This Week in The Journal

Impacts of early life stress on auditory processing

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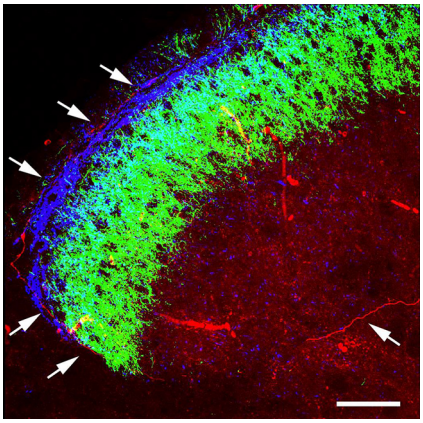
(see pages 3232–3244)

Early life stress (ELS) has far-reaching consequences on brain development and cognition, but sensory processing is also slow to mature and may be susceptible. New research from Ye et al. shows that ELS affects auditory processing of temporally varying sounds. The researchers developed a model of ELS in the Mongolian gerbil, a rodent commonly used to study auditory processing, to investigate the impact of stress. They induced ELS with a combination of unpredictable maternal separation and restraint during the developmental window postnatal day 9 (P9) to P24 when auditory cortex (ACx) is maturing. Two measures indicated that the animals were indeed affected by ELS: at P25, plasma corticosterone, a biomarker for stress, was reduced compared with control animals, and gerbils that received ELS had a lower-amplitude acoustic startle response. The researchers next wanted to assess the animals' behavioral auditory sensitivity to temporally varying sounds requiring ACx processing. They measured the detection of short gaps in ongoing sound, using the acoustic startle method in which an unexpected acoustic stimulus provokes a reflexive startle response. This response can be inhibited by a detectable change in sound just before stimulus presentation—in this case, a silent gap in background noise. The strength of this inhibition reflects the animal's awareness, or detection, of this gap. Because this is a reflexive measure yet requires auditory cortex, gap detection threshold (GDT) measures auditory processing without the confounds of attention or cognition, which can be affected by stress. ELS gerbils had significantly impaired and more variable GDT compared with controls. Auditory brainstem responses to gaps were also compromised by ELS and were correlated with poorer behavioral GDT responses, signifying that auditory processing was affected by stress at the level of the auditory nerve. Electrophysiological recordings of single-unit and multiunit activity from primary ACx in anesthetized animals indicated that cortical processing was also affected by ELS, as were individual neuronal firing properties. The study confirms that early life stress affects temporal auditory processing—in the cortex and even at the level of afferent sensory neurons—which could affect other higher-order functions such as speech perception and cognition.



Primary afferent sensory neurons (red) decussate the spinal cord, traverse the dorsal surface of the dorsal horn, and form synapse-like connections with contralateral afferent neurons expressing calcitonin gene-related peptide (blue) and isolectin B4 (green) in an optical section of the rat spinal cord. Scale bar, 50 μm.

Complex Spinal Nociceptive Circuitry Underlies Mirror-Image Pain

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(see pages 3245–3258)

After an injury, some people experience pain not only at the injury site but also in the corresponding location on the other side of the body, referred to as mirror-image pain. It might be tempting to dismiss this phenomenon as psychosomatic, but it arises from pathological changes in the spinal circuitry of nociception, where sensations from both sides of the body are integrated, but how this happens had remained a mystery. This week, Luz et al. map out the physiology in the rat spinal cord. Like many forms of pathological or chronic pain—particularly involving nerve injury—mirror-image pain is characterized by hypersensitivity to painful stimuli and allodynia, or painful sensation arising from normally innocuous stimuli. And like many other types of pain, the pathology stems from a loss of neural inhibition, as the authors found here. Mirror-image pain is more common in bodily sites innervated by neurons projecting to areas of the spinal cord where nociceptive neurons decussate, but is less common in nerves innervating the lumbar spine. The authors began by examining the lumbar spinal morphology; viral labeling revealed that afferents occasionally crossed the midline at the spinal cord to the contralateral dorsal horn and appeared to form synaptic connections with second-order neurons in the termination field of their ipsilateral primary afferents that expressed calcitonin gene-related peptide and isolectin B4, markers of nociceptive afferent neurons. Whole-cell recordings from *ex vivo* spinal cord preparations showed that about two-thirds of dorsal horn second-order neurons received only ipsilateral afferent input, but about one-third also received contralateral inputs, most of which were excitatory and smaller than ipsilateral inputs. They also found both presynaptic and postsynaptic forms of feedforward inhibition of lamina I neurons, and disinhibition of presynaptic afferents led to increased excitatory synaptic drive from contralateral inputs. The findings suggested that network disinhibition could allow contralateral excitatory drive to reach ascending neurons that would normally receive inhibitory or no contralateral afferent inputs. Contralateral neurons also provided presynaptic inhibitory inputs via GABAergic signaling, and that contralateral inhibition of ipsilateral afferents supplying lamina I neurons was driven by A-beta-delta rather than C afferents. Together the results suggest that disinhibition of inhibitory decussating afferents could lead to pathological nociceptive processing and mirror-image pain.

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