This Week in The Journal

Acetylcholine May Help People Use New Strategies

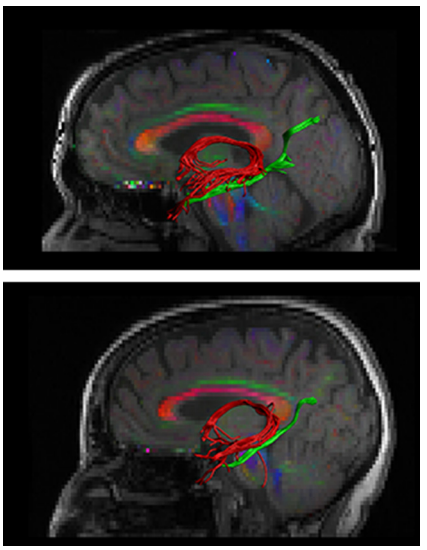
Nicola J. Ray, Claudia Metzler-Baddeley, Mizanur R. Khondoker, Michel J. Grothe, Stefan Teipel, et al.

(see pages 739–747)

Cholinergic neurons in the basal forebrain project throughout the cortex and to other brain structures, regulating arousal, attention, learning, and working memory. Cholinergic innervation declines with age, with initial loss of synapses followed by axonal degeneration and cell death. These losses are exacerbated in mild cognitive impairment (MCI) and become still more pronounced in Alzheimer's disease. Cholinergic pathology likely contributes to cognitive deficits in these diseases, and treatment with cholinesterase inhibitors slows cognitive decline.

Because attention is required for effective memory encoding, teasing apart acetylcholine's roles in memory and attention is difficult. Assessing the role of acetylcholine in memory is further complicated by the fact that degeneration of cholinergic pathways is typically accompanied by damage to medial temporal lobe structures that are essential for learning and memory. Even lesion studies in monkeys have not definitively defined acetylcholine's role in memory, because precisely targeting cholinergic pathways is difficult. Nonetheless, one study (Browning et al., 2010, Cerebral Cortex 20:282) found that selectively damaging cholinergic basal forebrain neurons did not by itself impair memory, but it greatly exacerbated the effects of fornix lesions. These authors suggested that rather than enhancing memory encoding, cholinergic projections facilitate cognitive flexibility, enabling animals to use alternative strategies when first-choice pathways are damaged.

Ray et al. provide support for this hypothesis with studies examining the relationship between the volume of brain structures and performance on memory tests in MCI patients and controls. Previous studies indicated that the fornix—a fiber tract that connects the hippocampus to other brain areas and is essential for memory functions—is damaged in MCI and that patients may engage other tracts, including the parahippocampal cingulum (PHC), during recall tasks. Consistent with this, a regression model indicated that the link between recall and fornix structure was weaker in patients. Adding left PHC volume into the model improved the fit, suggesting this tract contributes to recall performance in patients. Importantly, the PHC-linked improvement was greatest in patients that had the greatest basal forebrain volume, suggesting that patients with a relatively intact cholinergic system were better able to engage the PHC to compensate for fornix degeneration.



Volume of the fornix (red) is reduced in MCI patients (bottom) compared to controls (top). MCI patients may compensate for this loss by relying on the PHC (green). See the article by Ray et al. for details.

Neuropathic Pain Is Suppressed in Infants

Rebecca McKelvey, Temugin Berta, Elizabeth Old, Ru-Rong Ji, and Maria Fitzgerald

(see pages 457–466)

Peripheral nerve injury often causes neuropathic pain, characterized by hypersensitivity to mildly noxious stimuli and pain in the absence of stimulation. Injured nerves release cellular components that activate toll-like receptors on glia; activated glia, in turn, release cytokines that alter glial glutamate uptake and increase neuronal excitability. In adults, the increased sensitivity of neurons in nociceptive pathways causes neuropathic pain that persists for months. Neuropathic pain is rare in children under 6 years old, however, and when it occurs, it resolves more quickly than in adults. Nonetheless, injured toddlers sometimes develop neuropathic pain as they approach adolescence, and it has been suggested that seemingly unexplained pain syndromes arising in adolescence may actually stem from earlier injury. This hypothesis gains support from animal studies of spared nerve injury (SNI): SNI causes adult rats to exhibit neuropathic pain behaviors within a week, but does not produce such behaviors in pups until 3 weeks after injury.

Now McKelvey et al. provide evidence that neuropathic pain is actively suppressed by anti-inflammatory cytokines in young rodents. Like rats, adult mice exhibited cold and mechanical hypersensitivity as well as reduced weight-bearing within 7 d of SNI; but when SNI was administered on postnatal day 10 (P10), such hypersensitivity did not appear until P31. In both young and adult mice, the excitability of spared wide-dynamic-range sensory neurons and the expression of pro-inflammatory cytokines in the dorsal horn of the spinal cord increased in parallel with the appearance of behavioral hypersensitivity—within 1 week after SNI in adults, but not until 3 weeks after SNI in pups. Pups were unique, however, in showing increased expression of the anti-inflammatory cytokines IL-10 and IL-4 a week after injury. Notably, the expression of these cytokines subsided by 21 d after injury, when pro-inflammatory cytokine expression was elevated. Moreover, when IL-10 was blocked starting 7 d after SNI in pups, mechanical hypersensitivity appeared the next day. Likewise, injecting a pro-inflammatory cytokine 7 d after SNI quickly induced mechanical hypersensitivity in pups. Together, these data indicate that anti-inflammatory cytokines suppress neuropathic pain in injured mouse pups.

This Week in The Journal is written by Teresa Esch, Ph.D.