Midazolam and ketamine produce distinct neural changes in memory, pain, and fear networks during pain

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Video Abstract

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Abstract

Clinicians use a diversity of anesthetic drugs to regulate memory formation, the perception of pain, and other aspects of consciousness during otherwise painful, unpleasant, or anxiety-provoking experiences. These drugs are well known to vary in their effects on human behavior, but the neural processes in the brain that form the basis of this variation are now being uncovered with functional neuroimaging. In a new study published in the journal *Anesthesiology*, researchers compared the effects of midazolam and ketamine. These two commonly used anesthetics differ in their effects on memory formation, pain perception, and the regions of the brain involved in these processes. While inside an MRI scanner, 26 healthy volunteers received a saline infusion and were asked simple “yes-or-no” questions about a series of spoken words, one-third of which were immediately followed by a painful shock. This procedure was then repeated with one of the two anesthetic drugs in addition to the saline infusion, and the participants’ memory of the spoken words was evaluated the following day. Each participant was asked to return at least one week later to repeat the experiment with the other drug. While the two anesthetic drugs had similar sedative effects, the participants indicated that they felt lower levels of pain while receiving ketamine than they did under the other conditions. However, midazolam had stronger effects on memory formation, causing a significant reduction in long-term memory compared to that observed when they received ketamine or neither drug. Midazolam also increased the coordinated communication among different regions of the brain, a measure called functional connectivity. Functional MRI analysis showed that answering the questions and periodically receiving painful stimulation during the experiment engaged important regions of the brain involved in memory formation, pain processing, and fear conditioning when the saline was administered. But the functional connectivity between these regions and the rest of the brain was altered by the two drugs, with greater connectivity observed under midazolam and less connectivity observed under ketamine. These results highlight that different anesthetic drugs engage different neural processes to affect cognition when a patient experiences pain. They also suggest that painful stimulation during sedation with midazolam causes increased coherence in brain connectivity, although specific details are less likely to be recollected as explicit memories than they are when ketamine is used.