Amygdala and hippocampus are symptomatogenic zones for central apneic seizures

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ABSTRACT

Objective: To identify limbic sites of respiratory control in the human brain, and by extension, the symptomatogenic zone for central apnea.

Methods: We used direct stimulation of anatomically, precisely placed stereotactic EEG electrodes to analyze breathing responses. We prospectively studied 3 patients who were explored with stereotactically implanted depth electrodes. The amygdala and hippocampus, as well as extralimbic sites (orbitofrontal, temporal tip, and temporal neocortex), were investigated.

Results: Individual stimulation of the amygdala and hippocampal head consistently elicited central apnea in the expiratory phase, as did exquisitely focal hippocampal seizures.

Conclusions: These findings confirm that hippocampus and amygdala are limbic breathing control sites in humans, as well as the symptomatogenic zone for central apneic seizures. *Neurology*® 2017;88:701-705

GLOSSARY

SUDEP = sudden unexpected death in epilepsy.

Video-monitored sudden unexpected death in epilepsy (SUDEP) cases suggest breathing dysfunction following generalized tonic-clonic seizures is involved in mechanisms of death, and terminal apnea precedes asystole.¹ Some SUDEP and near SUDEP cases have occurred with complex partial seizures without secondarily generalized tonic-clonic seizures.¹ Apnea was seen in 16 of 35 (48%) complex partial seizures² and seizure-associated O₂ desaturations were seen in 127 out of 253 (50.3%) nongeneralized focal seizures (temporal > extratemporal).³ Apnea and O₂ desaturation mechanisms during partial seizures, and their relation to SUDEP, is not understood.⁴⁻⁶ The role of cortical breathing control sites, through seizure-induced, disordered, or inhibited function, may be the key. Although several animal studies identify respiratory cortical control structures, human studies of cortical breathing are few. Invasive studies of brains of patients with refractory epilepsy undergoing assessment for epilepsy surgery provide opportunities for mapping cortical functions. Their identification may help us understand why people die after an epileptic seizure.

METHODS Patients and clinical setting. Patients aged >18 years with medically intractable epilepsy were undergoing stereotactic EEG evaluations for epilepsy surgery in the epilepsy monitoring unit at University Hospital Cleveland Medical Center. We prospectively studied 3 such consecutive patients. All patients were consented participants in a University Hospitals Case Medical Center institutional review board–approved research project evaluating the role of cortical structures in human respiratory and autonomic function.

Procedure. Platinum-iridium depth electrodes measuring 1.1 mm in diameter and 2.5 mm in length, evenly spaced at 5-mm intervals, were implanted stereotactically in the hippocampus, amygdala, and lateral temporal, orbitofrontal, temporal tip, and posterior cingulate neocortex under general anesthesia. Implantation trajectories were simulated using iplan-stereotaxy 2.6 software (Brainlab, Munich, Germany) based on recent 3T MRI of the brain. X-ray and cranial CT were performed within 24 hours postsurgically. Using iplan-stereotaxy 2.6 software, postsurgical cranial CT and presurgical brain MRI were superimposed for precise localization of single electrode contacts within the patient's presurgical MRI.

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Stimulation. Bedside cortical electrical stimulation was carried out using the same parameters (bipolar stimulation, 50 Hz, and pulse width 0.2 ms) as for clinical brain mapping, with train durations of up to 30 seconds, using a Grass S-88X Stimulator (Astro-Med, Inc., West Warwick, RI). Current intensity started at 1 mA, and increased in 1 mA increments to a maximum of 10 mA. In case a seizure was induced, stimulation was discontinued and IV lorazepam (Ativan) was given to stop the seizure. Resuscitation equipment was always kept in intimate proximity to the patient in case of need.

Cardiorespiratory and EEG monitoring. Nasal airflow was recorded using a nasal thermistor (Pro-Tech airflow sensor). Chest and abdominal excursions were recorded using inductance plethysmography (Ambu [Ballerup, Denmark] Sleepmate). Arterial oxygen saturation (SpO₂) and heart rate were monitored using pulse oximetry (Nellcor OxiMax N600x; Medtronic, Langhorne, PA) and end tidal carbon dioxide (ETCO₂) using a capnograph (model 7900; Philips, Best, the Netherlands). EEG and ECG were acquired using a Nihon Kohden (Tokyo, Japan) EEG-1200 with 256-channel amplifier. We defined apnea as involuntary cessation of breathing where at least 2 breaths were missed, compared to baseline breathing rate, with a drop in peak signal excursion by $\geq 90\%$ of pre-event baseline. Apnea onset was measured from the nadir of the preceding breath (that was clearly reduced) to the beginning of the first breath that approximated baseline amplitude. During stimulation, all patients had nasal thermal sensors to confirm presence and type of apnea. EEG was then analyzed for seizures and afterdischarges during the stimulation.

RESULTS Patient characteristics are shown in table 1. Stimulation of the amygdala and hippocampal head elicited consistent (reproduction of the same response at the same or higher stimulation intensity at the same site) apnea in all 3 patients (table 2); no breathing responses were seen from the temporal tip, lateral temporal, or orbitofrontal neocortex. At stimulation onset, immediate inhibition of respiration was clearly evident on belt/plethysmography signal and video with the thorax assuming the expiratory position. Patients were able to breathe out once but unable to breathe in again. Apnea periods ended before stimulation ended in all cases. When amygdalo-hippocampal seizures were induced, apnea duration was prolonged, but always ended before seizures ended. Slight increases in ETCO₂ were noted, but with no clear relationship to onset of rebreathing. Patients were always agnostic of apnea. In subsequent experiments, patient 3 was instructed to breathe during hippocampal stimulation-induced apnea and was immediately able to do so. Heart rate decreased or remained constant during apnea periods but significantly increased when clinical seizures were induced (table 2). In patient 2, whereas amygdala stimulation at 10 mA induced apnea, intensities of 6, 7, and 8 mA produced clear and instant disordered breathing pattern, more evident in the initial phase of stimulation, without fulfilling our definition of apnea (figures 1 and 2).

Table 1 Patient characteristics

Case	Age, y	Sex	Epilepsy duration	Handedness	Epileptogenic zone	Sz semiology	Sz frequency	Etiology	Brain MRI	Comorbidities
1	43	F	12 mo	Right	Left temporal ^a	Apneic sz → aura → dialeptic sz	4/wk	Unknown	Normal	None
2	39	M	5 y	Right	Left temporal	Automotor sz → GTCS	3/wk	Unknown	Normal	None
3	39	M	10 y	Right	Left temporal	Dialeptic sz → GTCS	2/mo	Unknown	Normal	None

Abbreviations: Sz = seizure; GTCS = generalized tonic-clonic seizure.

^a All patients were left temporal, since dominant hemisphere patients are more likely to undergo invasive evaluations.

Table 2 Characteristics of stimulation-induced apnea

Case	Location	Discharges before apnea	Induced discharges (time after apnea), s	Clinical symptoms	Minimal stimulation intensity, mA	Time after apnea onset, s	Apnea duration, s	Prestimulation pO ₂ , %	Minimal pO ₂ , %	Prestimulation ETCO ₂ , mm Hg	Maximal ETCO ₂ , mm Hg	HR mean 10 seconds before stimulation, bpm	Maximum HR during stimulation, bpm
1	Amygdala (medial)	No	Yes (+2 s)	Yes	4	1.5	56	98	91	32	42	84	126
2	Amygdala (lateral)	No	No	No	10	2	8	95	92	38	43	60	60
2	Hippocampus head	No	Yes (+3 s)	No	3	1	14	95	95	38	40	60	54
3	Amygdala (lateral)	No	No	No	6	2	9	92	92	27	29	84	72
3	Hippocampus head	No	No	No	3	2	6	92	92	27	32	84	72
3	Hippocampus head	No	Yes (+8 s)	Yes	4	2	40	92	92	27	28	84	126

DISCUSSION Breathing responses have been described with electrical stimulation in cats, dogs, and monkeys in a variety of brain regions including amygdala, hippocampus, anterior cingulate, and anterior insular cortices. In humans, where opportunities for similar experiments are limited, few studies of cortical stimulation targeting breathing control structures exist. To our knowledge, there are only 2 studies in the literature describing amygdalar stimulation-induced apnea^{7,8} and none of hippocampal stimulation-induced apnea in the modern era.

Our study, through electrical stimulation, definitively establishes the role of major limbic structures, confirming the amygdala stimulation results of Dlouhy et al.⁸ and confirming the role of the hippocampus in breathing control. Inspiration was preferentially affected, and as an active process, is likely immediately inhibited, whereas expiration is allowed to occur as a passive phenomenon. The most likely mechanism for immediate apnea is stimulation-induced inhibition or disruption of brainstem inspiratory neuronal function. Inspiratory breathing rhythm is thought to be generated in the pre-Bötzinger complex, a group of neurons in the ventrolateral medulla of the brainstem. Perturbation of neural function in and around this area severely disrupts breathing rhythm.⁹ The different types of breathing responses (apnea and disordered, irregular breathing) seen in our studies likely represent varying degrees of magnitude of response, depending on stimulus intensity.

In all stimulation periods producing apnea, patients started rebreathing before stimulation ended. Similar findings have been described in electrical stimulation studies in animals. Brain adaptation may explain this phenomenon. Several mechanisms for the overriding of apnea are possible. A previous study assessing breathing responses after amygdala stimulation postulated increased pCO₂ as an override mechanism that compelled rebreathing. It is indeed well-known that small changes in CO₂/pH affect breathing. Another plausible explanation lies in a lessening of seizure discharge intensity. In our patients, there was distinct devolution in discharge frequency or amplitude coincident with rebreathing.

The central apnea induced by amygdalohippocampal stimulation is of particular interest given its potential role as a SUDEP pathomechanism. It seems plausible that some apneic seizures produce prolonged, potentially fatal apnea. Asphyxia in animal models results in decline of heart rate and cardiac arrest within 5 minutes.¹⁰ Based on our study and the most current observations, patients are able

Figure 1 Apnea after hippocampus and amygdala stimulation

(A) Hippocampus head stimulation at intensities of 3 and 4 mA induced instant central apnea in patient 2. Apnea periods ended before stimulation was discontinued. (C) Apnea with 3 mA intensity stimulation of the hippocampus head in patient 2. (B, D) Stimulation in patient 2 at 6, 7, and 8 mA current intensities induced immediate change in respiratory rhythm. Central apnea was elicited at 10 mA current intensity in the same patient.

to override ictal apnea when instructed to talk, and asking patients with preserved consciousness to breathe may be helpful. However, since patients frequently lose consciousness or comprehension during seizures, active attempts to abort seizures

producing apnea may be more crucial. It is worth emphasizing that respiratory monitoring of seizures in the epilepsy monitoring unit is an important facet to safety and the understanding of seizure, near-SUDEP, and SUDEP phenomena.

Figure 2 Apnea induced by amygdala stimulation and hippocampal seizure

Amygdala stimulation induced an immediate apnea in patient 1. Three seconds after apnea onset, a hippocampal seizure was seen. Breathing resumed when the seizure ended in the hippocampus and amygdala, but continued in the orbitofrontal cortex for a few seconds.

One of the limitations of our study is the small number of patients and the few structures that were stimulated. Involuntary suprapontine control of respiration may not be limited to the amygdala and hippocampus. Further studies including other brain regions are necessary for complete understanding of suprapontine breathing control.

AUTHOR CONTRIBUTIONS

Dr. Lhatoo: study supervision and critical revision of the manuscript for important intellectual content. Dr. Lacuey: study concept and design, analysis and interpretation. Dr. Zonjy: acquisition of data. Dr. Londono: acquisition of data.

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DISCLOSURE

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