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# AIR Hunger—Why Amygdala Seizures Suppress Breathing

**Failure to Breathe Persists Without Air Hunger or Alarm Following Amygdala Seizures**

Harmata GI, Rhone AE, Kovach CK, Kumar S, Mowla MR, Sainju RK, Nagahama Y, Oya H, Gehlbach BK, Ciliberto MA, Mueller RN, Kawasaki H, Pattinson KT, Simonyan K, Davenport PW, Howard MA III, Steinschneider M, Chan AC, Richerson GB, Wemmie JA, Dlouhy BJ. *JCI Insight*. 2023;8(22):e172423. doi:10.1172/jci.insight.172423

Postictal apnea is thought to be a major cause of sudden unexpected death in epilepsy (SUDEP). However, the mechanisms underlying postictal apnea are unknown. To understand causes of postictal apnea, we used a multimodal approach to study brain mechanisms of breathing control in 20 patients (ranging from pediatric to adult) undergoing intracranial electroencephalography for intractable epilepsy. Our results indicate that amygdala seizures can cause postictal apnea. Moreover, we identified a distinct region within the amygdala where electrical stimulation was sufficient to reproduce prolonged breathing loss persisting well beyond the end of stimulation. The persistent apnea was resistant to rising $CO_2$ levels, and air hunger failed to occur, suggesting impaired $CO_2$ chemosensitivity. Using es-fMRI, a potentially novel approach combining electrical stimulation with functional MRI, we found that amygdala stimulation altered blood oxygen level-dependent (BOLD) activity in the pons/medulla and ventral insula. Together, these findings suggest that seizure activity in a focal subregion of the amygdala is sufficient to suppress breathing and air hunger for prolonged periods of time in the postictal period, likely via brainstem and insula sites involved in chemosensation and interoception. They further provide insights into SUDEP, may help identify those at greatest risk, and may lead to treatments to prevent SUDEP.

## Commentary

Sudden unexpected death in epilepsy (SUDEP) is a leading cause of death in epilepsy. While multiple potential mechanisms may contribute to the incidence of SUDEP, the most compelling evidence to date suggests postictal apnea as the primary cause of most cases.[1] Further, it appears that seizure spread to brain respiratory networks may limit postictal respiration and reduce normal arousal mechanisms. For example, seizure spread to the amygdala, or experimental lesions in the amygdala, may promote seizure-induced respiratory arrest.[2-4] Thus, the amygdala appears to play a key role in ictal and postictal respiration, likely through connections to other (e.g., brainstem) breathing control sites. However, the extent to which seizure spread to the amygdala occurs in patients at greatest risk of SUDEP is not known. Further, the specific seizure types that may elicit postictal apnea and the nature of connections between the amygdala and other respiratory control regions also warrant deeper study. Importantly, can we identify patients at greatest risk of respiratory arrest following seizures? To address these questions, recently Harmata et al[5] endeavored to perform functional mapping of an amygdala subregion that, when activated, reduces breathing.

In patients with drug-resistant epilepsy undergoing invasive EEG monitoring as part of an epilepsy surgery evaluation, depth electrodes in the amygdala allowed for short stimulation periods that produced electrographic seizures, ictal apnea (in some cases), and postictal apnea. During this study only stimulation in the amygdala (vs other forebrain sites) produced apnea, and anatomical mapping further demonstrated the medial amygdala as a key subregion for induced apnea (previously identified as the Amygdala Inhibition of Respiration or AIR site).[3] Furthermore, some patients in the study group demonstrated a profound sensitivity for stimulation of the amygdala and breathing suppression. This interindividual variability highlights the importance of understanding patient-specific breathing regulation. Interestingly, poststimulation hypoventilation was observed in the presence of hypercapnia, which should typically increase breathing rate. Thus, not only does stimulation of the amygdala produce transient or lasting apnea but also desensitization of responses to elevated $CO_2$.

Results from this study raise several important questions and highlight the complexity of forebrain and brainstem interactions affecting respiration. First, what are the downstream connections affected by amygdala stimulation? Harmata et al

used an electrical stimulation paradigm paired with functional MRI (fMRI), allowing for identification of functional connections following amygdala stimulation. Regions of the medulla, pons, and insula were all identified through these means as functionally connected to the amygdala AIR site. The primary interpretation of these findings are that amygdala activation inhibits brainstem respiratory regions. However, it is noteworthy that regulation of breathing is more complex, and inhibitory control of one respiratory rhythm center may be affected by projections from other regions, and from both excitatory and inhibitory connections.[6,7]

One of the most interesting findings from this study was that following amygdala stimulation-induced apnea, patients did not experience air hunger or exhibit respiratory distress, even in the presence of prolonged periods without breathing. Sensation of breathing (i.e., respiratory interoception) may include, under normal circumstances, heightened anxiety in the presence of breath holding or apnea. This suggests a functional suppression of air hunger that may be exacerbated in some patients. Furthermore, suppression of higher interoceptive brain regions (e.g., insular cortex) contributing to physiologic responses to breathing may be a critical factor contributing to SUDEP in at-risk individuals. This may also inform opportunities for therapeutic biomarker development (e.g., fMRI studies) that can identify differential breathing regulation in patients at greatest risk of SUDEP.

Another important finding presented is that focal seizures can produce apnea and affect brainstem breathing control. The primary risk factor affecting SUDEP risk is the presence of generalized convulsive seizures.[8] However, since this study clearly demonstrates that focal seizures are sufficient to produce apnea, it is important to therefore recognize that this seizure type still carries a potential risk of respiratory disruption. Further, the presence of focal seizures should not preclude physician and caregiver awareness of the potential risk.

While this study centered around the amygdala, it is noteworthy that other forebrain regions are critical for respiration (recently reviewed by Schottelkotte and Crone).[9] Therefore, focal or secondarily generalized seizure activity in the hippocampus, thalamus, and hypothalamus could have significant impacts on breathing. Similarly, signaling between the amygdala and forebrain is not fully understood. Although the dominant pathway affecting respiratory suppression may involve inhibitory input from the amygdala to neurons in the pre-Bötzinger complex of the medulla,[10] other midbrain and medullary breathing centers may also be affected. Furthermore, the extent to which other brain regions are affected may be state-dependent. While a majority of discovered SUDEP cases are thought to occur at night and during sleep, it is not yet clear what role sleep may play in seizure-induced activation of amygdala-brainstem circuits.

The study was conducted in a small number of patients receiving electrical stimulation of the amygdala while under close observation. The stimulation paradigm allowed for regional, but not neuron-specific stimulation. Further evaluation of this brain region may benefit from single cell recordings (e.g., in rodent models of temporal lobe epilepsy). It is also unclear the extent to which patients suffering from SUDEP also have seizures that involve amygdala-brainstem connections sufficient to produce apnea. Naturally occurring seizures in patients with epilepsy that affect the amygdala may not match the stimulation paradigm used in the study. Additional studies will therefore be important to further study the AIR site of the amygdala, and other regions, in the context of spontaneous seizures. For example, preclinical studies may allow for continuous recordings of such brain regions with concomitant assessment of respiration. Such studies may be informative to design prospective clinical studies.

In conclusion, the study presented by Harmata et al has provided some key insight into the outcomes of seizures affecting the AIR site in the amygdala. Stimulation of this region can suppress breathing ictally and postictally as well as suppress hypercapnic responses and occur in the absence of air hunger. One potential future direction emanating from this work may be the development of biomarkers that identify patients at greatest risk of SUDEP due to amygdala AIR site responsiveness. However, as not all patients with epilepsy will receive intracranial EEG to support this type of risk stratification, these studies also highlight the benefits of fMRI that may be leveraged to identify differential breathing regulation. High risk patients may also benefit from local drug administration strategies that limit seizure activity in this key amygdala subregion.

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## Declaration of Conflicting Interests

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