Brain regions identified that may play a role in breathing failure following seizures

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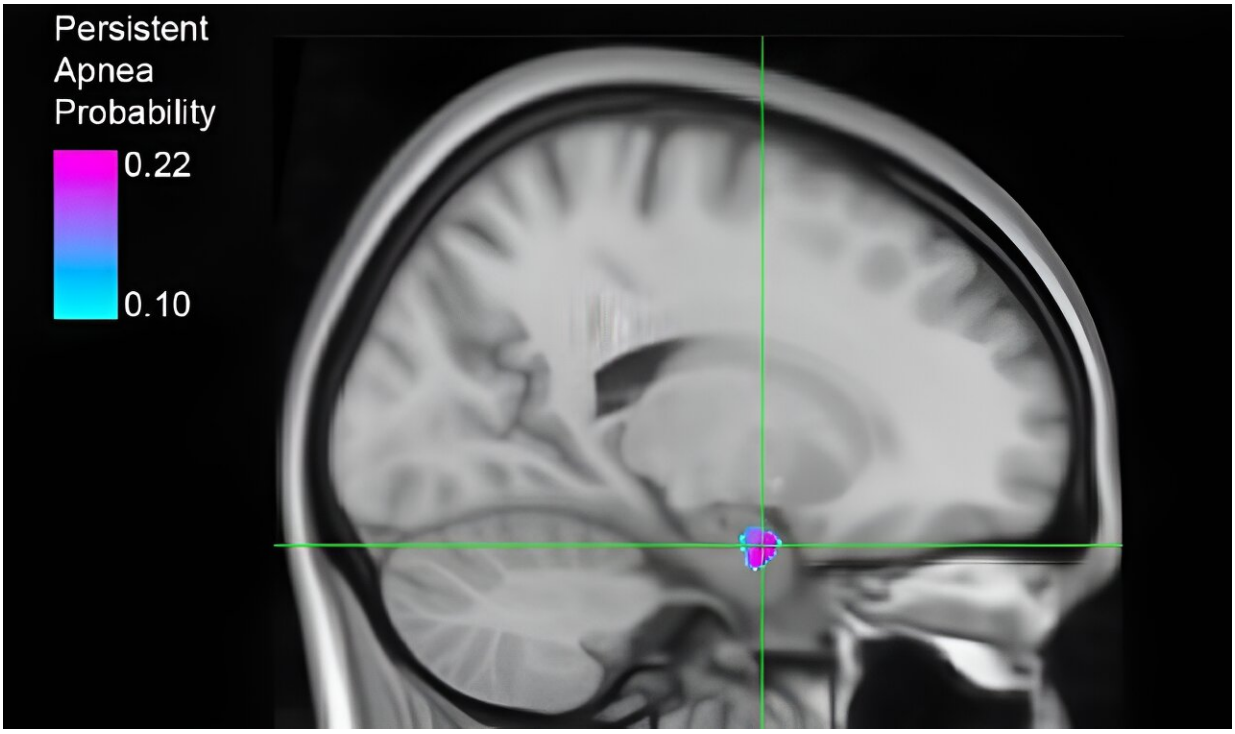


Researchers identified a site in the amygdala critical to breathing loss following a seizure. The purple and blue region represents a probability map of the region linked to persistent apnea, based on data from 20 subjects with uncontrolled epilepsy. Credit: Dlouhy lab, University of Iowa

New findings may take scientists a step closer to understanding what causes SUDEP—Sudden Unexpected Death in Epilepsy—a rare but fatal

complication of epilepsy.

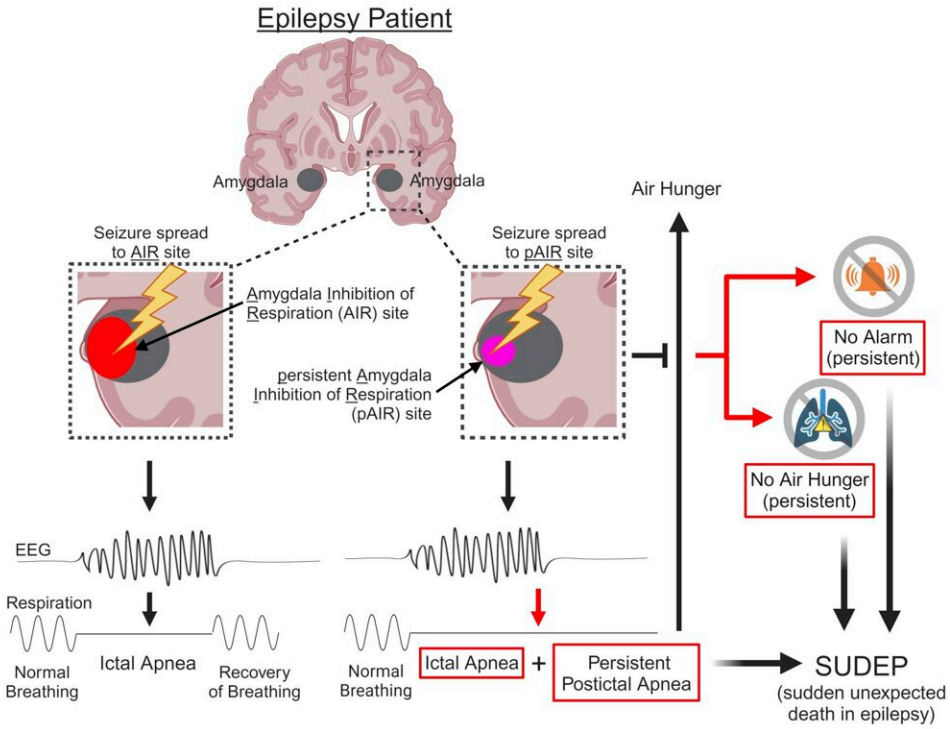
There are about 3,000 deaths from SUDEP each year in the U.S. The biggest risk factor is epilepsy that is not well controlled with medication or surgery, but the exact cause of SUDEP is not known. However, increasing evidence suggests that loss of breathing, or apnea, that persists after a seizure is a major cause of SUDEP.

In the new study, University of Iowa neuroscientists found that stimulating a specific area of the amygdala brain region provokes prolonged loss of breathing that continues even after a seizure has ended.

"This is the first study to identify a site in the brain that can cause persistent apnea after the seizure ends," says Brian Dlouhy, MD, UI associate professor of neurosurgery and pediatrics, and senior author on the new study published in *JCI Insight*. "We think this closely resembles the apnea that occurs and has been monitored in SUDEP cases reported in the literature, suggesting that this focal area of the amygdala underlies persistent apnea that can lead to death."

The study offers new insight into the mechanisms that underlie this probable cause of SUDEP.

"These new findings are a critical step in developing our understanding of what causes SUDEP and in the development of ways in which to identify those individuals at highest risk and ways to prevent SUDEP," says Vicky Whittemore, Ph.D., program director at the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health.



Graphical abstract. Credit: *JCI Insight* (2023). DOI: 10.1172/jci.insight.172423

Patients help advance SUDEP research

The UI research team, including lead authors Gail Harmata, a neuroscience graduate student, and Ariane Rhone, Ph.D., a research scientist, used multiple techniques to study the brain mechanisms linked to this loss of breathing. Specifically, they studied 20 patients, both children and adults, who were preparing for epilepsy surgery. The patients who participated in the study had intracranial electroencephalography (iEEG) electrodes implanted in their brain to help plan their surgeries.

Combining intracranial recordings from these electrodes with functional MRI brain imaging allowed the researchers to map the effect of stimulation at many amygdala sites, leading to the identification of the new focal site in the amygdala.

The study suggests that not every patient is at risk for this phenomenon; only five of the patients developed prolonged apnea following amygdala stimulation. In addition, the exact location within the amygdala was also important. Even within the same patient, stimulating one part of the amygdala caused only temporary loss of breathing while stimulating a different area led to persistent apnea after the stimulation stopped.

New brain imaging technique reveals network linked to persistent apnea

The team also used a new technique, called electrical stimulation concurrent with functional MRI, to trace the brain networks involved in the persistent post-seizure apnea.

Remarkably, during the experiment the patients were completely unaware that they had stopped breathing. They did not experience the normal sensations of breathlessness or "air hunger" that should have triggered deep breaths.

"Not only did the stimulation of these specific amygdala sites persistently inhibit breathing, it also persistently inhibited the normal alarm that you would get from not breathing and the typical air hunger that you should experience from elevated carbon dioxide levels," explains Dlouhy, who also is a member of the Iowa Neuroscience Institute.

"This novel technique allows us to look at causal effects from

stimulating one site in the brain to see what else it is doing at other sites. It allows us to look at circuitry," he adds.

The brain circuitry revealed through the experiments showed that stimulation of the amygdala reduced the activity of sites in the brainstem, a key area for controlling breathing and sensing carbon dioxide levels. Elevated levels of carbon dioxide that accumulate when breathing stops usually prompt deep breathing. The fact that the focal amygdala stimulation blocked this normal response suggests that chemo-sensing is disrupted in these patients. The studies also showed altered activity in another brain region called the insula, which is involved in air hunger.

Dlouhy is excited by the new findings and hopes that they will lead to an increased understanding of SUDEP that may eventually allow physicians to identify patients who are at risk and even lead to clinical trials of treatments to prevent SUDEP from occurring.

"We're homing in on more of a focused target in the amygdala, which is key if we want to translate this to a therapeutic or preventative strategy," he says.

More information: Gail I.S. Harmata et al, Failure to breath persists without air hunger or alarm following amygdala seizures, *JCI Insight* (2023). DOI: 10.1172/jci.insight.172423

Provided by University of Iowa