Neural signals of aversive memory formation under anesthesia

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Video Abstract

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Abstract

Along with preventing pain, one function of anesthesia is to keep a person from remembering unpleasant experiences. And yet, after surgery, a very small number of patients report distressing events, which can have long-term effects, including PTSD. Anesthesia usually ensures patients lack explicit memory, but implicit memories can still form. Previous studies have suggested that implicit memory formation can occur under sedation, via circuits in the amygdala. To investigate this phenomenon, researchers in Israel conducted experiments on monkeys undergoing anesthesia using two different drugs: ketamine, an NMDA receptor antagonist; and midazolam, a GABA coagonist. The team made single-cell neuron recordings on sedated animals while the animals underwent classical conditioning using tones and an aversive odor. Specifically, the monkeys were conditioned to take a deeper breath after hearing a tone, in anticipation of a noxious odor that would make them inhale less deeply. Cleverly, the paradigm relied on respiratory responses that occur regardless of consciousness. In the set-up, the animals were first habituated to tones and sedated. The monkeys were then presented with 12 conditioned stimulus–unconditioned response pairs. Following recovery, the animals were tested for retention. The monkeys showed conditioned responses when tested for retention in 44% of sessions, across different dosages of the two drugs. In sessions with subsequent retention, the size of the conditioned response during acquisition was positively correlated with the size of the conditioned response during retention, indicating a learning effect. The single-neuron responses also showed similar patterns. During acquisition, the neuron responses in the amygdala and dorsal anterior cingulate cortex were stronger during sessions with evidence of memory formation. The responses were also correlated between acquisition and retention, with the change in the firing rate of neurons in the amygdala during acquisition predicting memory retention. The researchers also tested whether the anesthetics changed the response to the noxious odor, since the drugs might reduce the valence of the aversive stimulus. But there was no change in the respiratory unconditioned response to the aversive odor in anesthetized animals versus controls receiving saline. This indicates that the negative valence of the odor is preserved under anesthesia and contributes to memory formation. The findings support the notion that implicit memories of negative experiences can form during anesthesia. They also indicate that implicit memory formation under anesthesia is similar to what occurs in the awake state – and that it involves the amygdala–dorsal anterior cingulate cortex circuit.