

## Temporal dynamics of Huntington's disease: insights from systems modelling into compensation

S E M I N A

Neurodegenerative diseases are associated to the production of toxic RNAs and proteins leading to disruption of brain homeostasis at multiple levels. Understanding how the brain can use canonical stress response mechanisms to resist neurodegenerative disease and maintain function over time — compensation — has strong therapeutic potential. Compensation in neurodegenerative diseases such as Huntington's disease (HD), a genetic and tractable disease, can be viewed as a biological program prescribing the system dynamics, governed by remodelling molecular and cellular networks in response to HD and age. The problem is to extract the rules that may govern the molecular and cellular dynamics of HD in such ways that precise testable hypotheses can be generated about the regulation of stress response and neuronal homeostasis. Using graph theory for cross-integrating HD networks and biological models of HD for testing network predictions supports a model in which successive waves of gene deregulation during the disease process may persistently alter stress response, neuronal identity and cell integrity.

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