

Introduction to MND research

Information Sheet A

The purpose of this information sheet is to provide an introduction to motor neurone disease (MND) research, including an explanation of what happens in motor neurones in MND, overview of the possible causes, and how the MND Association supports cutting-edge research to find the causes and treatments for MND.

The content is split into the following sections:

- 1: **What is MND?**
- 2: **What causes MND?**
- 3: **What goes wrong in motor neurones?**
- 4: **Funding MND research**
- 5: **International Symposium on ALS/MND**
- 6: **How do I find out more?**

Disclaimer: *Please note that information provided in this information sheet is based on a review of the currently available literature. This information sheet was written by the MND Association staff who are not clinicians and so any information provided in this sheet should not be considered as clinical advice. You should always discuss potential treatments with your clinician.*



This symbol is used to highlight **our other publications**. To find out how to access these, see *Further information* at the end of this sheet.

What do the words and abbreviations mean?

Axon	A long projection carrying the electrical impulse from the cell body to the end of the neurone.
Dendrites	Projections stemming from the neuronal body that receive messages from preceding neurones.
Electromyogram (EMG)	Procedure for detecting muscle fasciculations.
Frontotemporal dementia (FTD)	A condition causing severe cognitive and behavioural changes, found in 15% of people with MND.
Glial cells	Cells that surround motor neurones, providing them support and nourishment.
Lower motor neurones	Motor neurones connecting the spinal cord to the muscles of the body.
Magnetic resonance imaging (MRI)	A type of scan that can visualise certain areas of the body (most often the brain).
Neurotrophic factors	A group of chemicals that provide nutrients to motor neurones.
Primary Lateral Sclerosis (PLS)	A type of MND predominantly affecting upper motor neurones.
Progressive Bulbar Palsy (PBP)	A type of MND affecting muscles involved in speech and swallowing.
Progressive Muscular Atrophy (PMA)	A type of MND predominantly affecting lower motor neurones.
Upper motor neurones	Motor neurones connecting the brain with the spinal cord.

1: What is MND?

MND is an umbrella term covering a number of progressive degenerative conditions involving selective degeneration of motor neurones. MND can affect adults at any age, but it most commonly appears in people aged between 50 and 70.

Motor neurones are the nerve cells along which the brain sends instructions to the muscles in the form of electrical impulses (Fig 1). Motor neurones form the link between a person thinking about moving and the movement itself.

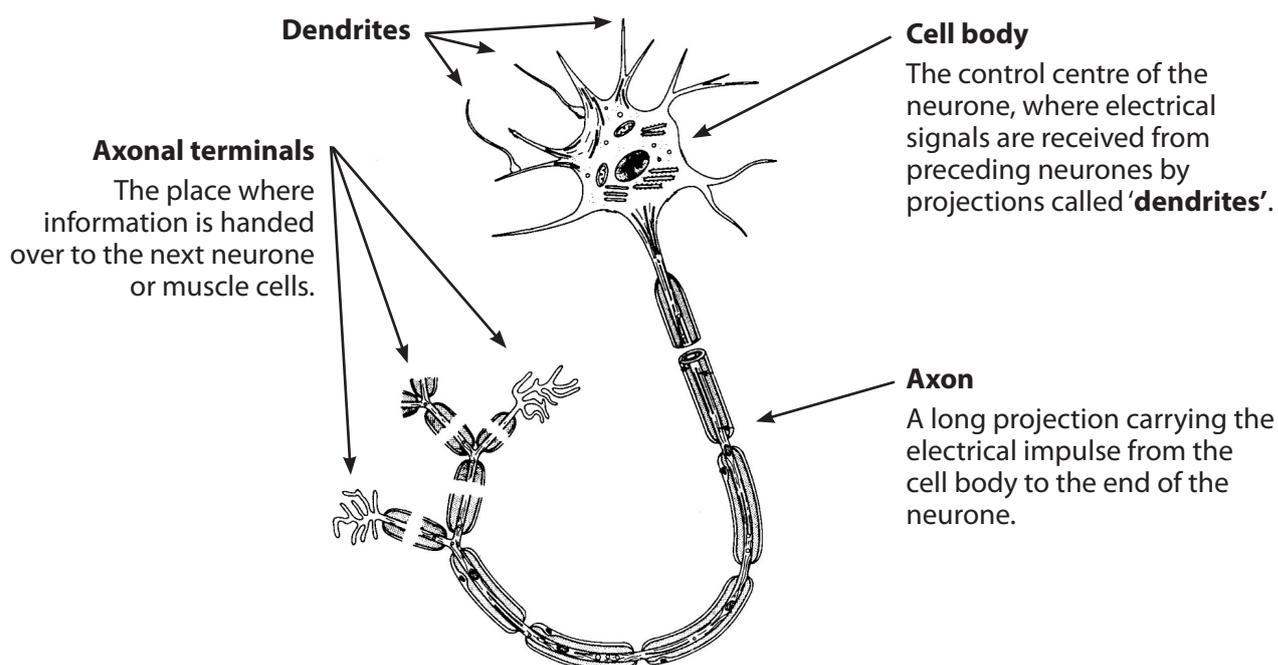


Figure 1. Illustration of a motor neurone. In MND, motor neurones lose the ability to communicate the message from the brain to the muscle.

While the 'wiring' is a bit more complicated, the process of making the muscles work essentially involves two types of neurones that form a 'chain of commands' from the brain to the muscles.

The two types of motor neurones are **upper motor neurones**, connecting the brain to the spinal cord, and **lower motor neurones**, connecting upper motor neurones in the spine to the muscles of the body. These neurones communicate by sending electrical messages from one neurone to another, until they reach the desired location (muscles). In MND, this line of neuronal communication collapses; motor neurones are unable to bring electrical information from the brain and spinal cord to the muscle, which then becomes inactive (paralysed) as a result. If a muscle is paralysed for a long time, it starts to decrease in mass – it atrophies. This is why muscle wasting is a common symptom of MND.

Types of MND

In the most common form of MND, **amyotrophic lateral sclerosis** (ALS), degeneration of both the upper and lower motor neurones occurs, leading to paralysis of all voluntary muscles in the body (especially limbs). When only the muscles involved in speech and swallowing are affected, this is known as **progressive bulbar palsy**, causing slurred speech and difficulty swallowing.

In less common forms of MND, there is a more selective degeneration of either the upper motor neurones (**primary lateral sclerosis**; PLS) or lower motor neurones (such as **progressive muscular atrophy**; PMA).

Another type of motor neurone degeneration, **Kennedy's disease**, is sometimes misdiagnosed as MND despite not being classed as a type of MND. The disease causes damage to voluntary muscles, leading to weakness, wasting of muscles and hormonal changes. It is caused by a genetic mutation, which can be found through genetic testing.



For further information about the different types of MND, see: Information sheet 2B – *Kennedy's disease*, 2C – *Primary Lateral Sclerosis*, or 2D – *Progressive Muscular Atrophy*.

Cognitive and behavioural symptoms

Up to half of the people living with MND may also experience difficulties with learning, language and concentration. This is generally known as cognitive impairment. Around 15% of people with MND experience severe cognitive and behavioural changes that will be diagnosed as frontotemporal dementia (FTD). FTD is an increasingly recognised form of dementia, with different signs and symptoms to the more common Alzheimer's disease (behavioural changes and speech problems are more prominent in FTD).

Mutations in the gene C9ORF72 have been shown to be the most common cause of inherited FTD, MND and MND-FTD. Importantly, up to 10% of cases of sporadic MND (where there is no known family history) are also strongly associated with this same gene.



For further information about cognitive change in MND, see: Information sheet 9A – *Will the way I think be affected?*.

2: What causes MND?

Understanding the causes and mechanisms of motor neurone degeneration is essential to allow the development of treatments. Only by understanding what goes wrong in MND can scientists know how to design and where to target drugs and other therapies.

At the moment, the cause of MND is still not fully understood. The majority of MND cases are thought to be caused by a number of contributory factors, including subtle **genetic, environmental and lifestyle** influences. It is important to note that these factors must all coincide to trigger the disease. Below is the possible contribution the three factors might have on the development of MND.

Genetics

The instructions for the way our bodies develop and function are provided by genes, which we inherit from our parents. In approximately 5-10% of cases, MND is directly caused by a genetic mistake. This mistake can be passed down from parent to child, so the disease appears in the different generations of a family. This is known as familial, or **inherited MND**. Inheriting a copy of an MND-causing gene however doesn't necessarily mean that the person will go on to develop the disease, and the influence of the contributory factors is still likely to play a role.

In the majority of cases however, the disease appears for no apparent reason and without any known familial link. This is sometimes known as **sporadic MND**. It has not yet been established what causes this type of MND. Normal genetic variations may make people more susceptible, but on their own do not cause the disease. In these cases, MND is thought to result from a combination of subtle genetic, environmental and lifestyle factors.

Researchers believe that discovering the genetic causes of inherited MND will lead to a better understanding of what is going wrong in all forms of MND. As both the familial and sporadic form of MND are clinically indistinguishable, the mechanisms underlying both types of the disease are likely to be similar.

So far, a number of genes have been identified that can cause inherited MND, including SOD1, TDP-43, FUS, UNC13A, C9ORF72, MATR3, NEK1 and ANXA11.



For further information about inherited MND, see: Information sheet B1 – *Introduction to inherited MND*.

Lifestyle and environment

Exposure to lifestyle and environmental factors that might contribute to the development of MND has been extensively studied over the years. This research is known as **epidemiology**. Epidemiological studies have identified possible links with

prior exposure to mechanical and/or electrical trauma, military service, smoking, agricultural chemicals, high levels of physical activity, and a variety of heavy metals. However, it is important to note that these are only suspected contributory risk factors and the evidence obtained in these studies has often not been conclusive.

It is not known how environmental and lifestyle factors could increase the risk of MND. One possible explanation is that they have a cumulative effect in weakening of nerve cells, making them more susceptible to degeneration. Another explanation is that these factors interact with specific genes, triggering the disease through gene-environment interactions.

Some of the possible environmental and lifestyle factors that have been linked to MND are protective, whereas some may increase the risk of developing MND. An example of these are listed below:

Diet

Studies into the impact of diet on the risk of developing MND found that people who ate a healthier diet, inclusive of fruit and vegetables, were less likely to develop the disease. The findings of such studies apply only to the risk of developing MND, not its treatment, and often examine just one of the many factors that may 'tip the balance' towards somebody getting the disease.

Professional sportsmen

A number of studies identified that professional football or rugby players develop MND more often than the general population. This might be partly due a connection with a repeated exposure to head injuries, or exposure to other environmental factors. Other professional sportsmen however do not appear to be at any greater risk.

Physical activity/exercise

A large multi-centre study investigating the association between lifetime physical activity and the risk of developing MND found a slightly increased risk of developing the disease in people with substantially higher levels of activity. Further research is now ongoing to look at how physical activity may increase the risk of someone developing MND, including studying the genetic make-up of these individuals.

It is important to note that physical activity alone is not responsible for causing MND, and other contributory factors are needed to 'tip the balance' in predisposed individuals. The benefits of exercise also greatly outweigh the potential negatives, especially when we consider the high odds of developing cardiovascular diseases due to sedentary lifestyle.

The six steps theory

Using a mathematical model, previously used by cancer researchers, Al-Chalabi and colleagues (2014) suggested that it takes six steps to trigger MND. The number of steps might be different (and likely reduced) in MND caused by specific genes. Each step represents a separate event that could be a genetic, environmental or lifestyle factor,

with the last one triggering the disease. What exactly these factors are is yet unknown.

For more information on environmental and lifestyle factors associated with the development of MND, see www.mndassociation.org/whyme.

3: What goes wrong in motor neurones

To know what causes MND, we need to delve even deeper under the surface, to investigate the pathological mechanisms that lead to degeneration of motor neurones. Below are some of the mechanisms that are suspected to be involved in motor neurone degeneration.

Aggregation

Abnormal clumps (aggregates) of protein molecules cluster inside motor neurones affected by MND, disrupting their normal functioning.

Editors on strike

'Editors' copy, tidy and transport short sections of code, known as RNA, to produce instructions that can then be used to build proteins. If this process becomes faulty, the production of proteins could be adversely affected and cause MND.

Faulty scaffolding

Cellular 'scaffolding', called the cytoskeleton, ensures that the shape and structure of motor neurones and other cells is maintained. If the structure is defected, it could cause the cell to degenerate.

Disruption to chemical communication networks

Electrical messages are transmitted from one motor neurone to the next via the release of chemical messengers in the gap between them. For many motor neurones this chemical messenger is glutamate, which in high concentrations can be toxic.

Transport disruption

Motor neurones are large cells, with the largest axons measuring up to one metre in length. It is necessary that their transport systems for moving nutrients, waste and components from one end of the neurone to the other work well. If any part of the transport system becomes faulty, it may cause disruption to the whole system and lead to degeneration of the motor neurone.

Build-up of toxic waste

Oxygen free radicals are toxic chemicals formed as a normal by-product of cellular processes, which are normally mopped up by antioxidants. In MND however, the motor neurones' own antioxidant defence pathways may be suppressed, leading to a toxic build-up of waste.

Power failure

All cells contain tiny 'batteries' called mitochondria, which are responsible for producing

energy for the cell while maintaining the cell's normal function. The mitochondria in motor neurones of people with MND appear to be abnormal.

Lack of nerve nourishing factors

There is some evidence that motor neurones become more susceptible to MND because of the lack of nutrients. One form of motor neurone nutrients that are likely to be in shortage in MND, is a group of chemicals called neurotrophic factors, literally meaning 'nerve nourishing factors'.

Problematic neighbours

Motor neurones are surrounded by cells called glia, which normally provide the neurones with support and nourishment. However, researchers have now come to realise that glial cells, such as oligodendrocytes, can in fact contribute to motor neurone degeneration if they lose their supportive properties and become toxic.

4: Funding MND research

We are a leader in funding and promoting cutting-edge MND research both within the UK and across the world to lead us to new understanding and treatments, and bring us closer to a cure for MND. Our research portfolio is split into five themes:

Causes: Understanding what causes motor neurones to die.

These projects aim to understand the causes of motor neurone degeneration. This is essential to allow the development of treatments. Only by understanding what goes wrong in MND can scientists know how to design and where to target drug treatments.

Models of MND: Developing models to understand causes of MND.

One way in which to understand the function of a gene and how this goes wrong in a disease, or the impact of a biochemical pathway malfunctioning, is to use a model. This might be in mice or isolated cells in a dish. These projects aim to develop new and better models of MND to better understand the causes of MND.

Healthcare: Increasing quality of life of people living with MND.

These projects aim to increase the quality of life of people living with MND, as well as improving care. The projects have a direct impact on people living with MND here and now.

Markers: Identifying markers of disease progression.

There is currently no diagnostic test for MND and no specific 'biomarker' to monitor the disease. These projects aim to find a marker of disease progression to speed up diagnosis, prognosis and disease monitoring of MND.

Developing treatments: Turning scientific discoveries into potential treatments.

These projects aim to test the effectiveness of potential treatments. They aim to test

potential treatments from the laboratory stage to the clinical trial environment.



For further information about the projects we currently support, see: Information sheet E – *Research we fund*.

6: International Symposium on ALS/MND

The International Symposium on ALS/MND is the largest medical and scientific conference specific to MND. It is the premier event in the MND research calendar for discussion on the latest advances in research and clinical management.

Each year, we organize the three day event, now attracting over 1,000 delegates worldwide, representing the energy and dynamism of the global MND research community.

Find out more about the Symposium on our website:
www.mndassociation.org/symposium.



4: How do I find out more?

Useful resources

The contact details are correct at the time of publishing, but may change between revisions. If you need help to find an organisation, contact the Research Development Team (see *Further information* at the end of this sheet for details).

MND Association website - research webpages

We provide information about MND-related research, clinical trials, research we fund, and ways to get involved.

Website: www.mndassociation.org/research

MND Research blog

Our blog is continuously updated with the latest MND research news throughout the year. From the International Symposium on ALS/MND to MND research in the news, the blog keeps you up to date by demystifying the science and explaining what it really means for people living with MND.

Website: mndresearch.blog

MND Research newsletter

Monthly e-newsletter and quarterly research magazine focusing on the latest MND research, which contains recent MND research news, updates on MND Association-funded projects, conference news and current opportunities to get involved with research.

Website : www.mndassociation.org/mnd-research-newsletter

Further information

You may find these information sheets from the MND Association helpful:

2B – *Kennedy's disease*

2C – *Primary Lateral Sclerosis*

2D – *Progressive Muscular Atrophy*

9A – *Will the way I think be affected?*

B1 – Introduction to inherited MND

E – *Research we fund*

We also provide the following guides:

Living with motor neurone disease – our main guide to help you manage the impact of the disease

Caring and MND: support for you – comprehensive information for unpaid or family carers, who support someone living with MND

Caring and MND: quick guide – the summary version of our information for carers

You can download most of our publications from our website at www.mndassociation.org/publications or order in print from the MND Connect helpline, who can provide further information and support.

MND Connect can also help locate external services and providers, and introduce you to our available services, including your local branch, group, Association visitor or regional care development adviser.



MND Connect

Telephone: 0808 802 6262

Email: mndconnect@mndassociation.org

MND Association, David Niven House, 10-15 Notre Dame Mews,
Northampton NN1 2BG

Research Development Team

Telephone: 01604 611 880

Email: research@mndassociation.org

MND Association website and online forum

Website: www.mndassociation.org

Online forum: forum.mndassociation.org or through the website

We welcome your views

Your feedback is really important to us, as it helps improve our information for the benefit of people living with MND and those who care for them. If you would like to provide feedback on any of our information sheets, you can access an online form at: www.surveymonkey.co.uk/r/infosheets_research

You can request a paper version of the form or provide direct feedback by email: research@mndassociation.org.