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Working Title: Neonatal Pain: Mechanisms and Consequences
Audience: NICU nurses who work directly with preterm neonates
Message: Neonatal pain exists and can cause permanent changes to the somatosensory system.

Treatment:
A common misconception is that neonates don't feel, or won't remember feeling, pain. However, neonates are in fact more sensitive to pain than adults and persistent neonatal pain experiences can have permanent effects on the developing neonatal somatosensory system. Inside an NICU, a preterm baby is about to get a heel lance. Neonates visibly react to painful stimuli through facial expressions and kick reflexes (Show facial expression footage?). However, painful stimuli also have physiological effects on the neonate. The heel is pricked, and the live footage transforms into a 3D rendering of a translucent neonate with its somatosensory system & brain visible. Pain signals from the heel are sent to the brain. During the first 10 days after birth, the neonatal somatosensory system undergoes heavy fine-tuning.

Zooming into a cross section of the skin of the heel, sensory neurons and surrounding trophic factors are seen. A large number of neurons are active due to large receptive fields of the immature somatosensory system. More activated neurons means more pain signals.
Under normal development, around half of the somatosensory nerves die during the critical period. Survival of a somatosensory nerve depends on presence of trophic factors and proper somatosensory input. Nerve endings that are not surrounded by trophic factors die off. Nerves that did not fire upon the heel prick also die off. The number of nerves active is now few and concentrated. A split screen compares the immature and mature systems.

C and Aβ fibres entering lamina II are seen as the viewer is shown a cross section of a dorsal horn. C fibres are exclusively in lamina II, while Aβ fibres are in lamina III and lamina II. Zooming in, a single lamina II second order neuron comes into focus. Synapsing onto it is a strong Aβ fibre, a weak C fibre, a weak inhibitory interneuron, a strong excitatory interneuron, and a weak descending fibre from brainstem centres. The Aβ fibre also synapses with the excitatory interneuron. Upon a nociceptive input, both the C fibre and Aβ fibres synapse onto the second order neuron. The inhibitory interneuron and descending fibre fire weak inhibitory signals that only have a minimal effect to the excitatory signals. Zoom into cell membrane of the second order neuron. A main contributor to neonates' sensitivity to pain is due to their lack of proper inhibition. Potassium chloride co-transporter, responsible for keeping intracellular Cl- levels low in mature cells, is lacking in immature cells. Upon GABA binding, Cl- rushes out of the cell, depolarizing it instead of hyperpolarizing it like in the adult case. However, this phenomenon does not cause the cell to depolarize – it merely hinders GABA's inhibitory effects. During normal development, the C fibre and descending input strengthens and develops synapses with the inhibitory interneuron. The inhibitory interneuron input signal becomes more

effective against excitatory pain signals. The Aβ fibre loses its synapse with the second order neuron and exits Lamina II. Split screen is used to compare the immature and mature systems. With the split screen, we zoom out to see the entire dorsal horn. The Aβ fibres are now no longer in Lamina II in the mature system.

Persistent pain experiences during the critical period can have an effect on the development of the somatosensory system. We return to a close up of the heel in its immature state, pricked repeatedly this time. Trophic factors are released in the injured areas. Zoom into the end of a nerve fibre showing growth cones. Ephrin A4 is normally present in the skin to down regulate the growth of nerve fibres by growth cone collapse. Upon injury, Ephrin A4 is down regulated in near the site of injury and trophic factors are released at the same time. This causes sprouting of nerves near the injury site resulting in hyperinnervation. Zoom out to see nerve fibres sprout into the injured skin. Very few cells die during the process of natural cell death due to increased amount trophic factors and the increased activation due to nociceptive input. A split screen is used to compare the normal and abnormal mature systems. The split screen travels to the second order lamina II neuron, receiving normal and abnormal mature inputs. The excitatory signals from the C fibre are much more frequent and stronger in the abnormal case.

2D graphs show that children who had early pain experiences have no pain habituation towards nociceptive input. MRI images of brains show that children with early pain experiences have more brain activation during pain experiences. More research is needed in neonatal pain management to prevent permanent effects from early pain experiences.