

Early Neuromuscular Junction Denervation in Progressive TDP-43 Δ NLS Pathology

Pasquale Esposito, Lionel Breuillaud, Robin Guay-Lord, Kristina DeDuck, Barry J. Bedell
Biospective Inc., Montreal, Quebec, Canada. Contact: info@biospective.com

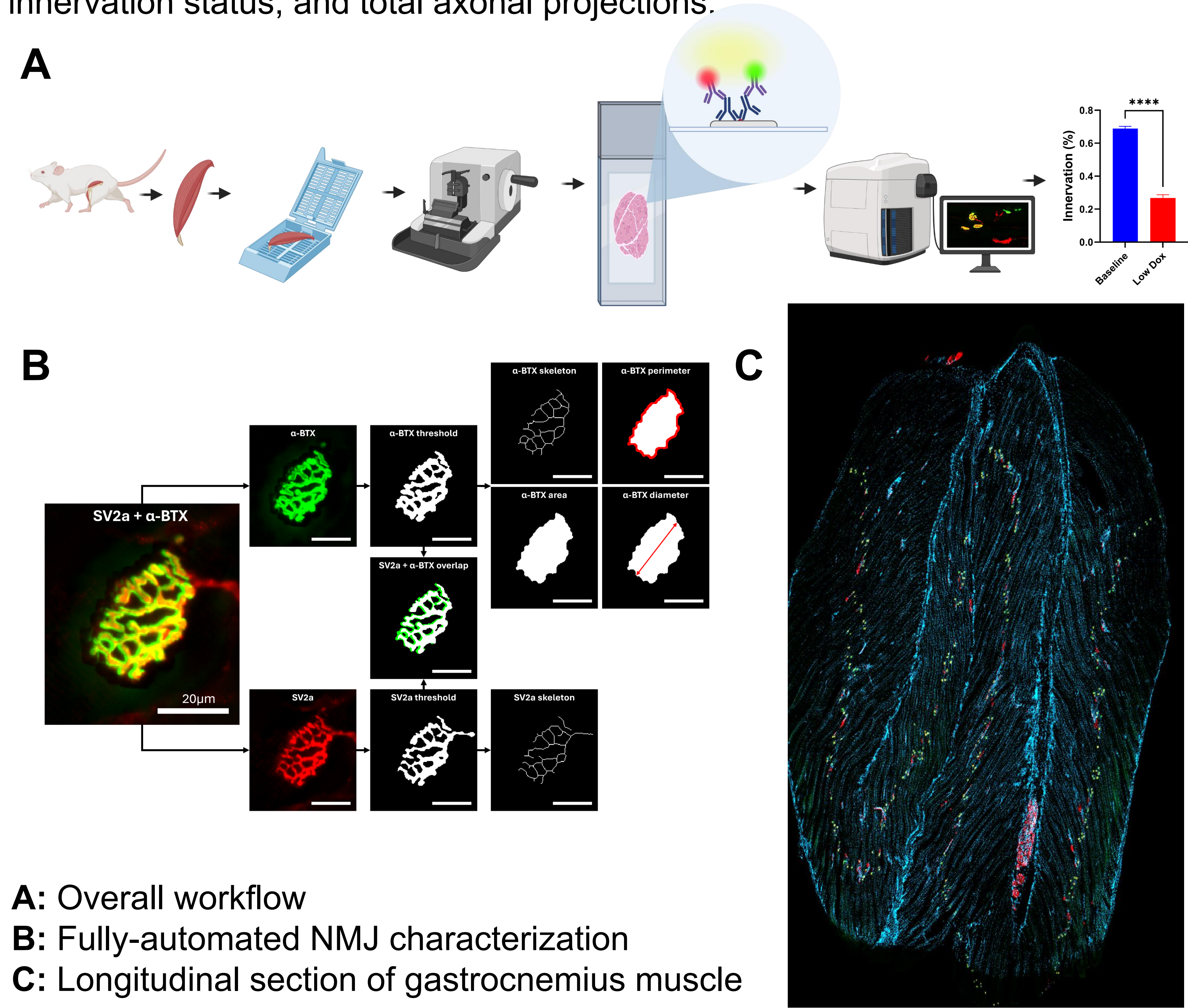


Introduction

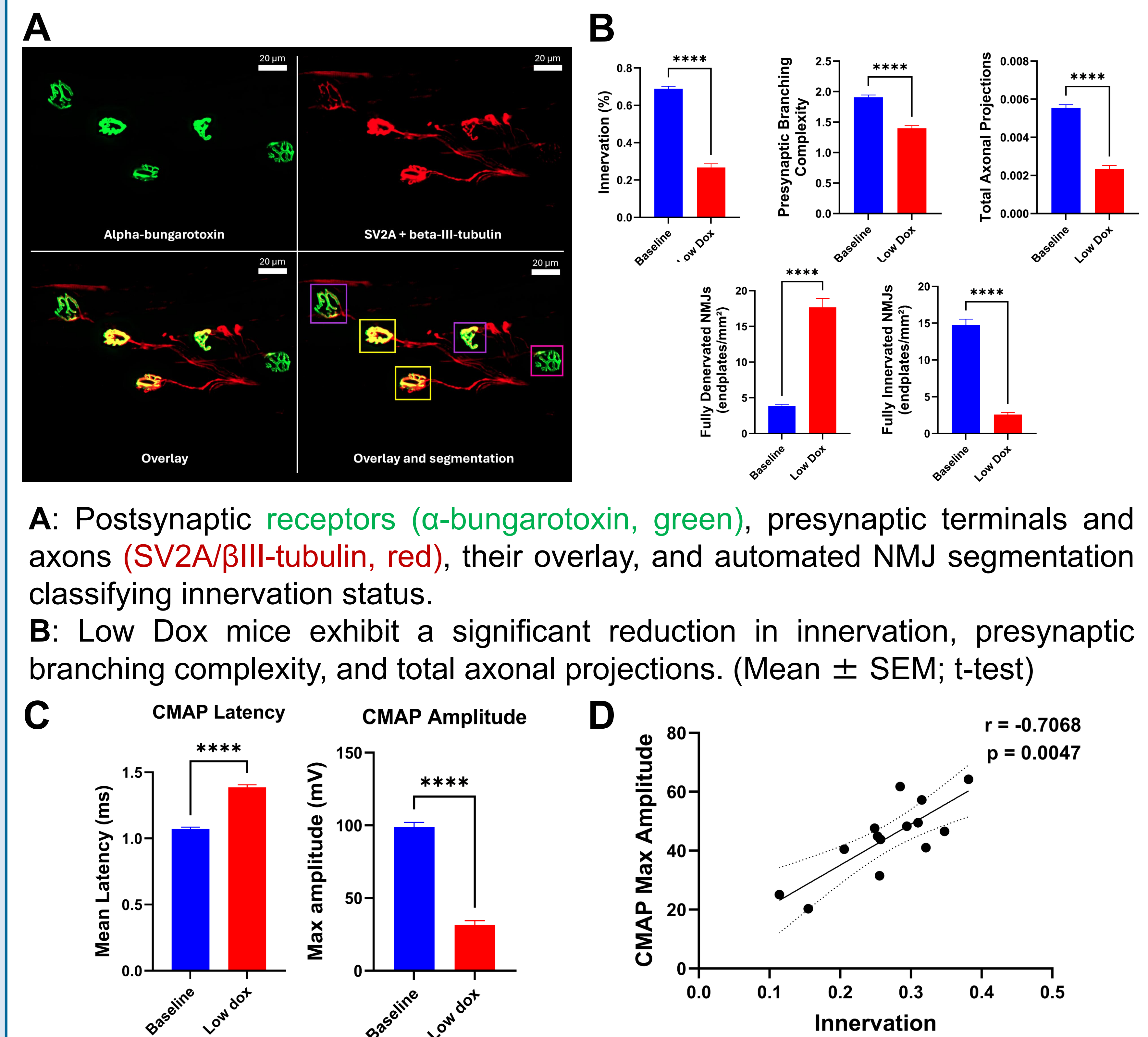
Rationale: Modeling early synaptic dysfunction in ALS is critical for identifying therapies that preserve NMJ integrity and delay motor impairment.
Study focus: NMJ pathology was examined in a mouse model overexpressing human TDP-43 with a defective nuclear localization signal.
Objective: To determine how progressive ALS-like pathology affects neuromuscular innervation.

Methods

Mouse model: Transgenic rNLS8 mice expressing Dox-regulated human TDP-43 Δ NLS were used to model inducible ALS-like pathology.
Disease induction: Mice on Biospective’s Low Dox protocol were used to induce gradual disease progression and provide an extended therapeutic window (≥ 8 weeks) .
Experimental groups: 28 mice total (N=14 Low Dox; N=14 tTA-matched controls); NMJ pathology was assessed 8 weeks post-induction.
Tissue processing & staining: Gastrocnemius muscles were collected after perfusion and co-stained with α -bungarotoxin (postsynaptic AChRs), SV2A (presynaptic terminals), and β III-tubulin (motor axons).
Analysis: NMJ morphology and innervation were quantified using Biospective’s PERMITS™ platform, including presynaptic branching complexity, innervation status, and total axonal projections.



Results



C: Low Dox mice exhibit higher mean latency and lower max amplitude in Compound Muscle Action Potential (CMAP). (Mean $\pm$ SEM; t-test)
D: A strong correlation exists between CMAP amplitude and NMJ innervation

	NMJ Sample Size Estimation				
	25%	33%	50%	66%	75%
Innervation	14	8	4	2	2
Presynaptic Branching Complexity	45	26	12	7	5
Total Axonal Projections	27	16	7	4	3

Sample size estimation for various NMJ metrics between Control (tTA) and Low Dox rNLS8. mice

Conclusions

An 8-week Low Dox regimen in rNLS8 mice captures key features of ALS progression, including synaptic denervation, reduced presynaptic complexity, and impaired axonal connectivity. It provides a robust, translationally relevant platform for preclinical evaluation of therapeutics aimed at preserving NMJ integrity, muscle strength, and delaying motor decline.