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Mechanisms Regulating the Alternative Splicing of Synaptic Adhesion Molecules in Somatosensory Neurons

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Processing external stimuli from distinct sensory modalities is vital for the diversity of somatic sensation. Nociceptive transmission pathways exhibit vast plasticity in response to injury or prolonged exposure to noxious stimuli and can result in chronic pain states. While the plasticity of nociceptive circuits is well established, we possess a limited understanding of the molecular mechanisms that establish the wiring of sensory circuitry, and how this connectivity may be altered in chronic pain.

Neurexins are presynaptic cell-adhesion molecules which are essential in coordinating synapse formation through trans-synaptic interactions with myriad post-synaptic ligands. Mutations in neurexin genes are associated with a multitude of neuropsychiatric diseases, particularly autism spectrum disorders, Tourette's syndrome, and schizophrenia. Previous work suggests that neurexins regulate synaptic properties critical to coordinating neuronal circuitry in the central nervous system, yet the role of neurexins in somatosensory circuits remains largely unexplored. Extensive alternative splicing of neurexins generates thousands of different isoforms which has been proposed to impart a combinatorial "splice-code" for connectivity. Investigating the role of individual splice sites is an incipient area of study, and little is known about the regulation of neurexin splice variant expression in sensory neurons and its role in specifying sensory connectivity. Here, we test sensory neuron regulation of splice site 4 (SS4), a splice site shown to be modulated by neuronal activity, and physiologically relevant in synaptic plasticity, learning, and memory. We hypothesize that peripheral sensory neurons regulate neurexin alternative splicing in response to changes in activity or injury to alter somatosensory circuit connectivity.