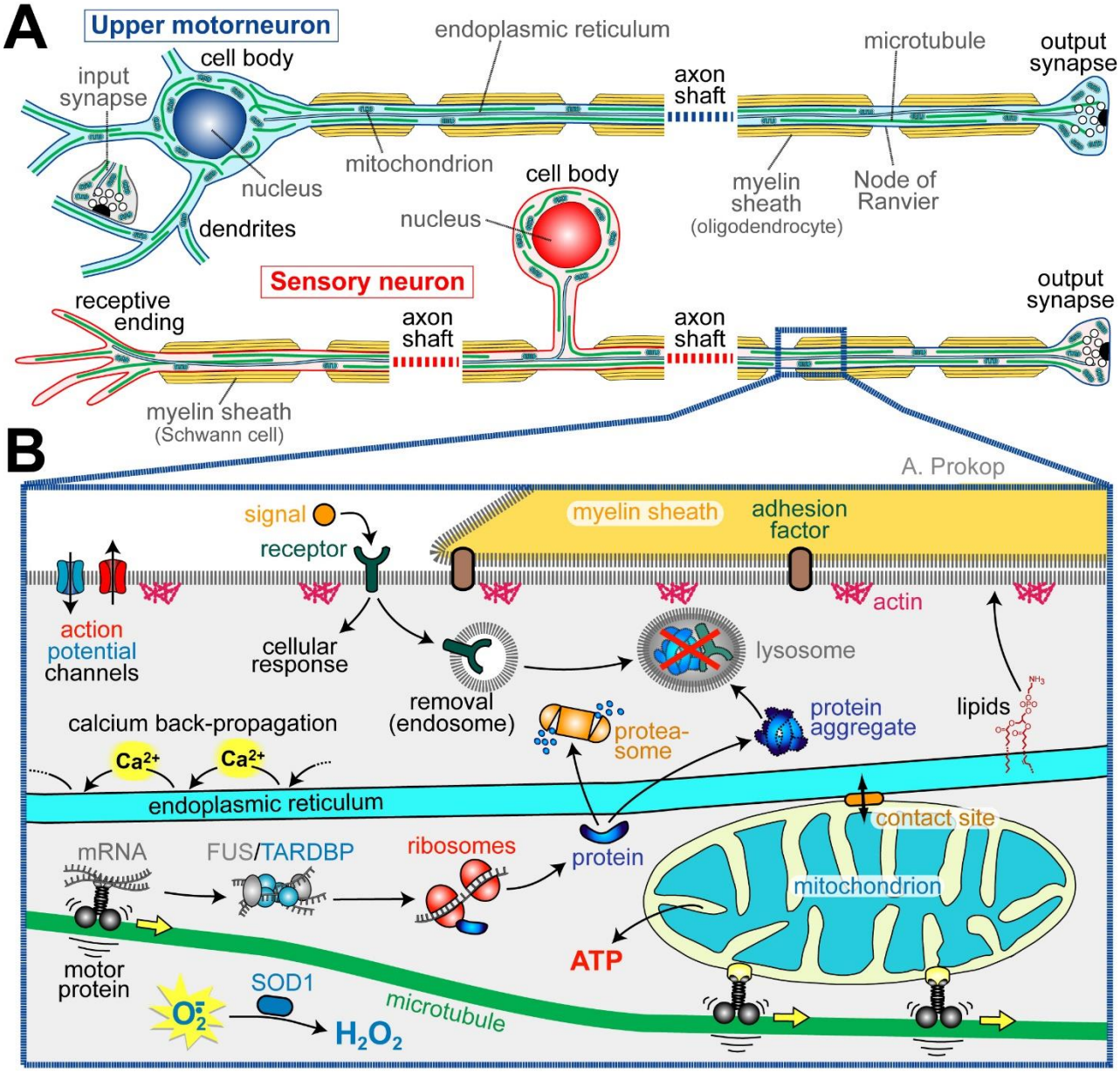

***Figure 2. The organisation of motor and sensory neurons (A) and intracellular machinery of their axons (B)**. All details are explained in the figure, Box 4 and the main text.*

This said, axon loss may not be the primary event, but axonal dysfunction can be caused by the depletion of specialised glial support cells. These cells, called oligodendrocytes in the CNS and Schwann cells in the PNS, form laminar processes that periodically wrap around many axons to form an insulating myelin sheath (Fig.2A). The myelin sheath enables efficient nerve impulse propagation which, if interrupted upon myelin loss, causes paralysis (Stassart et al., 2018). Myelin loss is observed in multiple sclerosis or certain types of spastic paraplegia (affecting oligodendrocyte glia in the CNS and optic nerve), and in certain types of Charcot Marie Tooth disease (affecting Schwann cell glia in the PNS). In multiple sclerosis, periods of functional loss (relapse) can be followed by partial recovery of axonal function due to myelin sheath regeneration (remission). However, over time the repeated loss of glia and concurrent inflammation tend to cause irreversible axon loss.

Nerve fibres are maintained through a balanced system of intracellular machinery

Axons are not only highly delicate structures that have to be maintained for extremely long periods, but they must achieve this often far away from the nucleus located in the distant neuronal

cell body (Figs.1A,2A; Smith et al., 2023). In all cells, the nucleus contains the genes providing the information from which the proteins can be generated that maintain cells and their functions in healthy balance; many of these functions take place in highly specialised intracellular compartments referred to as organelles. Axons have most of this essential machinery locally available (Smith et al., 2023) including many organelles and proteins required for their maintenance; they can even perform on-site protein and lipid production to replenish local pools (Fig.2B, Box 3). Through this, axons have a high degree of independence enabling them to survive for a century up to a meter away from the nucleus (Figs.1A,2A).

Box 3. Potential causes of DNDs (in alphabetical order)

- **Ageing** - the entire cellular machinery of the nervous system weakens, thus increasing its vulnerability for genetic or environmental predispositions; ageing is considered the biggest risk factor for DNDs.
- **Diabetes** – the increase in blood sugar impacts body metabolism including the uncontrolled production of harmful substances; this inhibits processes such as wound healing and it affects the nervous system.
- **Familial/hereditary DNDs** – improving methods of human genetics pinpoint ever more gene mutations linked to certain DNDs passed on in affected families; this said, patients affected by such a mutation can show variable severities of symptoms caused by their individual genetic backgrounds (modifying effects caused by subtle genetic differences in an individual's genome).
- **Multiple sclerosis** – is characterised by phases of loss (relapse) and regeneration (remission) of the myelin sheath in the central nervous system (Fig.2A); loss of the myelin sheath affects the propagation of nerve impulses (thus explaining paralysis) and will eventually cause the degeneration of the ensheathed axons.
- **Substance-induced neuropathies** – nerve cells can be directly affected when exposed to alcohol abuse or heavy metal poisoning, but also by the drugs used for chemotherapy.
- **Trauma** – is being discussed and suggested to cause premature ageing of the nervous system, thus increasing the vulnerability for DNDs.

Two internal structures, the endoplasmic reticulum (ER) and microtubules, run uninterrupted from the cell bodies to the tips of axons, thus establishing means of intracellular communication (Fig.2A). The ER forms a continuous tubular network which can back-propagate calcium signals as a relatively fast means to inform the cell body, for example about axon injury (Fig.2B; Öztürk et al., 2020). Microtubules are filamentous structures that are arranged into continuous bundles in axons; they serve as transport highways between cell bodies and axon tips: specialised motor proteins walk along them to transport cargo including mRNAs, proteins, or entire organelles (Fig.2B). Although this transport can take over a week to travel through a long axon (up to 80 mm per day), it provides principal access to products synthesised exclusively in cell bodies. Motor proteins also distribute contents locally within axons, which is essential for the working of almost every aspect of axonal machinery (Maday et al., 2014).

Since axons depend on this complex cellular machinery for their long-term survival, it appears logical that mutations impairing a single important gene and its associated protein functions may lead to axon deterioration that is eventually diagnosed as DND. This is best understood in cases of hereditary DNDs that are passed on within families, as will be explained in the following.

A case study: inherited forms of motor neuron disease can have surprisingly different causes

Motor neuron diseases (MND), of which Amyotrophic Lateral Sclerosis (ALS) is the most common type, are characterised by the functional loss of upper and lower motor neurons. Many prominent MND patients can be named (Wikipedia, 2024), among them the late astrophysicist Stephen Hawking who suffered from a rare, slow-progressing form of MND.

To gain a better understanding of the cellular causes of the disease, research tends to focus on the 10% of patients with inherited familial forms of MND. Currently, the 'Online Mendelian Inheritance in Man' database lists ~40 genes with assigned ALS-linked mutations (Online Mendelian Inheritance in Man), but modern techniques to analyse the genomes of MND patients continue to increase this number (Chunn et al., 2020). The genes uncovered so far reveal that MND is not a disease which relates to one certain aspect of cellular machinery, but MND-linked genes encode proteins with a wide range of very different cellular functions (Box 4; Kim et al., 2020).

Box 4. Some examples of genes linked to MND/ALS (compare Fig.2B)

- About 21% of familial MND cases are linked to mutations in the **SOD1** gene (type 1 ALS); the healthy SOD1 protein is an enzyme that protects cells against 'oxidative stress' by inactivating harmful oxygen radicals.
- About 34% of familial MND cases are caused by abnormal DNA sequences inserted into the **C9ORF72** gene (type 1 ALS); these DNA sequences give rise to highly repetitive dipeptide repeat proteins that form harmful aggregates in neurons.
- About 8% of familial MND cases are linked to mutations in either of two genes: **TARDBP** (type 10 ALS) or **FUS** (type 6 ALS); the healthy proteins encoded by these genes can bind the mRNAs of hundreds of other genes and regulate their protein production. Even if the TARDBP gene itself is not affected, its protein is found accumulated in harmful neuronal aggregates in 97% of all MND patients.
- Rarer familial MND cases are linked to mutations in the **TUBA4A** (type 22 ALS) or **KIF5A** (type 25 ALS) genes. Healthy TUBA4A proteins are the building blocks that polymerise to form microtubules, and healthy KIF5A proteins are motors that transports cargo along microtubules; both are therefore required to distribute live-sustaining cellular components in axons.

As can be seen from the examples in Box 4, the gene mutations linking to MND relate to very different aspects of cellular machinery. Nevertheless, they all converge primarily on the deterioration of upper and lower motor neurons with shared features, such as the aggregation of TARDBP protein in ~97% of ALS patients (Box 4; Kim et al., 2020). Similarly to MND, also other DNDs are known to be linked to mutations in genes with very different functions that nevertheless converge to affect the same brain areas or cell types (Tab.1).

A model explaining how different causes converge on a shared outcome

But how can the same class of DND be triggered by a range of very different causes? The answer lies in the fact that different aspects of axonal machinery involved in long-term maintenance do not act in isolation but display functional links and interdependencies (Wilson III et al., 2023). For example, most organelles form physical contact sites with one another to exchange materials and regulate each other (Fig.2B). Particularly, the tubular ER networks can connect organelles even over distances and mediate communication between them. Furthermore, as pointed out earlier, microtubules underpin the function of virtually all components and organelles by ensuring their proper distribution through transport (Maday et al., 2014).

To bring order into this closely interwoven machinery, the 'Dependency Cycle of Local Axon Homeostasis' was recently put forward (Fig.3; Prokop, 2021; Smith et al., 2023). It proposes that the motor protein-driven transport along microtubules is indispensable and beneficial for axons, but it also damages microtubules: like cars running on motorways cause potholes, motor proteins induce breakage or looping of microtubules. If such microtubule damage persists, it will lead to perilous collapse of axonal transport; it must be rectified through highway maintenance. In axons, this is performed by microtubule-binding proteins that can repair and replace damaged microtubules, thus keeping the system in homeostatic balance ('structural homeostasis' in Fig.3). For example, the microtubule-binding protein DYSTONIN functions by guiding growing microtubules into straight bundles; in its absence severe microtubule curling is observed (Dalpe et al., 1998) which links to 'Hereditary sensory and autonomous neuropathy, type 6' in humans (HSAN6; Tab.1).

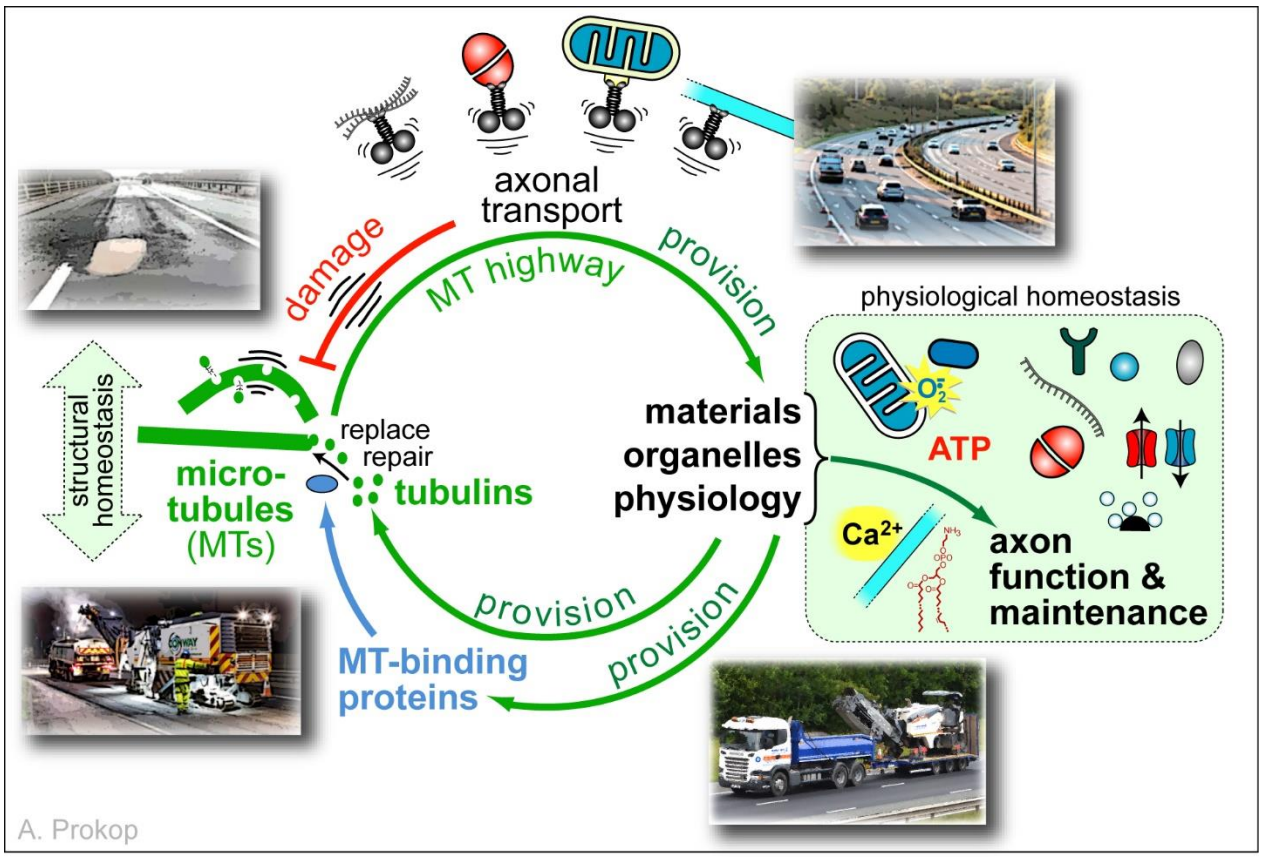

Figure 3. The dependency cycle of local axon homeostasis and its motorway analogy*. All steps are explained in the main text; used symbols correspond to Fig.2.*

However, just like machinery and materials must be transported to building sites on motorways (Fig.3), microtubule maintenance in axons depends on the provision of the necessary proteins and the right physiological conditions. For example, tubulins as the building blocks of microtubules or the maintenance protein DYSTONIN must be transported to the site of repair. A recent finding also suggests that proper transport of organelles is important: if organelles are not properly distributed this breaks the physiological homeostasis (Fig.3), for example causing harmful imbalance of oxygen radicals (often referred to as oxidative stress) which has deleterious effects on microtubule maintenance. If the axonal repair machinery itself depends on motor protein-mediated transport of materials and organelles, this establishes a circular dependency (Fig.3) that offers new explanations for DNDs.

The dependency cycle offers new perspectives for research and treatment of DNDs

Circular dependency would predict that major break-down of any part of axonal machinery will have serial knock-on effects that eventually collapse the entire cycle, resulting in axon degeneration with shared features. Indeed different DNDs tend to display shared features, such as the breakdown of axonal transport or the fact that axons start dying-back from the distal tips (Adalbert and Coleman, 2012). Good examples of how different parts of cellular machinery can break down are the MND-linked mutations in Box 4: the loss of tubulins (TUBA4A) and motor proteins (KIF5A) directly inhibit axonal transport; the loss of SOD1 causes oxidative stress known to impair microtubules, hence transport (see previous section); the loss of TARDB and FUS disturbs the production of many different proteins, thus providing multiple potential causes for structural and physiological dyshomeostasis.

A slightly different case are protein aggregates inside neurons as a typical feature in many DNDs which tend to have disease-specific protein contents: aggregates enriched with TARDBP proteins are observed in most cases of MND (Box 4; see also type I ALS cases with CORF72-related aggregates), TAU-containing tangles in Alzheimer's disease, α-SYNUCLEIN-rich Lewy bodies in various dementias and Parkinson's disease, PRION PROTEIN aggregates in spongiform encephalopathies including Creutzfeldt–Jakob disease, and tripeptide repeat-containing inclusion bodies in Huntington's disease. Such aggregates may disturb neuronal homeostasis in many ways, for example by blocking axonal transport or overwhelming the lysosome removal system (Fig.2B) which may then cause oxidative stress. Other hypotheses suggest that dysfunctional proteins are toxic and disease-inducing, and that aggregate formation protects neurons by sequestering and neutralising such proteins. This may explain why clinical trials with drug-induced inhibition of TAU tangles in Alzheimer's patients don't look promising so far (Huang, 2020). More studies into the underlying mechanisms are required, and the dependency cycle might provide a helpful framework.

The dependency cycle can also help to explain degeneration upon non-familial causes (Box 5). For example, during ageing many aspects of the cellular machinery are known to become dysfunctional including microtubules and ROS homeostases (Salvadores et al., 2017). This predisposes the cycle for collapse and can explain why ageing is the greatest risk factor for DNDs.

Future opportunities and challenges

The dependency cycle suggests that microtubule breakdown and oxidative stress are common nominators in many DNDs, suggesting microtubule stabilisation or antioxidants as broader therapy options. For example, vitamin E is an effective antioxidant and might prove helpful if adequately dosed to avoid dangerous side effects.

However, an important open question remains: many DND-linked genes are widely expressed throughout the nervous system, but their mutations show a bias for certain neuron types. For example, mutations in certain genes important for endoplasmic reticulum function, affect primarily upper motor neurons causing hereditary spastic paraplegia. Why are not all neurons equally affected, since they all depend on the endoplasmic reticulum? These neuron-specific effects of DND-linked genes remain a central conundrum. Solving this conundrum in future research would further improve our fundamental understanding of DNDs with a view to treatment strategies that may one day improve the life quality of patients suffering from these devastating diseases.

Key points

- Different DNDs tend to primarily affect certain regions of the nervous system explaining the disease-specific symptoms.
- The most delicate parts of neurons are their cable-like axonal processes which must be maintained for life; axons are therefore prime lesion sites in DNDs.
- Long-term maintenance of axons requires genetically encoded multifaceted local cell machinery, the different parts of which are interdependent and arranged into a cycle of mutual dependencies.
- In this scenario, it does not matter which part of axonal machinery breaks down first; it will have knock-on effects that can collapse the entire dependency cycle and trigger axon degeneration.
- This circular dependency can explain why mutations in very different genes can cause the same class of DND.

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