

# Mechanism for sudden unexpected death in epilepsy (SUDEP): the amygdala as a pathway to seizure-induced apnea, respiratory agnosia and sudden death

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## Introduction

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in patients with chronic refractory epilepsy. Case studies suggest that the cause of SUDEP may be respiratory depression induced by seizures. Consistent with this possibility, non-fatal seizures, both focal and generalized, are often associated with apnea and oxygen desaturation. However, the mechanisms for the respiratory effects in both fatal and non-fatal seizures remain unclear.

## Methods

Because impaired breathing is thought to play a critical role in SUDEP, we sought to identify forebrain sites underlying seizure-evoked hypoventilation in humans. We monitored breathing in a medically refractory epilepsy patient (JK) during seizures recorded by intracranial electrodes and mapped by high-resolution brain imaging. We used intracranial electrical stimulation to examine the function of candidate forebrain sites in three subjects.

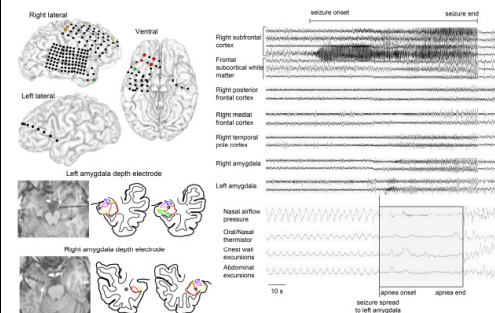
## Results

We found that central apnea and oxygen (O<sub>2</sub>) desaturation occurred when seizures spread to the left amygdala. Localized electrical stimulation of the left amygdala reproduced the apnea and O<sub>2</sub> desaturation. Localized electrical stimulation of the right amygdala also produced apnea and O<sub>2</sub> desaturation. These effects of amygdala stimulation were also observed in two additional subjects (KD and SP). Surprisingly, even when patients were awake and vigilant, they were completely unaware of the apnea evoked by stimulation and expressed no dyspnea. In contrast, voluntary breath holding of similar duration caused severe dyspnea. Using an intermittent stimulation paradigm, amygdala stimulation-evoked apnea and respiratory agnosia persisted over several minutes, as would likely be the case in a seizure that could lead to SUDEP.

## Conclusions

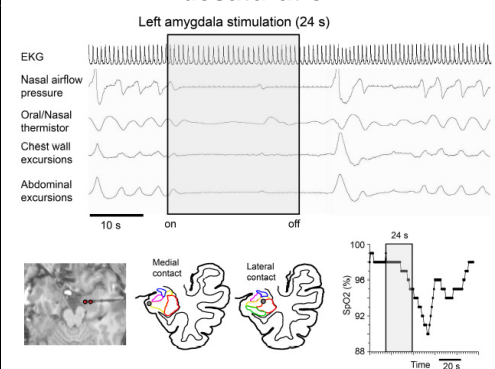
These findings indicate a functional connection between the amygdala and medullary respiratory network in humans. Due to inhibition of breathing, respiratory agnosia and loss of dyspnea, our data suggest that seizure activity within the amygdala may lead to SUDEP. Identifying strategies to target this process might prevent SUDEP.

### Central apnea occurred when seizures spread to the left amygdala



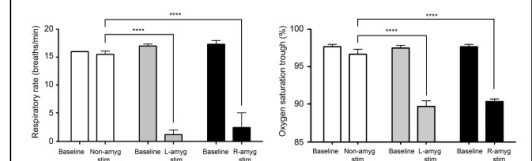
Apnea coincided with seizure spread to the left amygdala and prior to seizure spread to the right amygdala, right temporal pole (green circles), right medial frontal cortex (yellow circles), and right posterior frontal cortex (orange circles). Oxygen desaturation to 89%.

### Electrical stimulation of the amygdala reproduced apnea and oxygen desaturation



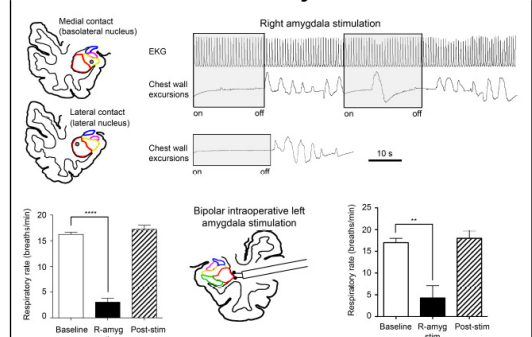
Stimulating the left basolateral and lateral amygdala caused apnea and decreased oxygen saturation (SpO<sub>2</sub>). Axial MR image showing the location of the left amygdala depth electrode contacts (red circles).

### Repeated trials of localized electrical stimulation of the amygdala produced central apnea and oxygen desaturation



Average respiratory rate and oxygen saturation at baseline and during 20-30 s electrical stimulation trials (non-amygdala stimulation, n = 3; left amygdala stimulation, n = 6; right amygdala stimulation, n = 3) \*\*\*\* indicates p < 0.0001; two-way ANOVA with Bonferroni post-hoc test.

### The respiratory effects of amygdala stimulation were reproduced in two other subjects



In the second subject, stimulating the right amygdala caused apnea and a slight slowing of the heart rate. In the third subject, intraoperative amygdala electrical stimulation using a hand-held device resulted in apnea.