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**The ‘dying forward’, ‘dying backward’ and ‘dying outward’ theories of motor neurone disease (MND): a review of the evidence.**

ALS is a common form of MND with localised symptoms which progress to become systemic, involving death of neurones from the brain to the spinal cord (UMN) and from the spinal cord to the muscles (LMN). Often only diagnosed once symptomatic, the therapeutic window is missed, hence the life expectancy after diagnosis is on average 2-3 years. Poor understanding of its early pathology means there are three hypotheses: that neurones die primarily due to pTDP-43 aggregation in the neocortex causing secondary death in the spinal cord (dying forward); that weakening in the junction between muscle and neurone spreads upwards (dying backward), or that the disease spreads from the corticospinal tract’s (specific UMN) end synapse (dying outward). By comparing the literature, I hope to evaluate each hypothesis, showing the most likely mechanism for MND. This could help identify early markers of the disease, and aid treatment by entering the therapeutic window.

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