Prefrontal GABAergic Depletion of TDP-43 Disrupts Cognition

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ABSTRACT

Cytoplasmic aggregation of TAR DNA binding protein 43 kDa (TARDBP, or TDP-43), was first shown to be a major pathological hallmark of amyotrophic lateral sclerosis (ALS) and in a major subtype of frontotemporal lobar degeneration (FTLD-TDP). Such pathology, known as TDP-43 proteinopathy, has also been found in 30–57% of Alzheimer's Disease (AD-TDP) cases. It remains unclear what is the consequence of dysfunctional TDP-43 in GABAergic neurons. We employed a genetic approach to determine the impact of TDP-43 loss restricted to GABAergic neurons of the prefrontal cortex (PFC). We observed significant neurodegeneration in GABAergic neurons and cognitive declines induced by TDP-43 depletion solely in GABAergic neurons of the PFC. We further demonstrated that stimulation of the PFC inhibitory circuit by enhancing the remaining GABAergic neural activity restored behavioral deficits. These findings suggest that TDP-43 plays a critical role in GABAergic neurons and that rebalancing the PFC GABAergic circuit may have therapeutic potential for the treatment of TDP-43 linked AD and AD related dementia.

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