NOCICEPTION
Acute pain is caused by the activation of nociceptive sensory neurons in the periphery. These neurons trigger the firing of a series of connected somatosensory neurons up the spinal cord and into the brain, transferring information about the intensity and duration of the painful stimulus.

TWO PAIN PATHS DIVERGE IN THE BODY
The acute pain that results from injury or disease, also known as nociception, is very different from the persistent pain that continues even after the damage is resolved, or in some cases, in the absence of an acute injury in the first place. The difference, researchers are learning, comes down to the neural mechanisms that trigger these distinct signals in the brain.

GLIA'S ROLE IN PERSISTENT PAIN
Microglia release cytokines and other proinflammatory molecules, as well as detect signaling factors from peripheral immune cells 1. Together, these signals can enhance the release of excitatory neurotransmitters from pain-transmitting neurons, leading to increased neuronal firing 2. Normally, when glial cells called astrocytes detect an increase in the extracellular concentrations of neurotransmitters, their cellular processes called endfeet begin to take up greater amounts of the molecules in an attempt to bring the hyperactive synapses under control 3. In persistent pain, these cells contain fewer of the molecular transporters responsible for this neurotransmitter removal. Glial cytokines and chemokines can also cause greater numbers of receptors to be displayed on the postsynaptic terminal of the pain-transmitting synapse, further promoting neuroexcitability 4.

PERSISTENT PAIN
Pain that persists long after or in the absence of injury can result from the misfiring of the normal nociceptive pathway. This can be triggered in the periphery—sometimes arising from a neutral stimulus, such as light touch—with the signal becoming amplified on its way to the brain. Alternatively, persistent pain can arise in the absence of any stimulus with the firing of neurons in spinal cord or brain circuits responsible for pain processing. Immune-like cells of the central nervous system known as glia are now recognized to contribute to the aberrant neural activation that causes persistent pain.