AN AGE-BASED THEORY OF NEURODEGENERATIVE DISEASE

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Introduction: Current theories of neurodegenerative disease focus heavily on pathology. Despite their acknowledged successes, however, each of these theories has had its critics. Experimental observations that clash with their premises have grown, but to date few comprehensive alternative models have been put forward.

Aims and methods: This prompted me to reconsider the pathways to dementia, an exercise that led to an age-based hypothesis.

Results: The most widely accepted risk factor for both Alzheimer's and Parkinson's is age. The new model thus begins with the idea that age weakens the brain and blunts its responses to change, but on its own leads only to a slow 'natural' decline in cognitive function. To progress from this path to full neurodegenerative disease, three key steps are envisioned:

1) an initiating injury,
2) a maladaptive chronic response - primarily inflammation in the case of Alzheimer's; oxidative changes in the case of Parkinson's and
3) a cellular change-of-state that permanently alters the physiology of neurons and several other cell types of the brain. In Alzheimer's, the pathology that triggers the amyloid cascade remains important in the model, but it is reconfigured as an amyloid deposition cycle - a feed-forward loop that links to the new 3-step process at step 2.

Conclusions: The model suggests that while the pathology may be highly correlated with disease, it is mechanistically distinct from the required three steps leading to neurodegeneration. The model is a work-in-progress; all suggestions for changes are welcome.