This Week in The Journal

Influences of Dopamine, Norepinephrine on Episodic Memory

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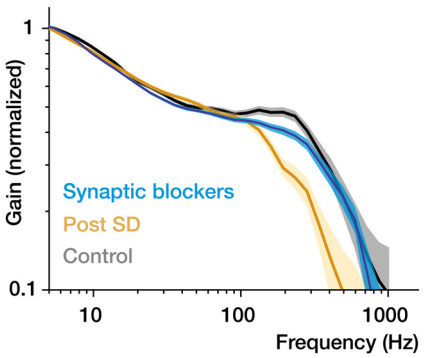
(see pages 7715–7721)

Episodic memories are the conscious recollections of our lived experiences with all their contextual richness. These long-term memory traces do not exist for all our experiences, and it is unclear what determines which ones are stored and what events are lost to us. The neurotransmitters dopamine and norepinephrine play important neuromodulatory roles, marking salient or rewarding experiences, but exactly how they influence memory storage is not known. This week, Hauser et al. show in humans that an arousal-related memory boost depended on signaling by norepinephrine, whereas dopamine was required for a memory selectivity bias.

Subjects were tasked with rating the readability of common words presented in uncommon text fonts; they were not told to remember them. Twenty minutes later, subjects were shown previously presented words mixed with novel words and asked whether they had seen each word before. In addition, one-quarter of the words presented in the initial phase were randomly paired with a £0.50 reward, making them particularly arousing. Some nonrewarded words were presented for the second time in a different font than the first time, resulting in poorer recall performance as a result of memory selectivity bias.

Before testing, subjects received an oral dose of placebo, a β-adrenergic receptor antagonist to block noradrenergic signaling, or a D_3/D_4 dopamine receptor antagonist. Subjects receiving placebo or the β-adrenergic receptor antagonist had worse recall when words were presented in a different font, but this memory selectivity bias was not detected in people receiving the dopamine receptor antagonist, indicating a role for dopamine but not norepinephrine signaling. Subjects did not differ in their overall performance on the tasks.

The researchers also measured pupil size in subjects, which they used as a measure of arousal. All subjects had larger pupil dilation following rewarded compared with nonrewarded words. Subjects given placebo or dopamine receptor antagonist showed an arousal-mediated memory boost in that their recall was better for rewarded words, but those receiving the β-adrenergic receptor blocker did not, demonstrating that norepinephrine was required for this effect. No subjects performed above chance when asked to express which words were rewarded or unrewarded. These results delineate more specific roles for these important neuromodulators in making episodic memories.



Neuronal dynamic gain vs input frequency. After SD, neurons (yellow) are compromised in their ability to phase lock with high-frequency inputs. Synaptic blockers (blue) prevented the deficit.

Neurons Not So Fine after Spreading Depression, after All

Omer Revah, Ohad Stoler, Andreas Neef, Fred Wolf, Ilya A. Fleidervish, et al.

(see pages 7790–7800)

A hallmark of cortical ischemia and other hypoxic insults is cortical spreading depression (SD), in which glutamate causes massive depolarization of neurons and glia, leading to a complete breakdown of ionic gradients that prevents spiking. Remarkably, cortical neurons recover from SD within minutes and appear electrophysiologically unimpaired. Nevertheless, clinical data suggest that cortical function may be compromised after hypoxic events. New work from Revah, Stoler et al. now shows that the ability of cortical neurons to track and encode fast inputs was compromised hours after SD as a result of structural damage done by the calcium-dependent protease calpain.

Hypoxia was induced in slices from mouse somatosensory cortex by flowing an oxygen-free gas over the slices in two episodes separated by several minutes. Several hours after SD, whole-cell patch-clamp recordings showed that layer 5 neurons in control and hypoxia-recovered slices responded similarly to depolarization with trains of action potentials. The researchers next tested the dynamic gain of the neurons, or their ability to encode subthreshold inputs, by injecting electrical current patterns meant to represent such inputs against a background of synaptic noise. At lower frequencies, both control and recovered neurons were able to phase lock with spike trains, but phase locking in hypoxia-recovered neurons was compromised at frequencies >100 Hz. Bath application of a mixture of synaptic ionotropic receptor blockers prevented the development of SD during hypoxia; neurons from these slices encoded spike trains similarly to those of control neurons.

The researchers next investigated the cytoskeletal architecture at the axon initial segment by staining for ankyrin G (AnkG). In slices recovered from hypoxia, AnkG staining was markedly reduced, indicating structural damage, although sodium channel distribution appeared intact. In slices recovered from hypoxia that were bathed in a calpain inhibitor, neurons were protected from both structural damage and encoding deficits, suggesting that SD-induced damage depended on calcium and calpain—a protease that targets structural proteins and ion channels. Cortical neurons fire at relatively low frequencies (1–20 Hz), so their power to encode complex signals arises from the activity of the population. The findings of SD-induced damage in cortical neurons suggest that they may no longer be able to effectively encode information despite their normal outward appearance.

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