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# Repetitive Molecular Architecture and Network Instability in Social Behaviour Insights from Neurodegeneration

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## ABSTRACT

*Frontotemporal Dementia (FTD), particularly its behavioural variant (bvFTD), is characterized by progressive disruption of social behaviour resulting from degeneration of frontal and anterior temporal brain networks. While these changes are traditionally interpreted at the level of neural circuitry, emerging evidence suggests that their origins may lie in molecular processes that compromise protein and cellular homeostasis.*

*A common feature of several neurodegenerative disorders, including FTD, is the involvement of proteins containing repetitive or low-complexity domains, such as tau, TDP-43, and repeat expansions in C9orf72, which are prone to misfolding and aggregation. Such structural repetition may contribute to instability in proteostasis, leading to synaptic dysfunction and large-scale network impairment. In contrast, repetitive motifs in other biological systems, such as glycine–alanine-rich sequences in spider silk spidroins, can produce highly stable and functional macromolecular structures, highlighting the context-dependent outcomes of molecular repetition.*

*Here, we propose a conceptual framework in which repetitive molecular architecture influences neural network stability, contributing to selective vulnerability of frontotemporal circuits involved in social cognition. This framework suggests that microscale molecular properties may have cascading effects on macroscale behavioural phenotypes in neurodegenerative disease. Although comparisons across biological systems are not mechanistically equivalent, they underscore a broader principle that structural repetition can yield divergent functional outcomes depending on cellular context and regulatory environment.*

*This perspective integrates molecular biophysics with systems neuroscience and highlights the need for further investigation into how protein-level properties contribute to network dysfunction and behavioural impairment in FTD and related disorders.*

**Keywords**
Frontotemporal dementia, Behavioural variant FTD, Protein aggregation, Low-complexity domains, Repetitive protein sequences.

Disruption of social behaviour in humans is a defining feature of Frontotemporal Dementia (FTD), particularly its behavioural variant (bvFTD), in which degeneration of frontal and anterior temporal networks leads to disinhibition, loss of empathy, and impaired social judgment. Although these changes are typically interpreted at the level of neural circuitry, their origins lie in molecular processes that compromise neuronal integrity.

A recurring feature of several neurodegenerative disorders, including FTD, is the presence of proteins containing repetitive or low-complexity domains—such as tau, TDP-43, and repeat expansions in C9orf72—that promote misfolding and aggregation [1-3]. Such structural repetition, while biologically common,

may predispose to instability in protein homeostasis, ultimately disrupting synaptic and network-level function. This raises the possibility that repetitive molecular architecture contributes indirectly to large-scale behavioural phenotypes through its effects on neural systems.

In contrast, repetitive protein motifs in other biological contexts can produce stable and functional structures. For example, spidroin proteins in spider silk contain glycine–alanine repeats that assemble into mechanically robust β-sheet nanostructures [4]. This illustrates how repetition can enhance structural resilience rather than induce dysfunction, highlighting the context-dependent consequences of molecular design.

We propose a conceptual framework linking molecular repetition to neural network stability, whereby pathological aggregation of repetitive protein domains contributes to selective vulnerability of frontotemporal circuits governing social cognition. In bvFTD, degeneration of these networks manifests as profound alterations in interpersonal behaviour, suggesting that microscale molecular features can have macroscale behavioural consequences [2,3].

Although comparisons with non-neural biological systems are not mechanistically equivalent, they underscore a broader principle: repetition in biological architecture can generate divergent outcomes depending on regulatory context and system complexity.

This perspective highlights the potential value of integrating molecular biophysics with systems neuroscience to clarify how protein-level properties influence network dynamics and behaviour, and to better understand mechanisms of selective neuronal vulnerability in FTD and related disorders.

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