Lay Summary

Could the different lengths of nerve fibres influence the patterns of disability we see in MS?

Mills 2025

Is multiple sclerosis a length-dependent central axonopathy? Some empirical data from the TONiC study

Some information about nerve pathways to set the scene

One important type of nerve cell is called a neurone, which consists of a cell body and a long extension called the axon. The axon carries messages to and from the neurone's cell body, often to another neurone but sometimes to muscle or some other structure. Axons in the brain may transmit over short distances, such as one millimetre, while other neurones have very long axons (more than 1,000 times longer). Examples of such very long axons are the ones that extend from the spinal cord down to the big toe to induce movement, which might be over a metre. Sensations from the body involve a chain of three neurones which pass the sensation signal from one to the next.

In multiple sclerosis (MS), we know that there may be damage to sections of the myelin sheath, which is a form of insulation surrounding the axon. Scientists have long suspected that in MS, longer axons may be more severely affected than shorter ones, because longer axons could be more vulnerable to damage. Think of a ball of many pieces of string of different lengths: if something causes the string pieces to break, a short piece might have one break and a longer piece more breaks. This idea is known as *length-dependent axonopathy*. However, until now, there hasn't been strong evidence to support this idea.

What did the study involve?

Using data from the Trajectories of Outcome in Neurological Conditions (TONiC) study, the researchers looked at responses from 5,925 people with MS.

Each participant filled in a body diagram ("manikin") showing which body parts were affected by MS symptoms. The team then used information from neuroanatomy to estimate the typical length of nerve pathways from the brain to each body part. For example, axons to the legs are much longer than those to the face.

They compared how often each body part was affected with how long its nerve pathway is. They also considered factors such as age, MS type (relapsing-remitting, secondary progressive, or primary progressive), sex, and disability level.

What was found?

- Body parts supplied by longer axons were more likely to be affected by MS.
- This pattern was seen in all types of MS, though it was strongest in progressive forms of MS.
- For example, legs (which have the longest nerve pathways) were affected most often, while speech and swallowing (shorter pathways) were least affected.
- Problems with balance were also very common, probably because balance involves long nerve loops between the different parts of the brain controlling balance and the spinal cord.
- Vision did not fit the pattern, perhaps because people ticking vision problems might have a problem with the nerve pathway for seeing, or the nerve pathway for moving the eyes, or even non-MS problems like short sightedness or cataracts.
- Involvement of the left side was more common across the whole group than the right, which fits with people having more capacity to compensate for damage to their preferred side, e.g. the right hand is more dextrous and can write, the right leg is the stronger lead leg for kicking.

The findings provide solid evidence that **MS behaves like a length-dependent axonopathy** — meaning that the longer a nerve pathway is, the more likely it is to show damage.

This supports earlier theories that MS-related disability may partly result from cumulative damage along long axons, leading to symptoms that start distally (for example, in the legs) and progress upward over time.

It's important to note that these findings required a very large number of people to tick the manikin, because we can detect these results clearly in a large group. On an individual level, there was considerable variation, such as people noting vision problems before leg problems, even though eye to brain is a much shorter pathway than leg to brain. We could not have found this result without the help of thousands of people with MS who spent a minute or two ticking the manikin to record their pattern.

Why this matters?

Understanding that MS is "length-dependent" helps explain why symptoms like walking difficulties often appear earlier and progress faster than problems with speech or vision. It could also guide future treatments and rehabilitation strategies by focusing on protecting or **repairing longer axons.**

Read Full Article Here: https://doi.org/10.1016/j.msard.2025.106594

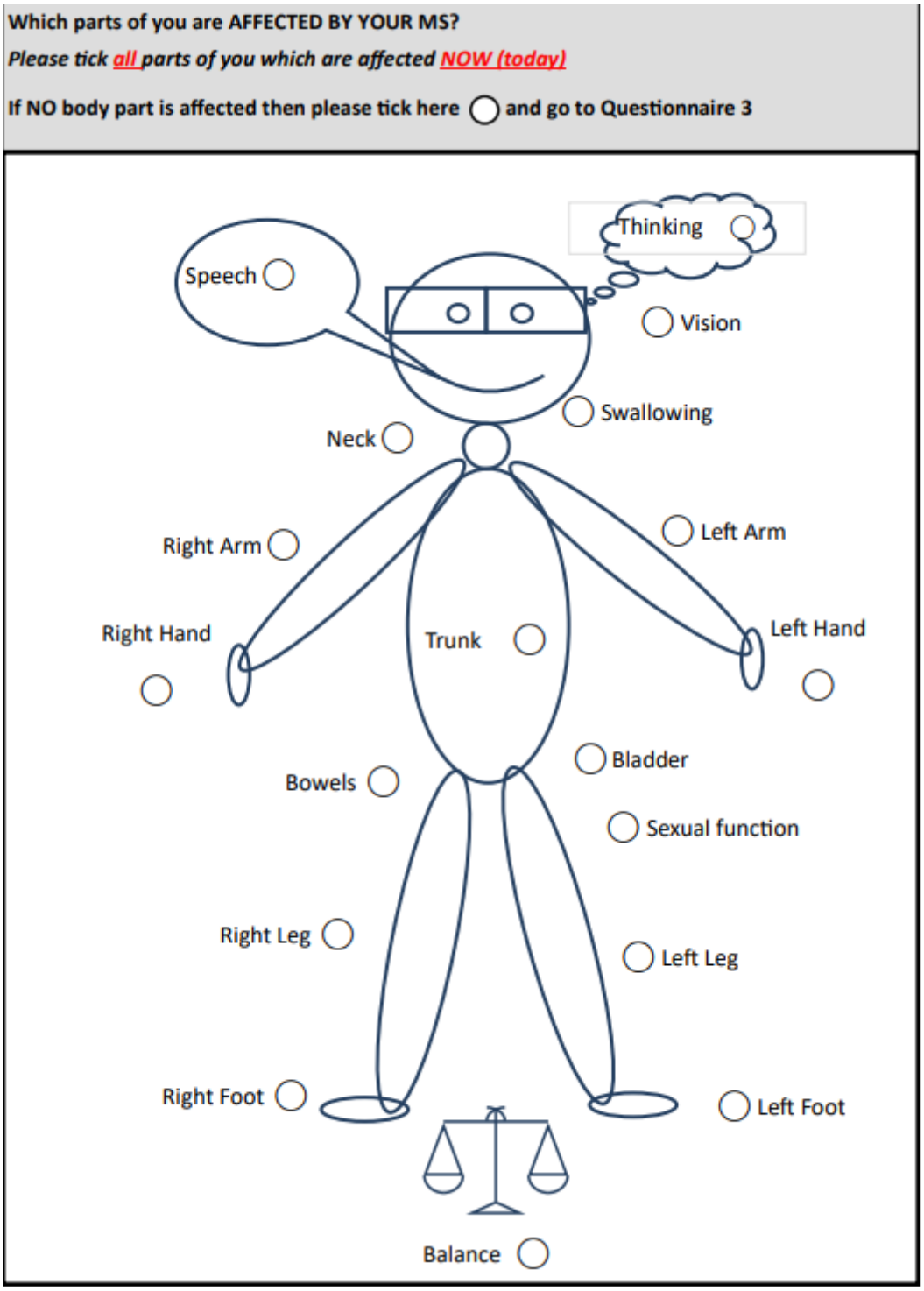

Figure 1: Demonstration of the body diagram (“manikin”) that was used in this study